Biochimica et Biophysica Acta 1855 (2015) 131–143

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Runx3 at the interface of immunity, inflammation and cancer

Joseph Lotem *, Ditsa Levanon, Varda Negreanu, Omri Bauer, Shay Hantisteanu, Joseph Dicken [1], Yoram Groner

Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel

ARTICLE INFO

Article history:
Received 27 October 2014
Received in revised form 8 January 2015
Accepted 9 January 2015
Available online 30 January 2015

Keywords:
RUNX3
Cancer
Tumor suppressor gene
DNA methylation
Immunity
Inflammation

ABSTRACT

Inactivation of tumor suppressor genes (TSG) in normal cells provides a viability/growth advantage that contributes cell-autonomously to cancer. More than a decade ago claims arose that the *RUNX3* member of the *RUNX* transcription factor family is a major TSG inactivated in gastric cancer, a postulate extended later to other cancers. However, evidence that Runx3 is not expressed in normal gastric and other epithelia has challenged the *RUNX3*-TSG paradigm. Here we critically re-appraise this paradigm in light of recent high-throughput, quantitative genome-wide studies on thousands of human samples of various tumors and new investigations of the role of *Runx3* in mouse cancer models. Collectively, these studies unequivocally demonstrate that *RUNX3* is not a bona fide cell-autonomous TSG. Accordingly, *RUNX3* is not recognized as a TSG and is not included among the 2000 cancer genes listed in the "Cancer Gene Census" or "Network for Cancer Genes" repositories. In contrast, RUNX3 does play important functions in immunity and inflammation and may thereby indirectly influence epithelial tumor development.

Contents

Abbreviations: Ab, antibody; CD, Crohn's disease; CGH, comparative genomic hybridization; DC, dendritic cell; DMBA, 7, 12-dimethylbez(a)anthracene; DRG, dorsal root ganglia; FISH, fluorescent in-situ hybridization; FL, fetal liver; GC, gastric cancer; GIT, gastrointestinal tract; GWAS, genome-wide association study; HSC, hematopoietic stem cell; IBD, inflammatory bowel disease; IHC, immunohistochemistry; IL-1 and IL-6, interleukins 1 and 6, respectively; LOH, loss of heterozygosity; MNU, N-methyl-N-nitrosourea; MSP, methylation specific polymerase chain reaction; NK, natural killer; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; RISH, RNA in situ hybridization; SNP, single nucleotide polymorphic marker; TF, transcription factor; TPA, 12-*O*-tetra decanoylphorbol-13-acetate; TSG, tumor suppressor gene; UC, ulcerative colitis; WT, wild type

* Corresponding author. Tel.: +972 8 934 3972; fax: +972 8 934 4108.
E-mail address: joseph.lotem@weizmann.ac.il (J. Lotem).
[1] Current address: Compugen Ltd, Israel.

http://dx.doi.org/10.1016/j.bbcan.2015.01.004

1. Introduction

RUNX3 is one of the three mammalian Runt-domain transcription factors (TFs) (RUNX1, RUNX2 and RUNX3) encoded by the highly conserved and structurally similar *RUNX* gene family. RUNX TFs are key gene-expression regulators in several important developmental processes including hematopoiesis, osteogenesis and neurogenesis [1]. *Runx3* was originally cloned based on its similarity to *Runx1* [2] and subsequently localized on human and mouse chromosomes 1 and 4, respectively [2,3]. *Runx3*$^{-/-}$ mice phenotypes reflect its expression pattern and vitality to the proper function of several important organs. These mice exhibit ataxia due to loss of TrkC proprioceptive neurons in the dorsal root ganglia (DRG) [4], delayed chondrocyte maturation during embryogenesis [5], altered hair shape [6], defective proliferation and differentiation of activated cytotoxic CD8$^+$ T cells [7–9], helper Th1 cells [10] and natural killer (NK) cells [11], spontaneous development of colitis [12], lung inflammation associated with accumulation of hyperactivated dendritic cells (DCs) [13] and lack of skin Langerhans cells [13] and dendritic epithelial T cells [14].

More than a decade ago, it was claimed that *RUNX3* functions as a novel TSG whose inactivation plays a major role in gastric cancer (GC) development [15]. This assertion was based on the following observations: i) high expression of *Runx3* in normal mouse gastrointestinal tract (GIT) epithelium; ii) gastric hyperplasia in *Runx3*$^{-/-}$ newborn mice; iii) detection of a *RUNX3* point mutation in a single GC patient; iv) *RUNX3* loss of heterozygosity (LOH) in 30% of GC patients; v) *RUNX3* promoter DNA hypermethylation in GC; and vi) reduced *RUNX3* mRNA in GC versus normal gastric tissue in 60% of GC patients assayed by RNA in-situ hybridization (RISH).

In view of the importance of TSGs in cancer development, hundreds of subsequent studies involving thousands of patients have attempted to verify and extend the suggested *RUNX3*-TSG paradigm in GC and other GIT cancers [16]. Many of these efforts (references included in Table S1 of [17]) focused on the issue of *RUNX3* promoter DNA hypermethylation in cancer, but have failed to ascertain whether *RUNX3* is indeed expressed in normal GIT epithelial cells and to determine the quantitative relationship between *RUNX3* hypermethylation and its expression.

For a gene to qualify as a cell-autonomous TSG in a given cell type, it has to be expressed in that cell type and its loss or inactivation should prove advantageous for viability or growth, thus promoting the malignancy. Compelling evidence from several laboratories [6,12, 17–30] (Table 1) and the human proteome atlas portal (http:www.proteinatlas.org) demonstrating the lack of RUNX3 expression in normal GIT epithelium and other epithelial tissues has challenged the claim that *RUNX3* is a TSG inactivated in GC or in other cancers. The large body of data disproving the claim that *RUNX3* is a bona fide TSG and highlighting its functions in immunity and inflammation is the subject of this review. Thus, we show that chasing the wrong gene for over a decade has been counter-productive to the quest for genuine TSGs.

Table 1
Evidence for lack of Runx3 expression in various epithelia.

Organ[a]	Cells	Detection method	Reference
Stomach (mouse)	Ep	LacZ, IHC	[12,17,23]
	Ep	RISH	[12]
	Ep	IHC	[22]
	Chief-Troy$^+$ SC	Microarray[b]	[26]
	Parietal	Microarray	[26]
	Organoids from SC	Microarray	[26]
Stomach (human)	Ep	IHC	[19]
	Ep-microdissected	IHC, RT-PCR	[20]
	Ep	IHC	[22]
Intestine (mouse)	Ep	IHC, LacZ	[12,17,23]
	Epcam$^+$	qRT-PCR	[17]
	Crypt-Lgr5$^+$ SC	Microarray	[21,25]
	Crypt-Lgr5^{dim}	Microarray	[25]
	Crypt-progenitors	Microarray	[21]
	Villi-enterocytes	Microarray	[21]
Lung (mouse)	Ep	IHC	[23]
	Epcam$^+$	RNA-seq[b]	[27]
Mammary gland (mouse)	Epcam$^+$	qRT-PCR	[24]
	Lin$^-$CD24$^+$CD29$^{low,\ high}$	qRT-PCR	[30]
Skin (mouse)	Keratinocytes	IHC	[6,18]
	Hair follicle matrix Ep	IHC	[23]

[a] Runx3 is also absent in esophagus, nasal olfactory and salivary gland ducts epithelia [23]. Ep, epithelium; IHC, immunohistochemistry; RISH, RNA in-situ hybridization; and SC, stem cells.

[b] *Runx3* expression levels were obtained from the following microarray and RNA-seq data sets deposited in Gene Expression Omnibus (GEO) corresponding to the cited references: GSE51398 [21], GSE33948 [25], GSE44060 [26], and GSE52583 [27]. In all these data sets *Runx3* expression was below background level.

2. Cancer mutations and genome-wide association studies (GWAS) do not support involvement of *RUNX3* in GC or other cancers

One of the attempts to justify the claim that *RUNX3* is a major TSG, and as such is inactivated in cancer, was based on the discovery of a *RUNX3* point mutation in a single GC patient [15]. A later study of 124 bladder cancer patients identified 2 of them as carriers of monoallelic *RUNX3* mutations, one of which had 4 different mutations on the same *RUNX3* allele [31]. However, no *RUNX3* mutations were detected in a whole-exome sequencing study of 15 GC samples, which did point out non-synonymous mutations in 661 genes, including frequent mutations in the TSG *TP53* and in several genes encoding chromatin-remodeling proteins [32]. Interestingly, one of these mutated chromatin-remodeling genes, *ARID1A*, resides on the same 1p36.11 chromosomal region as *RUNX3* (Fig. 1). Recent whole-genome and whole-exome DNA sequencing studies on 100 and 295 GC samples [33,34] and on thousands of samples from other cancers [35–43] likewise did not find *RUNX3* to be a significantly mutated cancer gene, whereas *ARID1A* was, thus solidifying *ARID1A* role as a bona fide TSG.

A common feature in cancer-prone human pedigrees is the presence of germ-line mutations in the same genes that are also frequently mutated in sporadic cancers. Approximately 10% of GC cases have a familial predisposition, half of which can be attributed to germ-line mutations in different TSGs [48] (Table 2). Likewise, ~5–7% of breast cancers are familial and are associated with germ-line mutations in TSGs that predispose to breast and/or ovarian cancer development [49] and germ-line mutations in different TSGs were found to predispose to colorectal cancer [50] (Table 2). However, as shown in Table 2, not a single germ-line *RUNX3* mutation was detected in GC-prone pedigrees [51], and *RUNX3* was also not found to be a cancer-predisposition gene across different cancer types [40].

Association studies of the distribution of polymorphic markers in control and disease populations can identify genomic susceptibility loci to various diseases. One such association study analyzed the distribution of ten *RUNX3* single nucleotide polymorphisms (SNPs) in ~300 GC and control Chinese patients and reported that three *RUNX3* SNPs located in introns 1, 3 and 4, were associated with an increased risk of GC [52]. However, another larger association study in which two *RUNX3* SNPs located in exon 1 and intron 3 were assessed in 583 GC and 1637 control patients, revealed that the intron 3 SNP rs760805 was associated with *Helicobacter pylori (H. pylori)*-induced gastric atrophy but neither SNP was associated with late/tumorigenic stages of GC [53]. Interestingly, while rs760805 (Fig. 2) was used in both studies [52, 53], it was found to be associated with increased risk for GC only in the smaller population size study [52].

The SNP rs7551188 in *RUNX3* intron 1 gave a strong association signal with CD in a Japanese population, but it did not reach the required GWAS significant level [54]. Importantly, none of the three *RUNX3* SNPs nor any other SNP in the whole 1p36.11 chromosomal region for that matter, was found to be a GC susceptibility locus in three GWAS on Chinese and Japanese populations, which did identify several GC

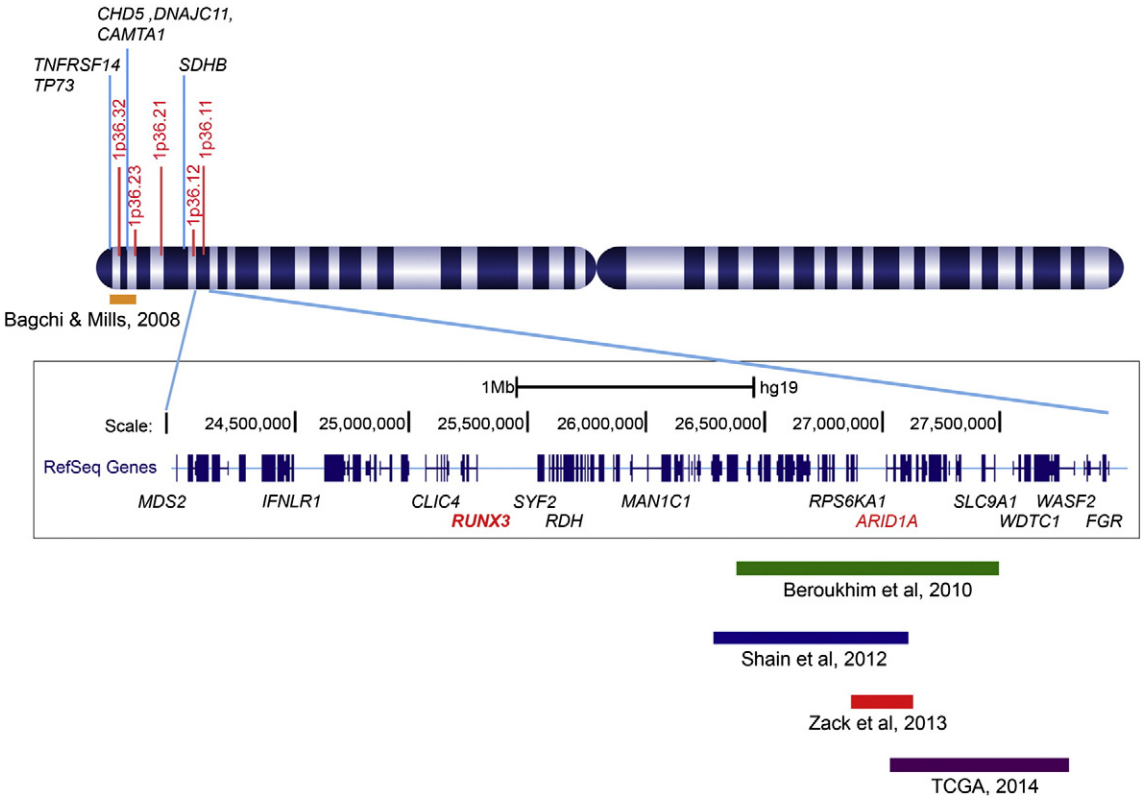

Fig. 1. Focal recurrently deleted regions in cancer on human chromosome 1p36 region. Schematic representation of human chromosome 1 and the UCSC Genome Browser blown-up map of the 24.1 Mb-long 1p36.11 region indicating some of its 86 RefSeq genes. *RUNX3* and *ARID1A* are marked in red. The colored bars below the genomic map mark the focal recurrently deleted 1.15 Mb, 850 kb, 250 kb and 746 kb 1p36.11 segments in cancers, all including *ARID1A* but excluding *RUNX3* [34,44–46]. The orange bar above the genomic map marks the 5.7 Mb 1p36.33-1.p36.23 segment recurrently deleted in multiple cancers, corresponding to the mouse 4.3 MB segment [47].

susceptibility loci on other chromosomes [55–57] (Table 3). GWAS also revealed many genomic loci associated with increased risk for breast [58–62], colorectal [63–65], cervical [66], lung [67–69], ovarian [70] and prostate [71,72] cancers, but no such association with increased cancer risk was detected on chromosome 1p36 (Table 3).

Taken together, these results indicate that although some *RUNX3* polymorphic markers may be associated with *H. pylori*-induced gastric changes, possibly due to an altered RUNX3 function in the infiltrating inflammatory immune cells, the absence of *RUNX3* mutations in cancer and the lack of any association of *RUNX3* with increased cancer risk do not support the *RUNX3*-TSG paradigm.

3. Genomic copy-number alterations in cancer do not typically involve the *RUNX3* locus

One of the hallmark features of cancer cells is the multitude of large genomic copy-number amplifications and deletions, often of an entire chromosomal arm. Such extensive genomic alterations involving hundreds of genes make it extremely difficult to identify the key genes within these regions that drive and/or contribute to cancer development. It has been reported [15] that in fluorescent in-situ hybridization (FISH) experiments, 14 out of 46 GC samples (30%) had a hemizygous deletion of *RUNX3*, based on a lower than 1:1 ratio between *RUNX3* and chromosome 1 centromere-specific FISH signals. However, the finding that in all GC samples there were at least two *RUNX3*-specific FISH signals per cell [19] indicates that there is no loss of *RUNX3* in GC but rather amplification of regions encompassing the chromosome 1 centromere [19]. Furthermore, two recent high-resolution comparative genomic hybridization (CGH) studies of GC biopsies one involving 193 patients and the other 64 patients, revealed that the chromosome 1p36 region, which harbors *RUNX3*, was not frequently deleted in GC [73,74]. The genomic regions that were recurrently deleted in GC harbored various known TSGs, while the frequently amplified ones housed known oncogenes [73] (Table 4). An earlier study on a smaller cohort of 40 GC patients, likewise did not find chromosome 1p36 region to be a frequently deleted region in GC [75]. High-resolution analysis of the landscape of somatic copy number alterations across more than 3000 cancer samples representing 26 cancer types including GC [45], revealed many focal alterations with an average of ~40 focal amplifications and ~35 focal deletions per GC sample. Interestingly, while focal deletions spanning *RUNX3* were not detected, a 1.15 Mb region on 1p36.11 containing 24 genes, including *ARID1A*, was recurrently deleted in multiple cancer types [45] (Fig. 1). Thus, the lack of convincing evidence for frequent 1p36.11 focal genomic deletions encompassing *RUNX3* in cancer further puts into question the concept of *RUNX3* serving as a TSG.

Table 2
Germ-line mutations predisposing to cancer.

Cancer	Genes mutated in familial cancer[a]	References
GC	*APC*, *BRCA1*, *BRCA2*, *CDH1*, *SMAD4*, *STK11*, *TP53*	[48]
BC	*BRCA1*, *BRCA2*, *TP53*, *CDH1*, *PTEN*, *STK11*, *ATM*, *RAD51B* *RAD51C*, *RAD51D* and others	[49]
CRC	*APC*, *MLH*, *MSH2*, *MSH6*, *MYH*, *PMS2*, *PTEN*, *SMAD4*, *STK11*	[50]

[a] No *RUNX3* germ-line mutations were detected in familial GC [51] and *RUNX3* is not a frequent cancer mutated gene in sporadic GC [32] or other cancers [40].

4. *RUNX3* promoter hypermethylation is not a driver of GC or other cancers

GC is associated with DNA hypermethylation of many genes [76], especially in EBV-positive GC [34]. Because DNA methylation at

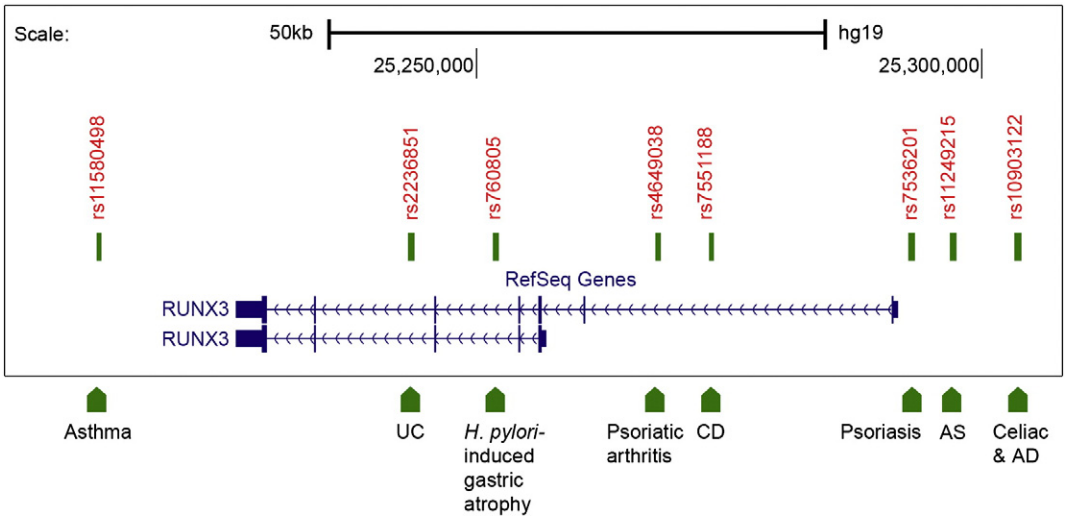

Fig. 2. Location of RUNX3 polymorphic markers associated with human immune-related diseases. UCSC Genome Browser map showing the positions of *RUNX3* SNPs associated with immune-related diseases in GIT and other tissues. AD, atopic dermatitis; AS, ankylosing spondylitis; CD, Crohn's disease; and UC, ulcerative colitis. References are given in the text.

gene-promoter regions can silence the expression of active genes, the finding of hypermethylation of the CpG-island adjacent to *RUNX3 P2* promoter in GC, interpreted as an indication for *RUNX3* silencing, was suggested as another *RUNX3* inactivation mechanism supporting a TSG role for *RUNX3* in GC [15]. In many subsequent studies on *RUNX3* hypermethylation in GC, summarized previously by Subramaniam et al. [16], ~55% of GC samples were reported as having *RUNX3 P2* promoter hypermethylation, measured by the bisulfite-modified methylation-specific PCR (MSP) method. Another more recent MSP study on 123 GC and 111 healthy patients also reported that 55% of the GC cases showed *RUNX3* hypermethylation [77]. Yet, MSP is not a quantitative technique, and a subsequent analysis of GC samples using a quantitative method, a methyl-specific DNA microarray, revealed that merely 23% of GC samples showed *RUNX3 P2* hypermethylation as compared to 46% with the conventional MSP technique [78]. Moreover, several more recent studies employing high-density DNA methylation microarrays of gastric, colorectal and breast cancer biopsies all gave the *RUNX3 P2* methylation ratio a low ranking among the DNA hypermethylated genes [79–84]. Therefore, the low frequency of *RUNX3 P2* hypermethylation and low methylation ratio in GC patients indicate that the role of *RUNX3* hypermethylation in cancer has been greatly overrated.

Moreover, even though methylation at gene promoters can lead to their silencing, hypermethylation in tumor versus healthy control samples, both of which contain heterogeneous cell populations, is not synonymous with gene silencing in the tumor cells. In fact, it has been shown that most hypermethylated genes in cancer are already silent in the normal tissue of origin of these cancers [85–87]. Therefore, a parallel analysis of gene expression must be carried out alongside the DNA methylation assay in order to establish the extent to which methylation is associated with silencing in each of the samples. However, in most of the studies summarized in [16], cancer samples were analyzed either only for *RUNX3 P2* methylation or only for RUNX3 by IHC staining, precluding the ability to determine the extent of *RUNX3* methylation and to compare it with reduced expression in each of the GC samples tested. In the study that analyzed both *RUNX3* methylation and RUNX3 expression by IHC or RT-PCR [77], it was shown that while 68% of the GC samples with no *RUNX3* methylation expressed RUNX3, 41% of those with *RUNX3* methylation also expressed RUNX3 [77]. These results suggest that there is no good correlation between *RUNX3* methylation and silencing of the gene.

Since RT-PCR and IHC are not quantitative techniques, they cannot accurately measure the level of RUNX3 expression at the RNA and protein levels. However, recent genome-wide quantitative analyses of both DNA methylation and gene expression in GC and other cancer types revealed that *RUNX3* was not listed among the genes that displayed both DNA hypermethylation and reduced expression [33, 79–84]. Hence, *RUNX3 P2* hypermethylation in cancer is not associated with its silencing. Of note, *RUNX3 P2* methylation in GC was found to be mostly monoallelic [88], so even if methylation completely silenced the expression of just one allele, the remaining allele could still be functional and express *RUNX3*. As mentioned earlier, *RUNX3* expression is regulated by two promoters. Interestingly, it was shown recently that the *RUNX3 P1* promoter is heavily methylated in gastric epithelial cells from *H. pylori* uninfected humans, which do not express RUNX3, but is completely unmethylated in RUNX3-expressing immune cells [22]. It is thus possible that *RUNX3 P1* heavy methylation is responsible for silencing its expression in normal gastric epithelium, providing an explanation for the lack of association between *RUNX3 P2* hypermethylation in GC and its expression.

Table 3
Association of genomic loci with increased cancer risk.

Type of study	Cancer associated loci	References
Individual SNPs		
GC	1p36.11 (3 SNPs, *RUNX3* introns 1, 3, 4)[a]	[52]
GWAS		
GC	1q22, 3q13.31, 5p13.1, 8q24.3, 10q23	[55–57]
BC	1p11.2, 2p24.1, 2q33, 2q35, 3p24, 4q31.22, 5p12, 5q11.2, 5p15.2, 6q25.1, 8q24.21, 8q24.1, 10q26.13, 11p15.5, 12p11, 12q24, 14q24.1, 16q12.1, 16q23.2, 17q23.2, 19q13.41, 21q21	[58–62]
CRC	2p22.1, 5p15.31, 5p15.33, 7q35, 8q23.3-24.11, 8q24.21, 10p14, 10q22.3, 10q25.2, 11q12.2, 11q23.1, 12p13.31, 12q24.21, 14q22.2, 15q13.3, 16q22.1, 17p13.3, 18q21.1, 19q13.1, 19q13.2, 20p12.3, 20q13.33	[63–65]
CC	4q12, 6p21.32, 17q12	[66]
LC	3q28, 5p15.33, 6p21.32, 6q22.2, 10q25.2, 17q24.3	[67–69]
OC	3q25, 8q21, 10p12, 17q12, 17q21	[70]
PC	1q21.3, 1q32.1, 2p25.1, 2q37.3, 3q13.2, 4q13.3, 5q35.2, 6p21.32, 6p21, 6q25.2, 7p15.3, 8p21.2, 10q24.32, 11q22.2, 12q24.21, 14q22.1, 14q24.1, 17p13.3, 17q21.32, 18q23, 19q13, 20p13, 20q13.33, 22q13, Xp22.2	[71,72]

[a] The *RUNX3* intron-3 SNP, rs760805, was used in 2 studies [52,53] but association with GC was found only in the smaller study [52]. *RUNX3* was not identified as a cancer predisposition gene across different cancer types [40]. BC, breast cancer; CRC, colorectal cancer; CC, cervical cancer; LC, lung cancer; OC, ovarian cancer; and PC, prostate cancer.

Table 4
Frequent genomic copy number alterations in GC.

Type of study	Genes	Chr. regions	Reference
CGH amplified	*BLK*, *CDK6*, *CCND1*, *CCNE1*, *EGFR*, *ERBB2*, *FGFR2*, *FGF4*, *FGF19*, *GATA6*, *KLF5*, *KRAS*, *MET*, *MYC* and others	1q, 3q, 5p, 6p, 7pq, 8q, 12pq, 13q, 18pq, 19p, 20p, 21p	[73,74]
CGH deleted[a]	*CDKN2A/B*, *CSMD1*, *FHIT*, *GMDS*, *PARK2*, *PDE4D*, *PTPRD*, *RB1*, *SMAD4*, *SMAD7*, *WWOX* and others	3p, 4pq, 5q, 6q, 8p, 9q, 11q, 14q, 16q, 17p, 18p, 18q, 19p, 21q, 22q	[73–75]

[a] Chromosomal region 1p36.1, in which *RUNX3* resides, is not deleted frequently in GC [73–75].

Lastly, analysis of the temporal relationship between accumulation of promoter DNA hypermethylation in transformed human fibroblasts grown in culture and its effect on gene expression has shown that while ~1900 transcriptionally active genes were never methylated and ~500 silent genes gradually accumulated DNA methylation with increasing number of cell generations, only ~60 genes showed concomitant accumulation of DNA methylation and reduced expression [89]. DNA methylation on the *RUNX3 P2* promoter CpG-island also increased gradually with the rise in cell generation number [89], with no consequential effect on its expression. Similarly, proliferation history-dependent DNA methylation events also underlie hematopoietic stem cell (HSC) aging and often occur at Polycomb PRC-2 complex-silenced target genes expressed in various other cell types, but not in HSC [90]. It is interesting to note that following *H. pylori* infection in mice, *Runx3 P2* remains unmethylated in gastric tissue, even at the precancerous gastric intestinal metaplasia stage, but becomes mildly hypermethylated in GC tissue from $gp130^{F/F}$ mice [22]. In addition, immortalization of mouse gastric epithelial cells from $gp130^{F/F}$ mice by serial passage in culture is associated with increased *Runx3 P2* methylation, and similarly the low methylation ratio of *RUNX3 P2* in primary human GC samples (<15%) is strongly increased to ~90% in GC cell lines [22]. It can be concluded that *RUNX3 P2* methylation in GC is (1) significantly lower than originally proposed; (2) does not correlate with *RUNX3* expression level; and (3) it is not an early driving event in the development of gastric or other cancers. Thus, promoter hypermethylation in cancer appears to be mostly a reflection of the proliferative history of the tumor cells rather than the cause of early gene silencing that might drive cancer progression.

5. The real TSGs in the 1p36 region

Large deletion events involving human chromosome 1p36 occur in a variety of cancers, including various neural, epithelial and hematopoietic malignancies, implicating the region as a possible location of one or more TSGs [47]. The part of 1p36 region commonly deleted in these cancers was narrowed down to a DNA segment spanning 4.3 Mb in the syntenic mouse chromosome 4 region. This 4.3 Mb segment does not include *RUNX3* (Fig. 1). An extra copy of this segment was shown to suppress proliferation and enhance apoptosis and senescence in cultured cells, whereas a heterozygous deficiency of the segment enhances proliferation and suppresses senescence [91], consistent with the possibility that it harbors a TSG. Knocking down *CHD5*, but not 10 other candidate genes located in this segment, reenacted the outcome effect of deleting one copy of the 4.3 Mb segment. Accordingly, $Chd5^{+/-}$ mice spontaneously developed certain solid tumors and lymphoma [91] but no GC or other GIT tumors were observed.

Large heterozygous deletions spanning chromosome regions 1p36-p34 were also frequently found in pancreatic cancer [44,92]. Interestingly, the recurrent deletion that occurred in 47% of pancreatic cancer patients spans 850 kb within chromosome 1p36.11 and contains 25 genes, including *ARID1A* [44] but not *RUNX3* (Fig. 1). This region overlaps the 1.15 Mb segment on 1p36.11 containing 24 genes that is recurrently deleted in multiple cancer types [45], which includes *ARID1A* but not *RUNX3* (Fig. 1). Analysis of somatic copy-number alterations in the framework of the Cancer Genome Atlas (TCGA) project, involving nearly 5000 cancer patients across 11 cancer types, revealed an even smaller recurrently deleted 1p36.11 region, spanning only ~250 kb and harboring just 2 genes, *ARID1A* and *PIGV* [46] (Fig. 1). Finally, a recent TCGA analysis of 295 GC patients detected another overlapping recurrent ~750 kb focally deleted region in 1p36.11 that contains 20 genes including *ARID1A* but excluding *RUNX3* [34] (Fig. 1). Together, these findings strongly suggest that while several known TSGs and TSG candidates are located on human chromosome 1p36, including *TNFRSF14*, *TP73*, *CHD5*, *DNAJC11*, *CAMTA1*, *SDHB* and *ARID1A* (Fig. 1), the real TSG on 1p36.11 is *ARID1A*, not *RUNX3*. This notion is supported by the observation noted earlier that *ARID1A* is significantly mutated in various cancer types [33–43].

6. Runx3-deficiency affects epithelial tumors in a non-cell autonomous manner

6.1. GIT tumors

The GIT was the first organ in which *RUNX3* was argued to serve as a TSG [15]. As indicated earlier, normal GIT epithelium does not express RUNX3 (Table 1) precluding the possibility that it functions as a cell-autonomous TSG in GIT epithelium. However, it has been shown that loss of a TSG in stromal cells [93–95] or T cells [96] leads to epithelial tumorigenesis. Therefore, the scenario in which Runx3 activity in GIT leukocytes might non-cell autonomously protect GIT epithelium against tumorigenesis is a possibility worth considering. Indeed, Runx3 is expressed in GIT leukocytes [12,17], including TCRγδCD8αα (E. Woolf, Ph.D. thesis, 2005) and TCRαβCD4$^+$CD8αα [97,98] intraepithelial lymphocytes, whose development requires Runx3 (E. Woolf, Ph.D. thesis, 2005 and [97,98]) and whose proper function is important for protecting the epithelium against pathogens and inflammation [99]. As noted above its absence in $Runx3^{-/-}$ mice is associated with early-onset colonic inflammation, epithelial hyperplasia, enlarged mesenteric lymph nodes and late-onset gastric hyperplasia [12]. Moreover, early-onset colitis also develops in $Runx3^{fl/fl}$/*Cd11c-Cre* mice, in which *Runx3* is specifically deleted in DCs [100], and can be transferred to immune-suppressed mice by fetal liver (FL) hematopoietic precursors from $Runx3^{-/-}$ embryos [100,101]. However, although inflammation can support tumor formation [102,103] and *H. pylori*-induced inflammation is a major contributing factor to GC [104], none of the $Runx3^{-/-}$ mice showed an increased incidence of GIT tumors or any other tumor [12,105]. Of note, while transferred $Runx3^{-/-}$ FL cells induced colitis but not tumor growth in irradiated $RAG2^{-/-}$ mice housed under pathogen-free conditions, colon and cecum tumors were reported to develop when these mice were housed under conventional conditions [101]. These results suggest that loss of Runx3 function in leukocytes can, under certain conditions, promote the development of colonic tumors derived from Runx3 non-expressing epithelium, presumably in a colitis-dependent mechanism influenced by the colonic flora. These results are clearly inconsistent with the idea that Runx3 functions as a cell-autonomous TSG in GIT epithelium.

Another study of interest involving a carcinogen-induced GC model in Balb/c mice, reported that while ~10% of WT and $Runx3^{+/-}$ mice treated with N-methyl-N-nitrosourea (MNU) developed gastric tumors,

a staggering 70% of MNU-treated *Runx3*$^{-/-}$ mice developed gastric tumors [106]. As indicated earlier, normal gastric epithelial cells do not express Runx3 [12,22,26] and it has been reported that MNU-induced gastric tumors in mice are associated with chronic infiltration of inflammatory cells and that inflammation promotes MNU-induced gastric tumors [107]. Moreover, it has been shown that gastric cancer development in mice transgenic for *Wnt1*, *Ptgs2 and Ptges* (*Gan* mice) is dependent on TNFα and tumor formation could be rescued in TNFα$^{-/-}$ mice by transfer of bone marrow-derived DCs from TNFα$^{+/+}$ mice, which infiltrated the tumors [108]. As indicated above, *H. pylori*-induced inflammation is a major contributing factor to GC [104]. Taken together, it is highly unlikely that loss of Runx3 in gastric epithelium is responsible for the reported higher incidence of MNU-induced gastric tumors in *Runx3*$^{-/-}$ Balb/c mice and suggests that lack of leukocytic Runx3 function may be responsible.

Nevertheless, this issue can be tested directly by specifically eliminating Runx3 activity from GIT epithelium or inflammatory cells. GIT epithelium-specific deletion of the TSG *Klf4*, using *Villin-Cre* transgenic mice, was shown to induce gastric tumors and accelerate MNU-induced gastric tumor development [109]. Similarly, *Villin-Cre*-mediated deletion of both *Fbw7* and *Tp53*, but not each of these TSGs alone, induced development of adenocarcinoma in the small intestine, cecum and colon [110]. It would thus be very interesting to see whether conditional deletion of *Runx3* specifically in GIT epithelium, or in inflammatory cells (using *MX1-Cre*, *Lck-Cre or CD11c-Cre*) recapitulates the high incidence of MNU-induced gastric tumors reported to occur in *Runx3*$^{-/-}$ Balb/c mice and whether it also results in development of intestinal adenocarcinoma.

It is important to note that although *Runx3*$^{-/-}$ Balb/c mice survived for more than a year without developing GIT tumors, peculiarly ~50% of *Runx3*$^{+/-}$ mice were reported to develop late-onset (15 months) small adenomas in the small intestine [105]. In contrast, while ~20% of *Runx3*$^{-/-}$ ICR mice developed inflammation of the small intestine, no intestinal adenomas were detected in *Runx3*$^{+/-}$ or *Runx3*$^{-/-}$ ICR mice [12]. The reported formation of intestinal adenomas in *Runx3*$^{+/-}$ but not in *Runx3*$^{-/-}$ Balb/c mice is even more puzzling, because none of the *Runx3*$^{-/-}$ phenotypic features, including ataxia due to loss of TrkC neurons in DRG [4], colitis [12], asthma-like lung inflammation [13] and defective silencing of CD4 expression in CD8^{+} T cells [8,9], is observed in *Runx3*$^{+/-}$ mice. These findings indicate that a sufficient amount of Runx3 is present in *Runx3*$^{+/-}$ mice to maintain homeostasis. It is thus unlikely that *RUNX3* is a bona fide TSG, since loss of only one TSG allele is generally not enough to induce tumors, and even in cases where tumor development does occur following the loss of one TSG allele (haploinsufficient TSG), the manifestation of the disease is less severe than when both alleles are lost [111].

6.2. Mammary gland tumors

The mammary gland is yet another organ in which *Runx3* was suggested to act as a novel TSG [112]. It was proposed that Runx3 targets estrogen receptors for degradation, promoting the argument that it is the presumed reduced level of Runx3 in *Runx3*$^{+/-}$ Balb/c mice that is responsible for the increased expression of estrogen receptors and the spontaneous development of breast ductal carcinoma in ~20% of 15-months old female mice [112]. Strangely enough, no data was provided for the incidence of mammary tumors in aged *Runx3*$^{-/-}$ mice [112]. The fact that *Runx3* is not expressed in normal mammary gland epithelium [24,30] makes it highly unlikely that the mammary tumors reported to develop in aged *Runx3*$^{+/-}$ Balb/c mice reflect a cell-autonomous loss of Runx3 in the mammary epithelium itself. Nonetheless, unequivocally demonstrating that the aged *Runx3*$^{+/-}$ Balb/c mice mammary tumors are in fact the product of a cell-autonomous reduced expression of Runx3 in mammary epithelium requires that such tumors also develop following deletion of *Runx3* specifically in that tissue. It will therefore be interesting to determine whether conditional deletion of *Runx3* in mammary gland epithelial cells (using *Wap-Cre*) or in immune cells will give rise to mammary adenocarcinoma in aged Balb/c mice. Notwithstanding, it should be stressed that the lack of mammary tumors or any other tumor in both *Runx3*$^{+/-}$ and *Runx3*$^{-/-}$ ICR mice, makes a Runx3-TSG scenario highly unlikely [12].

6.3. Lung tumors

The third tissue in which *Runx3* was suggested to function as a TSG is the lung. It was reported that *Runx3*$^{-/-}$ C57Bl/6 mouse embryos exhibit impaired lung development with alveolar epithelial hyperplasia, that newborn mice die within 24 h due to breathing abnormalities, and that 85% of 18-months old *Runx3*$^{+/-}$ mice develop lung adenomas, compared to ~5% in WT mice [113]. Treatment with urethane induced lung adenomas within 3 months in 85% of *Runx3*$^{+/-}$ mice, whereas this outcome occurred only in ~15% of WT mice [113]. In contrast, no lung adenomas were recorded in aged *Runx3*$^{+/-}$ or *Runx3*$^{-/-}$ ICR mice. In a more recent study, it was reported that post-natal deletion of *Runx3* in lung tissue of *Runx3*$^{fl/fl}$ mice by intranasal administration of Adeno-Cre (Ad-Cre) induced lung adenomas within 4 months and accelerated adenocarcinoma development due to oncogenic K-Ras activity in *K-Ras*$^{LSL\text{-}G12D/+}$/*Runx3*$^{fl/fl}$ mice [114]. However, because genuine Runx3 is not actually expressed in normal mouse lung alveolar or bronchiolar epithelium and in isolated lung Epcam^{+} cells [17,27], an implied cell-autonomous loss of Runx3 in lung epithelium leading to the reported development of lung adenomas is an unlikely scenario. Even so, to unequivocally affirm that deletion of *Runx3* specifically in lung bronchiolar or alveolar epithelium can induce adenomas and accelerate oncogenic K-Ras-induced adenocarcinoma would require conditional targeting of *Runx3* in lung epithelium using *CC10-Cre* or *SPC-Cre* deleting strains, respectively. This approach is suggested because it has been shown that activating oncogenic K-Ras in lung epithelium using either of these deleting strains effectively induces lung adenocarcinomas [115,116].

Since Runx3 is expressed in lung macrophages/DCs [13], the possibility arises that intranasal Ad-Cre-mediated deletion of *Runx3* in these cells within lung airways and alveoli of *Runx3*$^{fl/fl}$ mice may induce lung inflammation, thereby leading indirectly to epithelial hyperplasia and, possibly also to adenoma. This putative scenario is compatible with the reported rapid accumulation of myeloid cells in the lungs following intranasal Ad-Cre [117], activation of K-Ras in lung macrophages of *K-Ras*$^{LSL\text{-}G12D/+}$ mice following intranasal Ad-Cre [118] and accumulation of hyperactivated DCs and other inflammatory cells in the lungs of *Runx3*$^{-/-}$ [13] and lung-activated *K-Ras* mice [115,118]. It is also in line with the finding that lung adenomas formed in ~60% of *K-Ras*$^{LSL\text{-}G12D/+}$/*Mx1-Cre* mice in which oncogenic K-Ras was induced specifically in hematopoietic cells [119]. The development of lung tumors in *K-Ras*$^{LSL\text{-}G12D/+}$/*Ad-Cre* mice depends heavily on macrophage influx into the lung [120]. These and other myeloid cells express and secrete increased levels of inflammatory cytokines including IL-1, IL-6, TNFα and insulin-like growth factor 1, which activate NF-κB and Stat3 in lung epithelial cells, leading to their enhanced proliferation [103,121–123]. For example, deletion of *Ikkβ*, which is required for NF-κB activation, in myeloid cells (*LysM-Cre*/*Ikkβ*$^{fl/fl}$), but not in bronchiolar epithelial Clara cells (*CC10-Cre*/*Ikkb*$^{fl/fl}$), impairs myeloid cell accumulation, cytokine secretion in lungs of mice exposed to tobacco smoke and the proliferation of lung adenoma cells in chemically-induced lung tumors [123]. Together, these results strongly implicate Runx3 function in lung myeloid cells as an important regulator of lung inflammation, so its loss may contribute indirectly to lung adenoma development. It will be of great interest to determine whether deletion of *Runx3* specifically in myeloid cells using *Cd11c-Cre*/*Runx3*$^{fl/fl}$ and/or *LysM-Cre*/*Runx3*$^{fl/fl}$, recapitulates the development of lung adenomas and the accelerated formation of K-Ras-induced lung adenocarcinomas, observed in *Runx3*$^{fl/fl}$ and *K-Ras*$^{LSL\text{-}G12D/+}$/*Runx3*$^{fl/fl}$ mice, respectively, following intranasal administration of *Ad-Cre*.

6.4. Skin tumors

Studies on carcinogen-induced skin cancer in mice involving treatment with the carcinogen 7, 12-dimethylbez(α)anthracene (DMBA) followed by the tumor-promoting phorbol ester 12-*O*-tetra decanoylphorbol-13-acetate (TPA) revealed that skin tumor formation is inflammation-dependent (reviewed in [124]). For example, expression of Cxcr3 in T cells [125] and the receptor for advanced glycation end-products RAGE [126] in immune cells, but not in keratinocytes, was found to be required for sustaining TPA-induced infiltration of inflammatory cells, epidermal hyperplasia and tumor promotion. Analysis of the role of Runx3 has shown that while 100% of DMBA/TPA WT ICR mice developed multiple skin papilloma tumors, the degree of inflammation-associated epithelial hyperplasia and the frequency of papilloma-bearing mice were strongly reduced in *Runx3*$^{-/-}$ mice [18]. *Runx3*$^{-/-}$ mice were also highly resistant to TPA-induced tumor promotion in skin already pre-initiated by an oncogenic Ha-Ras [18]. The reduced susceptibility of Runx3-deficient mice to skin carcinogenesis was associated with a marked reduction in TPA-recruited skin CD11b^{+} DCs and γδT cells and with an altered cytokine milieu in their skin, which together generated an anti-tumor environment [18]. Moreover, mice in which *Runx3* was specifically deleted in both DCs and T cells (using *Runx3*$^{fl/fl::CD11c\text{-}Cre::Lck\text{-}Cre}$ mice), but not in keratinocytes (using *Runx3*$^{fl/fl::K14\text{-}Cre}$ mice), fully simulate the resistance of *Runx3*$^{-/-}$ mice to skin carcinogenesis [18]. These results indicate that *Runx3*$^{-/-}$ mice protection against inflammation-dependent skin carcinogenesis is due to loss of Runx3 activity in immune cells and not in keratinocytes (Fig. 3). Hence, Runx3 function in immune cells is strongly implicated in TPA-induced skin tumor promotion, inconsistent with *Runx3* being a cell-autonomous TSG in epithelium. Moreover, the observation that RUNX3 is overexpressed in the nuclei of human skin basal cell carcinoma cells [127] suggests that its presence in epithelial cells does not prevent carcinoma development. In fact, it raises the possibility that RUNX3 overexpression and not its absence may promote human skin cancer by a cell-autonomous mechanism.

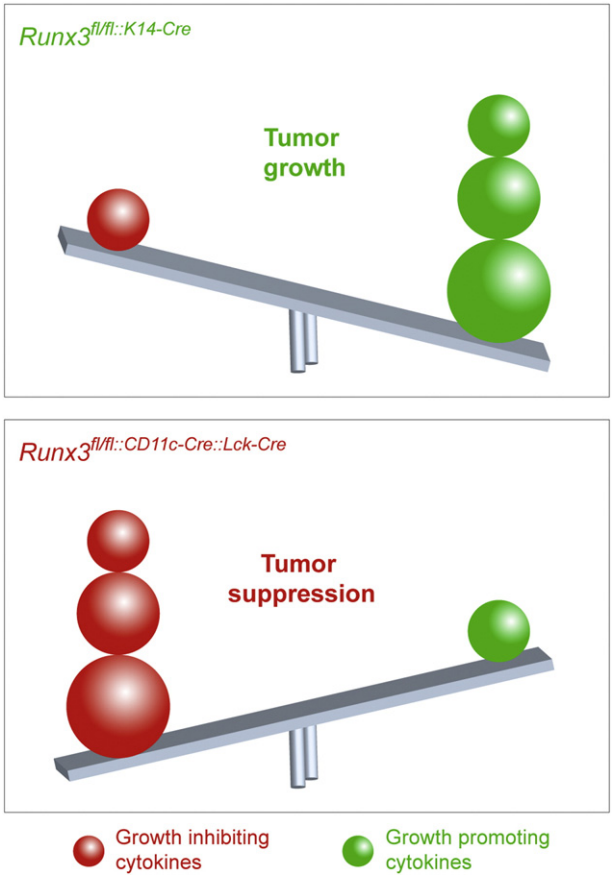

Fig. 3. Leukocytic Runx3 regulates the balance of cytokines and tumor promotion in the TPA-treated inflamed skin microenvironment. Deletion of *Runx3* in both dendritic and T cells (bottom) but not in keratinocytes (top) inhibits TPA-mediated skin inflammation and tumor promotion [18].

7. Association of *RUNX3* with immune-related inflammatory diseases and its possible implications to cancer development

Unlike the lack of convincing evidence for *RUNX3* direct participation in human cancers, several studies have implicated *RUNX3* in immune-related diseases in GIT and other organs. Two studies associated *RUNX3* SNP rs2236851 with increased risk for ulcerative colitis (UC) [128,129] and a GWAS of a Japanese population revealed a certain connection between *RUNX3* SNPs and an increased risk for two other GIT diseases, celiac [130] and Crohn's disease (CD) [54], although the latter did not reach GWAS significance level (Table 5 and Fig. 2). GWAS also revealed an association of *RUNX3* with ankylosing spondylitis [131] and psoriasis [132] (Table 5 and Fig. 2). Other relevant examples include the association of SNP rs10903122, located near *RUNX3*, with both celiac disease [130] and atopic dermatitis [133]; rs4649038 in *RUNX3* intron 1 with psoriatic arthritis [134]; and rs11580498, located 13 kb downstream of *RUNX3*, with asthma in a Canadian population [135] (Table 5 and Fig. 2). It is interesting to note that several SNPs in other genes associated with immune-related diseases, including Lupus erythematosus, psoriasis and rheumatoid arthritis, disrupt or alter the canonical RUNX-binding sites within these susceptibility loci [136–138].

As indicated earlier, Runx3-deficient mice spontaneously develop early-onset colitis [12], which can be transferred to immune-suppressed mice by FL hematopoietic precursors from *Runx3*$^{-/-}$ embryos [100,101]. It is thus possible that certain GIT and other inflammatory diseases are associated with particular *RUNX3* SNPs, which might affect RUNX3 functions in leukocytes, such as CD8^{+} T cells, NK and DCs, all of which display distinct phenotypes when Runx3 is absent [11,13,139,140]. Significantly, many of the genes reported to be associated with increased risk for inflammatory GIT diseases, including celiac [141], Crohn's [142], UC [143] and inflammatory bowel disease (IBD) [144], were identified as Runx3 targets in CD8^{+} T, NK and/or DCs [11,139,140] (Table 6). The Runx3 targets *Ets1*, *Ube2e3* and *Zmiz1* are also susceptibility genes for psoriasis [132] (Table 6). Together, these results implicate RUNX3 itself and many of its gene targets in immune and inflammatory cells as protectors against a range of immune-related diseases in various organs, including the GIT.

Several studies have underscored the role of various TSGs in inflammation in the tumor microenvironment. For example, deletion of the

Table 5
Association studies implicating *RUNX3* in human immune-related diseases.

Type of study	Association with disease[a]	References
Selected SNPs	*H. pylori*-induced GA	[53]
Selected SNPs	UC	[128,129]
GWAS	Celiac[b]	[130]
GWAS	CD	[54] [c]
GWAS	AS	[131]
GWAS	Psoriasis	[132]
GWAS	Asthma	[135]

[a] AS, ankylosing spondylitis; CD, Crohn's disease; GA, gastric atrophy; and UC, ulcerative colitis.

[b] The SNP rs10903122 near *RUNX3* associated with celiac disease is also associated with atopic dermatitis [133] and the SNP rs4649038 in *RUNX3* intron-1 is associated with psoriatic arthritis [134].

[c] The SNP rs7551188 in *RUNX3* intron-1 gave a strong association signal with CD in a Japanese population, but it did not reach the required GWAS significant level [54].

Table 6
Runx3 target genes in CD8$^+$ T, NK and/or DC that are associated with human immune-related diseases.

Disease	Susceptibility genes that are Runx3-targets in CD8$^+$ T, NK and/or DC[a]
Celiac	*Aldh2*, *Bach2*, *Ccr2*, *Ccr3*, *Ccr5*, *Ccrl2*, *Cd247*, *Cxcr6*, *Ctla4*, *Ets1*, *Fasl*, *Fli1*, *Icos*, *Il18rap*, *Irf4*, *Itga4*, *Park7*, *Plek*, *Ptpn2*, *Ptprk*, *Rgs1*, *Sh2b3*, *Tlr8*, *Tnfrsf9*, *Ube2e3*, *Xcr1*, *Zmiz1*
Crohn's	*Bach2*, *Cd19*, *Cd244*, *Cpeb4*, *Crem*, *Fasl*, *Galc*, *Icoslg*, *Ifnar1*, *Ifngr2*, *Ikzf1*, *Ikzf3*, *Il18rap*, *Il2ra*, *Irf1*, *Itln1*, *Jak2*, *Lat*, *Lta*, *Plcl1*, *Prdm1*, *Ptpn2*, *Ptpn22*, *Rasgrp1*, *Ripk2*, *Sh2b1*, *Smad3*, *Spred1*, *Tnfsf8*, *Vamp3*, *Zfp36l1*, *Zmiz1*
UC	*Calm3*, *Card11*, *Dap*, *Exoc3*, *Fcgr2a*, *Gmppb*, *Gna12*, *Icosl*, *Ifng*, *Ikzf3*, *Il1r2*, *Il7r*, *Inpp5e*, *Itgal*, *Jak2*, *Pim3*, *Ormdl3*, *Prdm1*, *Ptger4*, *Serinc3*, *Smad3*, *Tnfrsf9*, *Tnfsf8*, *Tnpo3*
IBD	*Adcy3*, *Bre*, *Cd226*, *Crem*, *Crtc3*, *Dap*, *Dok3*, *Fcgr2a*, *Galc*, *Gpr18*, *Gpr183*, *Icosl*, *Ifng*, *Ikzf1*, *Il18rap*, *Il2ra*, *Irf8*, *Jak2*, *Litaf*, *Loh12cr1*, *Lpxn*, *Nfil3*, *Ormdl3*, *Osm*, *Ptger4*, *Rorc*, *Rps6kb1*, *Smad3*, *Socs1*, *Spred2*, *Spry4*, *Stat1*, *Tnfrsf18*, *Tnfrsf4*, *Tnfrsf9*, *Tnfsf8*, *Traf3ip2*, *Tspan14*, *Zfp36l1*
Psoriasis	*Ets1*, *Irf4*, *Rps6ka4*, *Ube2e3* and *Zmiz1*

[a] The lists of susceptibility genes for celiac, Crohn's, ulcerative colitis, IBD and psoriasis [132,141–144] were intersected with the lists of Runx3-target genes in CD8$^+$ T, NK and/or DCs [11,139,140] and the common genes are indicated.

TSG *Smad4* in T cells, but not in epithelial cells, results in formation of epithelial GIT tumors, possibly mediated by enhanced expression of interleukins (IL) 5, 6 and 13 by Smad4-deficient T cells, which hyper-activate Stat3 in epithelium [96]. Similarly, deletion of *Tgfbr2* in stromal fibroblasts increases expression of inflammatory mediators and cytokines and the development of squamous cell carcinoma in the forestomach [93,145]. Deletion of *p53* in mesenchymal hepatic stellate cells promotes Ccl4-induced liver cirrhosis and accelerates carcinogen-induced liver epithelial tumorigenesis by secreting elevated levels of factors that stimulate polarization of macrophages into a tumor-promoting M2 state and their increased accumulation within the tumor microenvironment [95]. Deletion of *Sqstm1/p62* in the whole organism, or specifically in stromal fibroblasts, causes IL-6 levels to rise, induces inflammation and increases tumorigenesis of prostate epithelial cancer [146]. Interestingly, *Sqstm1/p62* is highly-expressed in prostate cancer epithelial cells [146] and is required for their proliferation in vitro and in xenografts via the mTORC1 pathway [147], indicating it is not an epithelium cell-autonomous TSG. Rather, the ensuing inflammation and IL-6 production following *Sqstm1/p62* deletion in stromal fibroblasts circumvents the requirement of this gene for cancer cell proliferation. It is thus tempting to speculate that loss of *Runx3* in immune cells, which results in colonic and lung inflammation in mice, and the association of *RUNX3* with several human inflammatory diseases might, under certain conditions, also indirectly promote the growth of epithelial cancer cells. But even if this scenario does indeed occur, it is incompatible with the notion that *RUNX3* serves as an epithelium cell-autonomous TSG.

8. Conclusions and future directions

Cancer is a major cause of mortality worldwide, highlighting the importance of studies aimed at identifying cancer-driving genes and promising gene targets for potential new therapies. More than a decade ago, *RUNX3* was suggested to be a major TSG in GIT epithelium, thus preventing the development of GC. Hundreds of following studies involving thousands of GC and other cancer patients have invested great effort in the attempt to verify and extend this *RUNX3*-TSG paradigm. Yet, as outlined above, all have failed to validate the first and foremost premise for a cell-autonomous TSG that it should be expressed in the normal tissue from which the cancer has arisen. This basic requirement concerning RUNX3 expression in normal GIT epithelium has been revealed to be false.

A second elementary criterion for proving that cell-autonomous loss of RUNX3 in the epithelium drives the formation of various epithelial cancers is that tumors should develop following *Runx3* targeting specifically in the epithelium, but such evidence is yet to be presented. Moreover, other premises inferring a *RUNX3*-TSG function, such as cancer-associated *RUNX3* inactivation by point mutations or focal loss of the 1p36.11 region that harbors *RUNX3*, are not supported by a string of genome-wide analyses, including ones carried out in the framework of TCGA. No germ-line *RUNX3* mutations have been found in cancer-prone pedigrees, and GWAS have likewise failed to show any association of *RUNX3* with increased cancer susceptibility. Finally, quantitative analysis of *RUNX3 P2* hypermethylation in cancer (the most studied aspect of its putative TSG function) reveals that *RUNX3* is not highly methylated in cancer and that its methylation does not impact its expression. Taken together, these findings do not support the paradigm of *RUNX3* being a cell-autonomous TSG in epithelial tissues. Accordingly, *RUNX3* is not mentioned in "Cancer Gene Census" repository (www.sanger.ac.uk/genetics/CGP/Census/), which lists 522 established cancer genes or in the "Network for Cancer Genes (NCG 4.0)" repository (ncg.kcl.ac.uk/), which contains 2000 known and candidate cancer genes based on 77 whole-genome or whole-exome sequencing screenings of more than 3000 cancer patients and 23 cancer types. It is interesting to note that unlike RUNX3, RUNX1 is expressed in normal epithelia [17,23,24,30], *RUNX1* mutations were associated with human breast cancer [148,149] and epithelium-specific conditional deletion of *Runx1* in mice induces the development of adenomas in the duodenum and significantly enhances development of GIT tumors in the colon, cecum and intestine in APC^{min} mice [150]. Accordingly, unlike *RUNX3*, *RUNX1* is listed in the "Cancer Gene Census" and "Network for Cancer Genes (NCG 4.0)" repositories as a cancer gene.

RUNX3 has important functions in innate and adaptive immune cell types and has been associated with several immune-related diseases. Since chronic inflammatory reactions/diseases can promote epithelial cancer development by providing a tumor-promoting microenvironment, it is possible that the ensuing inflammatory reactions requiring RUNX3 (in TPA-treated skin) or those occurring in its absence (in lung and GIT) might support epithelial tumor development in a non-cell autonomous manner. In fact, loss of *Runx3* in DCs induces colitis, and transfer of *Runx3*$^{-/-}$ FL cells into irradiated RAG2$^{-/-}$ mice induces colitis that can even lead to the rise of colonic tumors when mice are housed under conventional conditions, but not under pathogen-free conditions. Tumor-infiltrating leukocytes can also kill inflammation-independent tumor cells, so loss of RUNX3 in immune cells might also augment tumor growth by weakening immune-surveillance. On the other hand, deletion of *Runx3* in immune cells, but not in keratinocytes, actually inhibits the growth of inflammation-dependent skin tumors in a chemical carcinogenesis mouse model, indicating that Runx3 function in immune cells can also play an indirect role in tumor promotion.

The high frequency in tumors of *TP53* and *ARID1A* mutations and of deletions of regions harboring known TSGs, including *ARID1A*, which resides on chromosome 1p36.11, make them and not *RUNX3*, the relevant TSGs in cancer biology. The recurrent amplification of chromosomal regions harboring known oncogenes and activating mutations in these genes, especially the RAS/RTK family, makes them and not *RUNX3* the most promising targets for cancer therapy.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

The work was supported by the Israel Science Foundation (ISF) individual grant 447/11 to YG and DL.

References

[1] D. Levanon, Y. Groner, Structure and regulated expression of mammalian RUNX genes, Oncogene 23 (2004) 4211–4219.

[2] D. Levanon, V. Negreanu, Y. Bernstein, I. Bar-Am, L. Avivi, Y. Groner, AML1, AML2, and AML3, the human members of the runt domain gene-family: cDNA structure, expression, and chromosomal localization, Genomics 23 (1994) 425–432.
[3] K.B. Avraham, D. Levanon, V. Negreanu, Y. Bernstein, Y. Groner, N.G. Copeland, N.A. Jenkins, Mapping of the mouse homolog of the human runt domain gene, AML2, to the distal region of mouse chromosome 4, Genomics 25 (1995) 603–605.
[4] D. Levanon, D. Bettoun, C. Harris-Cerruti, E. Woolf, V. Negreanu, R. Eilam, Y. Bernstein, D. Goldenberg, C. Xiao, M. Fliegauf, E. Kremer, F. Otto, O. Brenner, A. Lev-Tov, Y. Groner, The Runx3 transcription factor regulates development and survival of TrkC dorsal root ganglia neurons, EMBO J. 21 (2002) 3454–3463.
[5] C.A. Yoshida, H. Yamamoto, T. Fujita, T. Furuichi, K. Ito, K. Inoue, K. Yamana, A. Zanma, K. Takada, Y. Ito, T. Komori, Runx2 and Runx3 are essential for chondrocyte maturation, and Runx2 regulates limb growth through induction of Indian hedgehog, Genes Dev. 18 (2004) 952–963.
[6] E. Raveh, S. Cohen, D. Levanon, Y. Groner, U. Gat, Runx3 is involved in hair shape determination, Dev. Dyn. 233 (2005) 1478–1487.
[7] F. Cruz-Guilloty, M.E. Pipkin, I.M. Djuretic, D. Levanon, J. Lotem, M.G. Lichtenheld, Y. Groner, A. Rao, Runx3 and T-box proteins cooperate to establish the transcriptional program of effector CTLs, J. Exp. Med. 206 (2009) 51–59.
[8] I. Taniuchi, M. Osato, T. Egawa, M.J. Sunshine, S.C. Bae, T. Komori, Y. Ito, D.R. Littman, Differential requirements for Runx proteins in CD4 repression and epigenetic silencing during T lymphocyte development, Cell 111 (2002) 621–633.
[9] E. Woolf, C. Xiao, O. Fainaru, J. Lotem, D. Rosen, V. Negreanu, Y. Bernstein, D. Goldenberg, O. Brenner, G. Berke, D. Levanon, Y. Groner, Runx3 and Runx1 are required for CD8 T cell development during thymopoiesis, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 7731–7736.
[10] I.M. Djuretic, D. Levanon, V. Negreanu, Y. Groner, A. Rao, K.M. Ansel, Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells, Nat. Immunol. 8 (2007) 145–153.
[11] D. Levanon, V. Negreanu, J. Lotem, K. Rae-Bone, O. Brenner, D. Leshkowitz, Y. Groner, Runx3 regulates interleukin-15 dependent natural killer cell activation, Mol. Cell. Biol. 34 (2014) 1158–1169.
[12] O. Brenner, D. Levanon, V. Negreanu, O. Golubkov, O. Fainaru, E. Woolf, Y. Groner, Loss of Runx3 function in leukocytes is associated with spontaneously developed colitis and gastric mucosal hyperplasia, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 16016–16021.
[13] O. Fainaru, E. Woolf, J. Lotem, M. Yarmus, O. Brenner, D. Goldenberg, V. Negreanu, Y. Bernstein, D. Levanon, S. Jung, Y. Groner, Runx3 regulates mouse TGF-beta-mediated dendritic cell function and its absence results in airway inflammation, EMBO J. 23 (2004) 969–979.
[14] E. Woolf, O. Brenner, D. Goldenberg, D. Levanon, Y. Groner, Runx3 regulates dendritic epidermal T cell development, Dev. Biol. 303 (2007) 703–714.
[15] Q.L. Li, K. Ito, C. Sakakura, H. Fukamachi, K. Inoue, X.Z. Chi, K.Y. Lee, S. Nomura, C.W. Lee, S.B. Han, H.M. Kim, W.J. Kim, H. Yamamoto, N. Yamashita, T. Yano, T. Ikeda, S. Itohara, J. Inazawa, T. Abe, A. Hagiwara, H. Yamagishi, A. Ooe, A. Kaneda, T. Sugimura, T. Ushijima, S.C. Bae, Y. Ito, Causal relationship between the loss of RUNX3 expression and gastric cancer, Cell 109 (2002) 113–124.
[16] M.M. Subramaniam, J.Y. Chan, K.G. Yeoh, T. Quek, K. Ito, M. Salto-Tellez, Molecular pathology of RUNX3 in human carcinogenesis, Biochim. Biophys. Acta 1796 (2009) 315–331.
[17] D. Levanon, Y. Bernstein, V. Negreanu, K.R. Bone, A. Pozner, R. Eilam, J. Lotem, O. Brenner, Y. Groner, Absence of Runx3 expression in normal gastrointestinal epithelium calls into question its tumour suppressor function, EMBO Mol. Med. 3 (2011) 593–604.
[18] O. Bauer, S. Hantisteanu, J. Lotem, Y. Groner, Carcinogen-induced skin tumor development requires leukocytic expression of the transcription factor Runx3, Cancer Prev. Res. 7 (2014) 913–926.
[19] R. Carvalho, A.N. Milne, M. Polak, W.E. Corver, G.J. Offerhaus, M.A. Weterman, Exclusion of RUNX3 as a tumour-suppressor gene in early-onset gastric carcinomas, Oncogene 24 (2005) 8252–8258.
[20] M.J. Friedrich, R. Rad, R. Langer, P. Voland, H. Hoefler, R.M. Schmid, C. Prinz, M. Gerhard, Lack of RUNX3 regulation in human gastric cancer, J. Pathol. 210 (2006) 141–146.
[21] T.H. Kim, F. Li, I. Ferreiro-Neira, L.L. Ho, A. Luyten, K. Nalapareddy, H. Long, M. Verzi, R.A. Shivdasani, Broadly permissive intestinal chromatin underlies lateral inhibition and cell plasticity, Nature 506 (2014) 511–515.
[22] B. Kurklu, R.H. Whitehead, E.K. Ong, T. Minamoto, J.G. Fox, J.R. Mann, L.M. Judd, A.S. Giraud, T.R. Menheniott, Lineage-specific RUNX3 hypomethylation marks the preneoplastic immune component of gastric cancer, Oncogene (2015). http://dx.doi.org/10.1038/onc.2014.233 (in press).
[23] D. Levanon, O. Brenner, V. Negreanu, D. Bettoun, E. Woolf, R. Eilam, J. Lotem, U. Gat, F. Otto, N. Speck, Y. Groner, Spatial and temporal expression pattern of Runx3 (Aml2) and Runx1 (Aml1) indicates non-redundant functions during mouse embryogenesis, Mech. Dev. 109 (2001) 413–417.
[24] L. McDonald, N. Ferrari, A. Terry, M. Bell, Z.M. Mohammed, C. Orange, A. Jenkins, W.J. Muller, B.A. Gusterson, J.C. Neil, J. Edwards, J.S. Morris, E.R. Cameron, K. Blyth, RUNX2 in subtype specific breast cancer and mammary gland differentiation, Dis. Model Mech. 7 (2014) 525–534.
[25] J. Munoz, D.E. Stange, A.G. Schepers, M. van de Wetering, B.K. Koo, S. Itzkovitz, R. Volckmann, K.S. Kung, J. Koster, S. Radulescu, K. Myant, R. Versteeg, O.J. Sansom, J.H. van Es, N. Barker, A. van Oudenaarden, S. Mohammed, A.J. Heck, H. Clevers, The Lgr5 intestinal stem cell signature: robust expression of proposed quiescent '+4' cell markers, EMBO J. 31 (2012) 3079–3091.
[26] D.E. Stange, B.K. Koo, M. Huch, G. Sibbel, O. Basak, A. Lyubimova, P. Kujala, S. Bartfeld, J. Koster, J.H. Geahlen, P.J. Peters, J.H. van Es, M. van de Wetering, J.C. Mills, H. Clevers, Differentiated Troy+ chief cells act as reserve stem cells to generate all lineages of the stomach epithelium, Cell 155 (2013) 357–368.
[27] B. Treutlein, D.G. Brownfield, A.R. Wu, N.F. Neff, G.L. Mantalas, F.H. Espinoza, T.J. Desai, M.A. Krasnow, S.R. Quake, Reconstructing lineage hierarchies of the distal lung epithelium using single-cell RNA-seq, Nature 509 (2014) 371–375.
[28] D. Levanon, Y. Groner, Runx3-deficient mouse strains circa 2008: resemblance and dissimilarity, Blood Cells Mol. Dis. 43 (2009) 1–5.
[29] J. Lotem, D. Levanon, V. Negreanu, Y. Groner, The false paradigm of Runx3 function as tumor suppressor in gastric cancer, J. Cancer Ther. 4 (2013) 16–25.
[30] M.P. van Bragt, X. Hu, Y. Xie, Z. Li, RUNX1, a transcription factor mutated in breast cancer, controls the fate of ER-positive mammary luminal cells, eLife 3 (2014) 03881.
[31] W.J. Kim, E.J. Kim, P. Jeong, C. Quan, J. Kim, Q.L. Li, J.O. Yang, Y. Ito, S.C. Bae, RUNX3 inactivation by point mutations and aberrant DNA methylation in bladder tumors, Cancer Res. 65 (2005) 9347–9354.
[32] Z.J. Zang, I. Cutcutache, S.L. Poon, S.L. Zhang, J.R. McPherson, J. Tao, V. Rajasegaran, H.L. Heng, N. Deng, A. Gan, K.H. Lim, C.K. Ong, D. Huang, S.Y. Chin, I.B. Tan, C.C. Ng, W. Yu, Y. Wu, M. Lee, J. Wu, D. Poh, W.K. Wan, S.Y. Rha, J. So, M. Salto-Tellez, K.G. Yeoh, W.K. Wong, Y.J. Zhu, P.A. Futreal, B. Pang, Y. Ruan, A.M. Hillmer, D. Bertrand, N. Nagarajan, S. Rozen, B.T. Teh, P. Tan, Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes, Nat. Genet. 44 (2012) 570–574.
[33] K. Wang, S.T. Yuen, J. Xu, S.P. Lee, H.H. Yan, S.T. Shi, H.C. Siu, S. Deng, K.M. Chu, S. Law, K.H. Chan, A.S. Chan, W.Y. Tsui, S.L. Ho, A.K. Chan, J.L. Man, V. Foglizzo, M.K. Ng, A.S. Chan, Y.P. Ching, G.H. Cheng, T. Xie, J. Fernandez, V.S. Li, H. Clevers, P.A. Rejto, M. Mao, S.Y. Leung, Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer, Nat. Genet. 46 (2014) 573–582.
[34] The Cancer Genome Atlas Research Network, Comprehensive molecular characterization of gastric adenocarcinoma, Nature 513 (2014) 201–209.
[35] A.M. Dulak, P. Stojanov, S. Peng, M.S. Lawrence, C. Fox, C. Stewart, S. Bandla, Y. Imamura, S.E. Schumacher, E. Shefler, A. McKenna, S.L. Carter, K. Cibulskis, A. Sivachenko, G. Saksena, D. Voet, A.H. Ramos, D. Auclair, K. Thompson, C. Sougnez, R.C. Onofrio, C. Guiducci, R. Beroukhim, Z. Zhou, L. Lin, J. Lin, R. Reddy, A. Chang, R. Landrenau, A. Pennathur, S. Ogino, J.D. Luketich, T.R. Golub, S.B. Gabriel, E.S. Lander, D.G. Beer, T.E. Godfrey, G. Getz, A.J. Bass, Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity, Nat. Genet. 45 (2013) 478–486.
[36] S. Jones, T.L. Wang, M. Shih Ie, T.L. Mao, K. Nakayama, R. Roden, R. Glas, D. Slamon, L.A. Diaz Jr., B. Vogelstein, K.W. Kinzler, V.E. Velculescu, N. Papadopoulos, Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma, Science 330 (2010) 228–231.
[37] C. Kandoth, M.D. McLellan, F. Vandin, K. Ye, B. Niu, C. Lu, M. Xie, Q. Zhang, J.F. McMichael, M.A. Wyczalkowski, M.D. Leiserson, C.A. Miller, J.S. Welch, M.J. Walter, M.C. Wendl, T.J. Ley, R.K. Wilson, B.J. Raphael, L. Ding, Mutational landscape and significance across 12 major cancer types, Nature 502 (2013) 333–339.
[38] H. Liang, L.W. Cheung, J. Li, Z. Ju, S. Yu, K. Stemke-Hale, T. Dogruluk, Y. Lu, X. Liu, C. Gu, W. Guo, S.E. Scherer, H. Carter, S.N. Westin, M.D. Dyer, R.G. Verhaak, F. Zhang, R. Karchin, C.G. Liu, K.H. Lu, R.R. Broaddus, K.L. Scott, B.T. Hennessy, G.B. Mills, Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer, Genome Res. 22 (2012) 2120–2129.
[39] P.J. Stephens, P.S. Tarpey, H. Davies, P. Van Loo, C. Greenman, D.C. Wedge, S. Nik-Zainal, S. Martin, I. Varela, G.R. Bignell, L.R. Yates, E. Papaemmanuil, D. Beare, A. Butler, A. Cheverton, J. Gamble, J. Hinton, M. Jia, A. Jayakumar, D. Jones, C. Latimer, K.W. Lau, S. McLaren, D.J. McBride, A. Menzies, L. Mudie, K. Raine, R. Rad, M.S. Chapman, J. Teague, D. Easton, A. Langerod, M.T. Lee, C.Y. Shen, B.T. Tee, B.W. Huimin, A. Broeks, A.C. Vargas, G. Turashvili, J. Martens, A. Fatima, P. Miron, S.F. Chin, G. Thomas, S. Boyault, O. Mariani, S.R. Lakhani, M. van de Vijver, L. van't Veer, J. Foekens, C. Desmedt, C. Sotiriou, A. Tutt, C. Caldas, J.S. Reis-Filho, S.A. Aparicio, A.V. Salomon, A.L. Borresen-Dale, A.L. Richardson, P.J. Campbell, P.A. Futreal, M.R. Stratton, The landscape of cancer genes and mutational processes in breast cancer, Nature 486 (2012) 400–404.
[40] B. Vogelstein, N. Papadopoulos, V.E. Velculescu, S. Zhou, L.A. Diaz Jr., K.W. Kinzler, Cancer genome landscapes, Science 339 (2013) 1546–1558.
[41] K.C. Wiegand, S.P. Shah, O.M. Al-Agha, Y. Zhao, K. Tse, T. Zeng, J. Senz, M.K. McConechy, M.S. Anglesio, S.E. Kalloger, W. Yang, A. Heravi-Moussavi, R. Giuliany, C. Chow, J. Fee, A. Zayed, L. Prentice, N. Melnyk, G. Turashvili, A.D. Delaney, J. Madore, S. Yip, A.W. McPherson, G. Ha, L. Bell, S. Fereday, A. Tam, L. Galletta, P.N. Tonin, D. Provencher, D. Miller, S.J. Jones, R.A. Moore, G.B. Morin, A. Oloumi, N. Boyd, S.A. Aparicio, M. Shih Ie, A.M. Mes-Masson, D.D. Bowtell, M. Hirst, B. Gilks, M.A. Marra, D.G. Huntsman, ARID1A mutations in endometriosis-associated ovarian carcinomas, N. Engl. J. Med. 363 (2010) 1532–1543.
[42] J.N. Wu, C.W. Roberts, ARID1A mutations in cancer: another epigenetic tumor suppressor? Cancer Discov. 3 (2013) 35–43.
[43] M.S. Lawrence, P. Stojanov, C.H. Mermel, J.T. Robinson, L.A. Garraway, T.R. Golub, M. Meyerson, S.B. Gabriel, E.S. Lander, G. Getz, Discovery and saturation analysis of cancer genes across 21 tumour types, Nature 505 (2014) 495–501.
[44] A.H. Shain, C.P. Giacomini, K. Matsukuma, C.A. Karikari, M.D. Bashyam, M. Hidalgo, A. Maitra, J.R. Pollack, Convergent structural alterations define SWItch/Sucrose nonfermentable (SWI/SNF) chromatin remodeler as a central tumor suppressive complex in pancreatic cancer, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) E252–E259.
[45] R. Beroukhim, C.H. Mermel, D. Porter, G. Wei, S. Raychaudhuri, J. Donovan, J. Barretina, J.S. Boehm, J. Dobson, M. Urashima, K.T. Mc Henry, R.M. Pinchback, A.H. Ligon, Y.J. Cho, L. Haery, H. Greulich, M. Reich, W. Winckler, M.S. Lawrence, B.A. Weir, K.E. Tanaka, D.Y. Chiang, A.J. Bass, A. Loo, C. Hoffman, J. Prensner, T. Liefeld, Q. Gao, D. Yecies, S. Signoretti, E. Maher, F.J. Kaye, H. Sasaki, J.E. Tepper, J.A. Fletcher, J. Tabernero, J. Baselga, M.S. Tsao, F. Demichelis, M.A. Rubin, P.A.

Janne, M.J. Daly, C. Nucera, R.L. Levine, B.L. Ebert, S. Gabriel, A.K. Rustgi, C.R. Antonescu, M. Ladanyi, A. Letai, L.A. Garraway, M. Loda, D.G. Beer, L.D. True, A. Okamoto, S.L. Pomeroy, S. Singer, T.R. Golub, E.S. Lander, G. Getz, W.R. Sellers, M. Meyerson, The landscape of somatic copy-number alteration across human cancers, Nature 463 (2010) 899–905.

[46] T.I. Zack, S.E. Schumacher, S.L. Carter, A.D. Cherniack, G. Saksena, B. Tabak, M.S. Lawrence, C.Z. Zhang, J. Wala, C.H. Mermel, C. Sougnez, S.B. Gabriel, B. Hernandez, H. Shen, P.W. Laird, G. Getz, M. Meyerson, R. Beroukhim, Pan-cancer patterns of somatic copy number alteration, Nat. Genet. 45 (2013) 1134–1140.

[47] A. Bagchi, A.A. Mills, The quest for the 1p36 tumor suppressor, Cancer Res. 68 (2008) 2551–2556.

[48] N. Chun, J.M. Ford, Genetic testing by cancer site: stomach, Cancer J. 18 (2012) 355–363.

[49] L. Melchor, J. Benitez, The complex genetic landscape of familial breast cancer, Hum. Genet. 132 (2013) 845–863.

[50] R. Burt, Inheritance of colorectal cancer, Drug Discov. Today Dis. Mech. 4 (2007) 293–300.

[51] G. Keller, H. Vogelsang, I. Becker, S. Plaschke, K. Ott, G. Suriano, A.R. Mateus, R. Seruca, K. Biedermann, D. Huntsman, C. Doring, E. Holinski-Feder, A. Neutzling, J.R. Siewert, H. Hofler, Germline mutations of the E-cadherin(CDH1) and TP53 genes, rather than of RUNX3 and HPP1, contribute to genetic predisposition in German gastric cancer patients, J. Med. Genet. 41 (2004) e89.

[52] D. Wu, Y. Tian, W. Gong, H. Zhu, Z. Zhang, M. Wang, S. Wang, M. Tan, H. Wu, Genetic variants in the Runt-related transcription factor 3 gene contribute to gastric cancer risk in a Chinese population, Cancer Sci. 100 (2009) 1688–1694.

[53] A. Hishida, K. Matsuo, Y. Goto, Y. Mitsuda, M. Naito, K. Wakai, K. Tajima, N. Hamajima, Significant association of RUNX3 T/A polymorphism at intron 3 (rs760805) with the risk of gastric atrophy in *Helicobacter pylori* seropositive Japanese, J. Gastroenterol. 44 (2009) 1165–1171.

[54] K. Yamazaki, J. Umeno, A. Takahashi, A. Hirano, T.A. Johnson, N. Kumasaka, T. Morizono, N. Hosono, T. Kawaguchi, M. Takazoe, T. Yamada, Y. Suzuki, H. Tanaka, S. Motoya, M. Hosokawa, Y. Arimura, Y. Shinomura, T. Matsui, T. Matsumoto, M. Iida, T. Tsunoda, Y. Nakamura, N. Kamatani, M. Kubo, A genome-wide association study identifies 2 susceptibility Loci for Crohn's disease in a Japanese population, Gastroenterology 144 (2013) 781–788.

[55] C.C. Abnet, N.D. Freedman, N. Hu, Z. Wang, K. Yu, X.O. Shu, J.M. Yuan, W. Zheng, S.M. Dawsey, L.M. Dong, M.P. Lee, T. Ding, Y.L. Qiao, Y.T. Gao, W.P. Koh, Y.B. Xiang, Z.Z. Tang, J.H. Fan, C. Wang, W. Wheeler, M.H. Gail, M. Yeager, J. Yuenger, A. Hutchinson, K.B. Jacobs, C.A. Giffen, L. Burdett, J.F. Fraumeni Jr., M.A. Tucker, W.H. Chow, A.M. Goldstein, S.J. Chanock, P.R. Taylor, A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma, Nat. Genet. 42 (2010) 764–767.

[56] H. Sakamoto, K. Yoshimura, N. Saeki, H. Katai, T. Shimoda, Y. Matsuno, D. Saito, H. Sugimura, F. Tanioka, S. Kato, N. Matsukura, N. Matsuda, T. Nakamura, I. Hyodo, T. Nishina, W. Yasui, H. Hirose, M. Hayashi, E. Toshiro, S. Ohnami, A. Sekine, Y. Sato, H. Totsuka, M. Ando, R. Takemura, Y. Takahashi, M. Ohdaira, K. Aoki, I. Honmyo, S. Chiku, K. Aoyagi, H. Sasaki, S. Ohnami, K. Yanagihara, K.A. Yoon, M.C. Kook, Y.S. Lee, S.R. Park, C.G. Kim, I.J. Choi, T. Yoshida, Y. Nakamura, S. Hirohashi, Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer, Nat. Genet. 40 (2008) 730–740.

[57] Y. Shi, Z. Hu, C. Wu, J. Dai, H. Li, J. Dong, M. Wang, X. Miao, Y. Zhou, F. Lu, H. Zhang, L. Hu, Y. Jiang, Z. Li, M. Chu, H. Ma, J. Chen, G. Jin, W. Tan, T. Wu, Z. Zhang, D. Lin, H. Shen, A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1, Nat. Genet. 43 (2011) 1215–1218.

[58] D.F. Easton, K.A. Pooley, A.M. Dunning, P.D. Pharoah, D. Thompson, D.G. Ballinger, J.P. Struewing, J. Morrison, H. Field, R. Luben, N. Wareham, S. Ahmed, C.S. Healey, R. Bowman, K.B. Meyer, C.A. Haiman, L.K. Kolonel, B.E. Henderson, L. Le Marchand, P. Brennan, S. Sangrajrang, V. Gaborieau, F. Odefrey, C.Y. Shen, P.E. Wu, H.C. Wang, D. Eccles, D.G. Evans, J. Peto, O. Fletcher, N. Johnson, S. Seal, M.R. Stratton, N. Rahman, G. Chenevix-Trench, S.E. Bojesen, B.G. Nordestgaard, C.K. Axelsson, M. Garcia-Closas, L. Brinton, S. Chanock, J. Lissowska, B. Peplonska, H. Nevanlinna, R. Fagerholm, H. Eerola, D. Kang, K.Y. Yoo, D.Y. Noh, S.H. Ahn, D.J. Hunter, S.E. Hankinson, D.G. Cox, P. Hall, S. Wedren, J. Liu, Y.L. Low, N. Bogdanova, P. Schurmann, T. Dork, R.A. Tollenaar, C.E. Jacobi, P. Devilee, J.G. Klijn, A.J. Sigurdson, M.M. Doody, B.H. Alexander, J. Zhang, A. Cox, I.W. Brock, G. MacPherson, M.W. Reed, F.J. Couch, E.L. Goode, J.E. Olson, H. Meijers-Heijboer, A. van den Ouweland, A. Uitterlinden, F. Rivadeneira, R.L. Milne, G. Ribas, A. Gonzalez-Neira, J. Benitez, J.L. Hopper, M. McCredie, M. Southey, G.G. Giles, C. Schroen, C. Justenhoven, H. Brauch, U. Hamann, Y.D. Ko, A.B. Spurdle, J. Beesley, X. Chen, A. Mannermaa, V.M. Kosma, V. Kataja, J. Hartikainen, N.E. Day, D.R. Cox, B.A. Ponder, Genome-wide association study identifies novel breast cancer susceptibility loci, Nature 447 (2007) 1087–1093.

[59] D. Fanale, V. Amodeo, L.R. Corsini, S. Rizzo, V. Bazan, A. Russo, Breast cancer genome-wide association studies: there is strength in numbers, Oncogene 31 (2012) 2121–2128.

[60] M. Ghoussaini, O. Fletcher, K. Michailidou, C. Turnbull, M.K. Schmidt, E. Dicks, J. Dennis, Q. Wang, M.K. Humphreys, C. Luccarini, C. Baynes, D. Conroy, M. Maranian, S. Ahmed, K. Driver, N. Johnson, N. Orr, I. dos Santos Silva, Q. Waisfisz, H. Meijers-Heijboer, A.G. Uitterlinden, F. Rivadeneira, P. Hall, K. Czene, A. Irwanto, J. Liu, H. Nevanlinna, K. Aittomaki, C. Blomqvist, A. Meindl, R.K. Schmutzler, B. Muller-Myhsok, P. Lichtner, J. Chang-Claude, R. Hein, S. Nickels, D. Flesch-Janys, H. Tsimiklis, E. Makalic, D. Schmidt, M. Bui, J.L. Hopper, C. Apicella, D.J. Park, M. Southey, D.J. Hunter, S.J. Chanock, A. Broeks, S. Verhoef, F.B. Hogervorst, P.A. Fasching, M.P. Lux, M.W. Beckmann, A.B. Ekici, E. Sawyer, I. Tomlinson, M. Kerin, F. Marme, A. Schneeweiss, C. Sohn, B. Burwinkel, P. Guenel, T. Truong, E. Cordina-Duverger, F. Menegaux, S.E. Bojesen, B.G. Nordestgaard, S.F. Nielsen, H. Flyger, R.L. Milne, M.R. Alonso, A. Gonzalez-Neira, J. Benitez, H. Anton-Culver, A. Ziogas, L. Bernstein, C.C. Dur, H. Brenner, H. Muller, V. Arndt, C. Stegmaier, C. Justenhoven, H. Brauch, T. Bruning, S. Wang-Gohrke, U. Eilber, T. Dork, P. Schurmann, M. Bremer, P. Hillemanns, N.V. Bogdanova, N.N. Antonenkova, Y.I. Rogov, J.H. Karstens, M. Bermisheva, D. Prokofieva, E. Khusnutdinova, A. Lindblom, S. Margolin, A. Mannermaa, V. Kataja, V.M. Kosma, J.M. Hartikainen, D. Lambrechts, B.T. Yesilyurt, G. Floris, K. Leunen, S. Manoukian, B. Bonanni, S. Fortuzzi, P. Peterlongo, F.J. Couch, X. Wang, K. Stevens, A. Lee, G.G. Giles, L. Baglietto, G. Severi, C. McLean, G.G. Alnaes, V. Kristensen, A.L. Borrensen-Dale, E.M. John, A. Miron, R. Winqvist, K. Pylkas, A. Jukkola-Vuorinen, S. Kauppila, I.L. Andrulis, G. Glendon, A.M. Mulligan, P. Devilee, C.J. van Asperen, R.A. Tollenaar, C. Seynaeve, J.D. Figueroa, M. Garcia-Closas, L. Brinton, J. Lissowska, M.J. Hooning, A. Hollestelle, R.A. Oldenburg, A.M. van den Ouweland, A. Cox, M.W. Reed, M. Shah, A. Jakubowska, J. Lubinski, K. Jaworska, K. Durda, M. Jones, M. Schoemaker, A. Ashworth, A. Swerdlow, J. Beesley, X. Chen, K.R. Muir, A. Lophatananon, S. Rattanamongkongul, A. Chaiwerawattana, D. Kang, K.Y. Yoo, D.Y. Noh, C.Y. Shen, J.C. Yu, P.E. Wu, C.N. Hsiung, A. Perkins, R. Swann, L. Velentzis, D.M. Eccles, W.J. Tapper, S.M. Gerty, N.J. Graham, B.A. Ponder, G. Chenevix-Trench, P.D. Pharoah, M. Lathrop, A.M. Dunning, N. Rahman, J. Peto, D.F. Easton, Genome-wide association analysis identifies three new breast cancer susceptibility loci, Nat. Genet. 44 (2012) 312–318.

[61] Y. Sapkota, Y. Yasui, R. Lai, M. Sridharan, P.J. Robson, C.E. Cass, J.R. Mackey, S. Damaraju, Identification of a breast cancer susceptibility locus at 4q31.22 using a genome-wide association study paradigm, PLoS One 8 (2013) e62550.

[62] C. Turnbull, S. Ahmed, J. Morrison, D. Pernet, A. Renwick, M. Maranian, S. Seal, M. Ghoussaini, S. Hines, C.S. Healey, D. Hughes, M. Warren-Perry, W. Tapper, D. Eccles, D.G. Evans, M. Hooning, M. Schutte, A. van den Ouweland, R. Houlston, G. Ross, C. Langford, P.D. Pharoah, M.R. Stratton, A.M. Dunning, N. Rahman, D.F. Easton, Genome-wide association study identifies five new breast cancer susceptibility loci, Nat. Genet. 42 (2010) 504–507.

[63] A. Tenesa, M.G. Dunlop, New insights into the aetiology of colorectal cancer from genome-wide association studies, Nat. Rev. Genet. 10 (2009) 353–358.

[64] U. Peters, C.M. Hutter, L. Hsu, F.R. Schumacher, D.V. Conti, C.S. Carlson, C.K. Edlund, R.W. Haile, S. Gallinger, B.W. Zanke, M. Lemire, J. Rangrej, R. Vijayaraghavan, A.T. Chan, A. Hazra, D.J. Hunter, J. Ma, C.S. Fuchs, E.L. Giovannucci, P. Kraft, Y. Liu, L. Chen, S. Jiao, K.W. Makar, D. Taverna, S.B. Gruber, G. Rennert, V. Moreno, C.M. Ulrich, M.O. Woods, R.C. Green, P.S. Parfrey, R.L. Prentice, C. Kooperberg, R.D. Jackson, A.Z. Lacroix, B.J. Caan, R.B. Hayes, S.I. Berndt, S.J. Chanock, R.E. Schoen, J. Chang-Claude, M. Hoffmeister, H. Brenner, B. Frank, S. Bezieau, S. Kury, M.L. Slattery, J.L. Hopper, M.A. Jenkins, L. Le Marchand, N.M. Lindor, P.A. Newcomb, D. Seminara, T.J. Hudson, D.J. Duggan, J.D. Potter, G. Casey, Meta-analysis of new genome-wide association studies of colorectal cancer risk, Hum. Genet. 131 (2012) 217–234.

[65] B. Zhang, W.H. Jia, K. Matsuda, S.S. Kweon, K. Matsuo, Y.B. Xiang, A. Shin, S.H. Jee, D.H. Kim, Q. Cai, J. Long, J. Shi, W. Wen, G. Yang, Y. Zhang, C. Li, B. Li, Y. Guo, Z. Ren, B.T. Ji, Z.Z. Pan, A. Takahashi, M.H. Shin, F. Matsuda, Y.T. Gao, J.H. Oh, S. Kim, Y.O. Ahn, A.T. Chan, J. Chang-Claude, M.L. Slattery, S.B. Gruber, F.R. Schumacher, S.L. Stenzel, G. Casey, H.R. Kim, J.Y. Jeong, J.W. Park, H.L. Li, S. Hosono, S.H. Cho, M. Kubo, X.O. Shu, Y.X. Zeng, W. Zheng, Large-scale genetic study in East Asians identifies six new loci associated with colorectal cancer risk, Nat. Genet. 46 (2014) 533–542.

[66] Y. Shi, L. Li, Z. Hu, S. Li, S. Wang, J. Liu, C. Wu, L. He, J. Zhou, Z. Li, T. Hu, Y. Chen, Y. Jia, S. Wang, L. Wu, X. Cheng, Z. Yang, R. Yang, X. Li, K. Huang, Q. Zhang, H. Zhou, F. Tang, Z. Chen, J. Shen, J. Jiang, H. Ding, H. Xing, S. Zhang, P. Qu, X. Song, Z. Lin, D. Deng, L. Xi, W. Lv, X. Han, G. Tao, L. Yan, Z. Han, Z. Li, X. Miao, S. Pan, Y. Shen, H. Wang, D. Liu, E. Gong, Z. Li, L. Zhou, X. Luan, C. Wang, Q. Song, S. Wu, H. Xu, J. Shen, F. Qiang, G. Ma, L. Liu, X. Chen, J. Liu, J. Wu, Y. Shen, Y. Wen, M. Chu, J. Yu, X. Hu, Y. Fan, H. He, Y. Jiang, Z. Lei, C. Liu, J. Chen, Y. Zhang, C. Yi, S. Chen, W. Li, D. Wang, Z. Wang, W. Di, K. Shen, D. Lin, H. Shen, Y. Feng, X. Xie, D. Ma, A genome-wide association study identifies two new cervical cancer susceptibility loci at 4q12 and 17q12, Nat. Genet. 45 (2013) 918–922.

[67] Q. Lan, C.A. Hsiung, K. Matsuo, Y.C. Hong, A. Seow, Z.M. Wang, H.D. Hosgood, K.X. Chen, J.C. Wang, N. Chatterjee, W. Hu, M.P. Wong, W. Zheng, N. Caporaso, J.Y. Park, C.J. Chen, Y.H. Kim, Y.T. Kim, M.T. Landi, H.B. Shen, C. Lawrence, L. Burdett, M. Yeager, J. Yuenger, K.B. Jacobs, I.S. Chang, T. Mitsudomi, H.N. Kim, G.C. Chang, B.A. Bassig, M. Tucker, F.S. Wei, Z.H. Yin, C. Wu, S.J. An, B.Y. Qian, V.H.F. Lee, D.R. Lu, J.J. Liu, H.S. Jeon, C.F. Hsiao, J.S. Sung, J.H. Kim, Y.T. Gao, Y.H. Tsai, Y.J. Jung, H. Guo, Z.B. Hu, A. Hutchinson, W.C. Wang, R. Klein, C.C. Chung, I.J. Oh, K.Y. Chen, S.I. Berndt, X.Z. He, W. Wu, J. Chang, X.C. Zhang, M.S. Huang, H. Zheng, J.W. Wang, X.Y. Zhao, Y.Q. Li, J.E. Choi, W.C. Su, K.H. Park, S.W. Sung, X.O. Shu, Y.M. Chen, L. Liu, C.H. Kang, L.M. Hu, C.H. Chen, W. Pao, Y.C. Kim, T.Y. Yang, J. Xu, P. Guan, W. Tan, J. Su, C.L. Wang, H.X. Li, A.D.L. Sihoe, Z.H. Zhao, Y. Chen, Y.Y. Choi, J.Y. Hung, J.S. Kim, H.I. Yoon, Q.Y. Cai, C.C. Lin, I.K. Park, P. Xu, J. Dong, C. Kim, Q.C. He, R.P. Perng, T. Kohno, S.S. Kweon, C.Y. Chen, R. Vermeulen, J.J. Wu, W.Y. Lim, K.C. Chen, W.H. Chow, B.T. Ji, J.K.C. Chan, M.J. Chu, Y.J. Li, J. Yokota, J.H. Li, H.Y. Chen, Y.B. Xiang, C.J. Yu, H. Kunitoh, G.P. Wu, L. Jin, Y.L. Lo, K. Shiraishi, Y.H. Chen, H.C. Lin, T.C. Wu, Y.L. Wu, P.C. Yang, B.S. Zhou, M.H. Shin, J.F. Fraumeni, D.X. Lin, S.J. Chanock, N. Rothman, Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia, Nat. Genet. 44 (2012) 1330–1335.

[68] M.T. Landi, N. Chatterjee, K. Yu, L.R. Goldin, A.M. Goldstein, M. Rotunno, L. Mirabello, K. Jacobs, W. Wheeler, M. Yeager, A.W. Bergen, Q.Z. Li, D. Consonni, A.C. Pesatori, S. Wacholder, M. Thun, R. Diver, M. Oken, J. Virtamo, D. Albanes, Z.M. Wang, L. Burdette, K.F. Doheny, E.W. Pugh, C. Laurie, P. Brennan, R. Hung, V. Gaborieau, J.D. McKay, M. Lathrop, J. McLaughlin, Y. Wang, M.S. Tsao, M.R. Spitz, Y.F. Wang, H. Krokan, L. Vatten, F. Skorpen, E. Arnesen, S. Benhamou, C.

Bouchard, A. Metsapalu, T. Vooder, M. Nelis, K. Valk, J.K. Field, C. Chen, G. Goodman, P. Sulem, G. Thorleifsson, T. Rafnar, T. Eisen, W. Sauter, A. Rosenberger, H. Bickeboller, A. Risch, J. Chang-Claude, H.E. Wichmann, K. Stefansson, R. Houlston, C.I. Amos, J.F. Fraumeni, S.A. Savage, P.A. Bertazzi, M.A. Tucker, S. Chanock, N.E. Caporaso, A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma, Am. J. Hum. Genet. 85 (2009) 679–691.

[69] Y.F. Wang, P. Broderick, E. Webb, X.F. Wu, J. Vijayakrishnan, A. Matakidou, M. Qureshi, Q. Dong, X.J. Gu, W.V. Chen, M.R. Spitz, T. Eisen, C.I. Amos, R.S. Houlston, Common 5p15.33 and 6p21.33 variants influence lung cancer risk, Nat. Genet. 40 (2008) 1407–1409.

[70] P.D. Pharoah, Y.Y. Tsai, S.J. Ramus, C.M. Phelan, E.L. Goode, K. Lawrenson, M. Buckley, B.L. Fridley, J.P. Tyrer, H. Shen, R. Weber, R. Karevan, M.C. Larson, H. Song, D.C. Tessier, F. Bacot, D. Vincent, J.M. Cunningham, J. Dennis, E. Dicks, K.K. Aben, H. Anton-Culver, N. Antonenkova, S.M. Armasu, L. Baglietto, E.V. Bandera, M.W. Beckmann, M.J. Birrer, G. Bloom, N. Bogdanova, J.D. Brenton, L.A. Brinton, A. Brooks-Wilson, R. Brown, R. Butzow, I. Campbell, M.E. Carney, R.S. Carvalho, J. Chang-Claude, Y.A. Chen, Z. Chen, W.H. Chow, M.S. Cicek, G. Coetzee, L.S. Cook, D.W. Cramer, C. Cybulski, A. Dansonka-Mieszkowska, E. Despierre, J.A. Doherty, T. Dork, A. du Bois, M. Durst, D. Eccles, R. Edwards, A.B. Ekici, P.A. Fasching, D. Fenstermacher, J. Flanagan, Y.T. Gao, M. Garcia-Closas, A. Gentry-Maharaj, G. Giles, A. Gjyshi, M. Gore, J. Gronwald, Q. Guo, M.K. Halle, P. Harter, A. Hein, F. Heitz, P. Hillemanns, M. Hoatlin, E. Hogdall, C.K. Hogdall, S. Hosono, A. Jakubowska, A. Jensen, K.R. Kalli, B.Y. Karlan, L.E. Kelemen, L.A. Kiemeney, S.K. Kjaer, G.E. Konecny, C. Krakstad, J. Kupryjanczyk, D. Lambrechts, S. Lambrechts, N.D. Le, N. Lee, J. Lee, A. Leminen, B.K. Lim, J. Lissowska, J. Lubinski, L. Lundvall, G. Lurie, L.F. Massuger, K. Matsuo, V. McGuire, J.R. McLaughlin, U. Menon, F. Modugno, K.B. Moysich, T. Nakanishi, S.A. Narod, R.B. Ness, H. Nevanlinna, S. Nickels, H. Noushmehr, K. Odunsi, S. Olson, I. Orlow, J. Paul, T. Pejovic, L.M. Pelttari, J. Permuth-Wey, M.C. Pike, E.M. Poole, X. Qu, H.A. Risch, L. Rodriguez-Rodriguez, M.A. Rossing, A. Rudolph, I. Runnebaum, I.K. Rzepecka, H.B. Salvesen, I. Schwaab, G. Severi, H. Shen, V. Shridhar, X.O. Shu, W. Sieh, M.C. Southey, P. Spellman, K. Tajima, S.H. Teo, K.L. Terry, P.J. Thompson, A. Timorek, S.S. Tworoger, A.M. van Altena, D. van den Berg, I. Vergote, R.A. Vierkant, A.F. Vitonis, S. Wang-Gohrke, N. Wentzensen, A.S. Whittemore, E. Wik, B. Winterhoff, Y.L. Woo, A.H. Wu, H.P. Yang, W. Zheng, A. Ziogas, F. Zulkifli, M.T. Goodman, P. Hall, D.F. Easton, C.L. Pearce, A. Berchuck, G. Chenevix-Trench, E. Iversen, A.N. Monteiro, S.A. Gayther, J.M. Schildkraut, T.A. Sellers, GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer, Nat. Genet. 45 (2013) 362–370.

[71] A.A. Al Olama, Z. Kote-Jarai, F.R. Schumacher, F. Wiklund, S.I. Berndt, S. Benlloch, G.G. Giles, G. Severi, D.E. Neal, F.C. Hamdy, J.L. Donovan, D.J. Hunter, B.E. Henderson, M.J. Thun, M. Gaziano, E.L. Giovannucci, A. Siddiq, R.C. Travis, D.G. Cox, F. Canzian, E. Riboli, T.J. Key, G. Andriole, D. Albanes, R.B. Hayes, J. Schleutker, A. Auvinen, T.L.J. Tammela, M. Weischer, J.L. Stanford, E.A. Ostrander, C. Cybulski, J. Lubinski, S.N. Thibodeau, D.J. Schaid, K.D. Sorensen, J. Batra, J.A. Clements, S. Chambers, J. Aitken, R.A. Gardiner, C. Maier, W. Vogel, T. Dork, H. Brenner, T. Habuchi, S. Ingles, E.M. John, J.L. Dickinson, L. Cannon-Albright, M.R. Teixeira, R. Kaneva, H.W. Zhang, Y.J. Lu, J.Y. Park, K.A. Cooney, K.R. Muir, D.A. Leongamornlert, E. Saunders, M. Tymrakiewicz, N. Mahmud, M. Guy, K. Govindasami, L.T. O'Brien, R.A. Wilkinson, A.L. Hall, E.J. Sawyer, T. Dadaev, J. Morrison, D.P. Dearnaley, A. Horwich, R.A. Huddart, V.S. Khoo, C.C. Parker, N. Van As, C.J. Woodhouse, A. Thompson, T. Dudderidge, C. Ogden, C.S. Cooper, A. Lophatonanon, M.C. Southey, J.L. Hopper, D. English, J. Virtamo, L. Le Marchand, D. Campa, R. Kaaks, S. Lindstrom, W.R. Diver, S. Gapstur, M. Yeager, A. Cox, M.C. Stern, R. Corral, M. Aly, W. Isaacs, J. Adolfsson, J.F. Xu, S.L. Zheng, T. Wahlfors, K. Taari, P. Kujala, P. Klarskov, B.G. Nordestgaard, M.A. Roder, R. Frikke-Schmidt, S.E. Bojesen, L.M. FitzGerald, S. Kolb, E.M. Kwon, D.M. Karyadi, T.F. Orntoft, M. Borre, A. Rinckleb, M. Luedeke, K. Herkommer, A. Meyer, J. Serth, J.R. Marthick, B. Patterson, D. Wokolorczyk, A. Spurdle, F. Lose, S.K. McDonnell, A.D. Joshi, A. Shahabi, P. Pinto, J. Santos, A. Ray, T.A. Sellers, H.Y. Lin, R.A. Stephenson, C. Teerlink, H. Muller, D. Rothenbacher, N. Tsuchiya, S. Narita, G.W. Cao, C. Slavov, V. Mitev, S. Chanock, H. Gronberg, C.A. Haiman, P. Kraft, D.F. Easton, and R.A. Eeles, A meta-analysis of genome-wide association studies to identify prostate cancer susceptibility loci associated with aggressive and non-aggressive disease, Hum. Mol. Genet. 22 (2013) 408–415.

[72] R.A. Eeles, A.A. Olama, S. Benlloch, E.J. Saunders, D.A. Leongamornlert, M. Tymrakiewicz, M. Ghoussaini, C. Luccarini, J. Dennis, S. Jugurnauth-Little, T. Dadaev, D.E. Neal, F.C. Hamdy, J.L. Donovan, K. Muir, G.G. Giles, G. Severi, F. Wiklund, H. Gronberg, C.A. Haiman, F. Schumacher, B.E. Henderson, L. Le Marchand, S. Lindstrom, P. Kraft, D.J. Hunter, S. Gapstur, S.J. Chanock, S.I. Berndt, D. Albanes, G. Andriole, J. Schleutker, M. Weischer, F. Canzian, E. Riboli, T.J. Key, R.C. Travis, D. Campa, S.A. Ingles, E.M. John, R.B. Hayes, P.D. Pharoah, N. Pashayan, K.T. Khaw, J.L. Stanford, E.A. Ostrander, L.B. Signorello, S.N. Thibodeau, D. Schaid, C. Maier, W. Vogel, A.S. Kibel, C. Cybulski, J. Lubinski, L. Cannon-Albright, H. Brenner, J.Y. Park, R. Kaneva, J. Batra, A.B. Spurdle, J.A. Clements, M.R. Teixeira, E. Dicks, A. Lee, A.M. Dunning, C. Baynes, D. Conroy, M.J. Maranian, S. Ahmed, K. Govindasami, M. Guy, R.A. Wilkinson, E.J. Sawyer, A. Morgan, D.P. Dearnaley, A. Horwich, R.A. Huddart, V.S. Khoo, C.C. Parker, N.J. Van As, C.J. Woodhouse, A. Thompson, T. Dudderidge, C. Ogden, C.S. Cooper, A. Lophatananon, A. Cox, M.C. Southey, J.L. Hopper, D.R. English, M. Aly, J. Adolfsson, J. Xu, S.L. Zheng, M. Yeager, R. Kaaks, W.R. Diver, M.M. Gaudet, M.C. Stern, R. Corral, A.D. Joshi, A. Shahabi, T. Wahlfors, T.L. Tammela, A. Auvinen, J. Virtamo, P. Klarskov, B.G. Nordestgaard, M.A. Roder, S.F. Nielsen, S.E. Bojesen, A. Siddiq, L.M. Fitzgerald, S. Kolb, E.M. Kwon, D.M. Karyadi, W.J. Blot, W. Zheng, Q. Cai, S.K. McDonnell, A.E. Rinckleb, B. Drake, G. Colditz, D. Wokolorczyk, R.A. Stephenson, C. Teerlink, H. Muller, D. Rothenbacher, T.A. Sellers, H.Y. Lin, C. Slavov, V. Mitev, F. Lose, S. Srinivasan, S. Maia, P. Paulo, E. Lange, K.A. Cooney, A.C. Antoniou, D. Vincent, F. Bacot, D.C. Tessier, Z. Kote-Jarai, D.F. Easton, Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array, Nat. Genet. 45 (2013) 385–391.

[73] N. Deng, L.K. Goh, H. Wang, K. Das, J. Tao, I.B. Tan, S. Zhang, M. Lee, J. Wu, K.H. Lim, Z. Lei, G. Goh, Q.Y. Lim, A.L. Tan, D.Y. Sin Poh, S. Riahi, S. Bell, M.M. Shi, R. Linnartz, F. Zhu, K.G. Yeoh, H.C. Toh, W.P. Yong, H.C. Cheong, S.Y. Rha, A. Boussioutas, H. Grabsch, S. Rozen, P. Tan, A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets, Gut 61 (2012) 673–684.

[74] B. Fan, S. Dachrut, H. Coral, S.T. Yuen, K.M. Chu, S. Law, L. Zhang, J. Ji, S.Y. Leung, X. Chen, Integration of DNA copy number alterations and transcriptional expression analysis in human gastric cancer, PLoS One 7 (2012) e29824.

[75] Y. Tsukamoto, T. Uchida, S. Karnan, T. Noguchi, L.T. Nguyen, M. Tanigawa, I. Takeuchi, K. Matsuura, N. Hijiya, C. Nakada, T. Kishida, K. Kawahara, H. Ito, K. Murakami, T. Fujioka, M. Seto, M. Moriyama, Genome-wide analysis of DNA copy number alterations and gene expression in gastric cancer, J. Pathol. 216 (2008) 471–482.

[76] C. Zhao, X. Bu, Promoter methylation of tumor-related genes in gastric carcinogenesis, Histol. Histopathol. 27 (2012) 1271–1282.

[77] S.L. Hu, D.B. Huang, Y.B. Sun, L. Wu, W.P. Xu, S. Yin, J. Chen, X.D. Jiang, G. Shen, Pathobiologic implications of methylation and expression status of Runx3 and CHFR genes in gastric cancer, Med. Oncol. 28 (2011) 447–454.

[78] G. Tamura, K. So, H. Miyoshi, T. Honda, S. Nishizuka, T. Motoyama, Quantitative assessment of gene methylation in neoplastic and non-neoplastic gastric epithelia using methylation-specific DNA microarray, Pathol. Int. 59 (2009) 895–899.

[79] S. Dedeurwaerder, C. Desmedt, E. Calonne, S.K. Singhal, B. Haibe-Kains, M. Defrance, S. Michiels, M. Volkmar, R. Deplus, J. Luciani, F. Lallemand, D. Larsimont, J. Toussaint, S. Haussy, F. Rothe, G. Rouas, O. Metzger, S. Majjaj, K. Saini, P. Putmans, G. Hames, N. van Baren, P.G. Coulie, M. Piccart, C. Sotiriou, F. Fuks, DNA methylation profiling reveals a predominant immune component in breast cancers, EMBO Mol. Med. 3 (2011) 726–741.

[80] M.G. Kibriya, M. Raza, F. Jasmine, S. Roy, R. Paul-Brutus, R. Rahaman, C. Dodsworth, M. Rakibuz-Zaman, M. Kamal, H. Ahsan, A genome-wide DNA methylation study in colorectal carcinoma, BMC Med. Genomics 4 (2011) 50.

[81] V.A. Naumov, E.V. Generozov, N.B. Zaharjevskaya, D.S. Matushkina, A.K. Larin, S.V. Chernyshov, M.V. Alekseev, Y.A. Shelygin, V.M. Govorun, Genome-scale analysis of DNA methylation in colorectal cancer using Infinium HumanMethylation450 BeadChips, Epigenetics 8 (2013) 8.

[82] J.H. Park, J. Park, J.K. Choi, J. Lyu, M.G. Bae, Y.G. Lee, J.B. Bae, D.Y. Park, H.K. Yang, T.Y. Kim, Y.J. Kim, Identification of DNA methylation changes associated with human gastric cancer, BMC Med. Genomics 4 (2011) 82.

[83] I. Van der Auwera, W. Yu, L. Suo, L. Van Neste, P. van Dam, E.A. Van Marck, P. Pauwels, P.B. Vermeulen, L.Y. Dirix, S.J. Van Laere, Array-based DNA methylation profiling for breast cancer subtype discrimination, PLoS One 5 (2010) e12616.

[84] H. Zouridis, N. Deng, T. Ivanova, Y. Zhu, B. Wong, D. Huang, Y.H. Wu, Y. Wu, I.B. Tan, N. Liem, V. Gopalakrishnan, Q. Luo, J. Wu, M. Lee, W.P. Yong, L.K. Goh, B.T. Teh, S. Rozen, P. Tan, Methylation subtypes and large-scale epigenetic alterations in gastric cancer, Sci. Transl. Med. 4 (2012) 156ra140.

[85] D. Sproul, C. Nestor, J. Culley, J.H. Dickson, J.M. Dixon, D.J. Harrison, R.R. Meehan, A.H. Sims, B.H. Ramsahoye, Transcriptionally repressed genes become aberrantly methylated and distinguish tumors of different lineages in breast cancer, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 4364–4369.

[86] E.N. Gal-Yam, G. Egger, L. Iniguez, H. Holster, S. Einarsson, X. Zhang, J.C. Lin, G. Liang, P.A. Jones, A. Tanay, Frequent switching of Polycomb repressive marks and DNA hypermethylation in the PC3 prostate cancer cell line, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 12979–12984.

[87] I. Keshet, Y. Schlesinger, S. Farkash, E. Rand, M. Hecht, E. Segal, E. Pikarski, R.A. Young, A. Niveleau, H. Cedar, I. Simon, Evidence for an instructive mechanism of de novo methylation in cancer cells, Nat. Genet. 38 (2006) 149–153.

[88] H.J. Song, K.N. Shim, Y.H. Joo, S.E. Kim, S.A. Jung, K. Yoo, Methylation of the tumor suppressor gene RUNX3 in human gastric carcinoma, Gut Liver 2 (2008) 119–125.

[89] G. Landan, N.M. Cohen, Z. Mukamel, A. Bar, A. Molchadsky, R. Brosh, S. Horn-Saban, D.A. Zalcenstein, N. Goldfinger, A. Zundelevich, E.N. Gal-Yam, V. Rotter, A. Tanay, Epigenetic polymorphism and the stochastic formation of differentially methylated regions in normal and cancerous tissues, Nat. Genet. 44 (2012) 1207–1214.

[90] I. Beerman, C. Bock, B.S. Garrison, Z.D. Smith, H. Gu, A. Meissner, D.J. Rossi, Proliferation-dependent alterations of the DNA methylation landscape underlie hematopoietic stem cell aging, Cell Stem Cell 12 (2013) 413–425.

[91] A. Bagchi, C. Papazoglu, Y. Wu, D. Capurso, M. Brodt, D. Francis, M. Bredel, H. Vogel, A.A. Mills, CHD5 is a tumor suppressor at human 1p36, Cell 128 (2007) 459–475.

[92] D.J. Birnbaum, J. Adelaide, E. Mamessier, P. Finetti, A. Lagarde, G. Monges, F. Viret, A. Goncalves, O. Turrini, J.R. Delpero, J. Iovanna, M. Giovannini, D. Birnbaum, M. Chaffanet, Genome profiling of pancreatic adenocarcinoma, Genes Chromosom. Cancer 50 (2011) 456–465.

[93] N.A. Bhowmick, E.G. Neilson, H.L. Moses, Stromal fibroblasts in cancer initiation and progression, Nature 432 (2004) 332–337.

[94] P. Katajisto, K. Vaahtomeri, N. Ekman, E. Ventela, A. Ristimaki, N. Bardeesy, R. Feil, R.A. DePinho, T.P. Makela, LKB1 signaling in mesenchymal cells required for suppression of gastrointestinal polyposis, Nat. Genet. 40 (2008) 455–459.

[95] A. Lujambio, L. Akkari, J. Simon, D. Grace, D.F. Tschaharganeh, J.E. Bolden, Z. Zhao, V. Thapar, J.A. Joyce, V. Krizhanovsky, S.W. Lowe, Non-cell-autonomous tumor suppression by p53, Cell 153 (2013) 449–460.

[96] B.G. Kim, C. Li, W. Qiao, M. Mamura, B. Kasprzak, M. Anver, L. Wolfraim, S. Hong, E. Mushinski, M. Potter, S.J. Kim, X.Y. Fu, C. Deng, J.J. Letterio, Smad4 signalling in T

cells is required for suppression of gastrointestinal cancer, Nature 441 (2006) 1015–1019.
[97] B.S. Reis, D.P. Hoytema van Konijnenburg, S.I. Grivennikov, D. Mucida, Transcription factor T-bet regulates intraepithelial lymphocyte functional maturation, Immunity 41 (2014) 244–256.
[98] B.S. Reis, A. Rogoz, F.A. Costa-Pinto, I. Taniuchi, D. Mucida, Mutual expression of the transcription factors Runx3 and ThPOK regulates intestinal CD4(+) T cell immunity, Nat. Immunol. 14 (2013) 271–280.
[99] H. Cheroutre, F. Lambolez, D. Mucida, The light and dark sides of intestinal intraepithelial lymphocytes, Nat. Rev. Immunol. 11 (2011) 445–456.
[100] D. Levanon, S. Hantisteanu, V. Negreanu, O. Brenner, Y. Groner, New insights into the mechanism of inflammatory bowel disease (IBD) etiology in Runx3-deficient mice, EMBO Worksop: RUNX Transcription Factors in Development & Disease, 2009, p. 20.
[101] M. Sugai, K. Aoki, M. Osato, Y. Nambu, K. Ito, M.M. Taketo, A. Shimizu, Runx3 is required for full activation of regulatory T cells to prevent colitis-associated tumor formation, J. Immunol. 186 (2011) 6515–6520.
[102] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[103] E. Elinav, R. Nowarski, C.A. Thaiss, B. Hu, C. Jin, R.A. Flavell, Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms, Nat. Rev. Cancer 13 (2013) 759–771.
[104] S. Nagini, Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention, World J. Gastrointest. Oncol. 4 (2012) 156–169.
[105] K. Ito, A.C. Lim, M. Salto-Tellez, L. Motoda, M. Osato, L.S. Chuang, C.W. Lee, D.C. Voon, J.K. Koo, H. Wang, H. Fukamachi, Y. Ito, RUNX3 attenuates beta-catenin/T cell factors in intestinal tumorigenesis, Cancer Cell 14 (2008) 226–237.
[106] K. Ito, L.S. Chuang, T. Ito, T.L. Chang, H. Fukamachi, M. Salto-Tellez, Y. Ito, Loss of Runx3 is a key event in inducing precancerous state of the stomach, Gastroenterology 140 (2011) (1536–1546.e8).
[107] W.K. Leung, K.C. Wu, C.Y. Wong, A.S. Cheng, A.K. Ching, A.W. Chan, W.W. Chong, M.Y. Go, J. Yu, K.F. To, X. Wang, Y.L. Chui, D.M. Fan, J.J. Sung, Transgenic cyclooxygenase-2 expression and high salt enhanced susceptibility to chemical-induced gastric cancer development in mice, Carcinogenesis 29 (2008) 1648–1654.
[108] H. Oshima, T. Ishikawa, G.J. Yoshida, K. Naoi, Y. Maeda, K. Naka, X. Ju, Y. Yamada, T. Minamoto, N. Mukaida, H. Saya, M. Oshima, TNF-alpha/TNFR1 signaling promotes gastric tumorigenesis through induction of Noxo1 and Gna14 in tumor cells, Oncogene 33 (2014) 3820–3829.
[109] Q. Li, Z. Jia, L. Wang, X. Kong, Q. Li, K. Guo, D. Tan, X. Le, D. Wei, S. Huang, L. Mishra, K. Xie, Disruption of Klf4 in villin-positive gastric progenitor cells promotes formation and progression of tumors of the antrum in mice, Gastroenterology 142 (2012) 531–542.
[110] J.E. Grim, S.E. Knoblaugh, K.A. Guthrie, A. Hagar, J. Swanger, J. Hespelt, J.J. Delrow, T. Small, W.M. Grady, K.I. Nakayama, B.E. Clurman, Fbw7 and p53 cooperatively suppress advanced and chromosomally unstable intestinal cancer, Mol. Cell. Biol. 32 (2012) 2160–2167.
[111] A.H. Berger, A.G. Knudson, P.P. Pandolfi, A continuum model for tumour suppression, Nature 476 (2011) 163–169.
[112] B. Huang, Z. Qu, C.W. Ong, Y.H.N. Tsang, G. Xiao, D. Shapiro, M. Salto-Tellez, K. Ito, Y. Ito, L.F. Chen, RUNX3 acts as a tumor suppressor in breast cancer by targeting estrogen receptor alpha, Oncogene 31 (2012) 527–534.
[113] K.S. Lee, Y.S. Lee, J.M. Lee, K. Ito, S. Cinghu, J.H. Kim, J.W. Jang, Y.H. Li, Y.M. Goh, X.Z. Chi, H. Wee, H.W. Lee, A. Hosoya, J.H. Chung, J.J. Jang, J.K. Kundu, Y.J. Surh, W.J. Kim, Y. Ito, H.S. Jung, S.C. Bae, Runx3 is required for the differentiation of lung epithelial cells and suppression of lung cancer, Oncogene 29 (2010) 3349–3361.
[114] Y.S. Lee, J.W. Lee, J.W. Jang, X.Z. Chi, J.H. Kim, Y.H. Li, M.K. Kim, D.M. Kim, B.S. Choi, E.G. Kim, J.H. Chung, O.J. Lee, Y.M. Lee, J.W. Suh, L.S. Chuang, Y. Ito, S.C. Bae, Runx3 inactivation is a crucial early event in the development of lung adenocarcinoma, Cancer Cell 24 (2013) 603–616.
[115] H. Ji, A.M. Houghton, T.J. Mariani, S. Perera, C.B. Kim, R. Padera, G. Tonon, K. McNamara, L.A. Marconcini, A. Hezel, N. El-Bardeesy, R.T. Bronson, D. Sugarbaker, R.S. Maser, S.D. Shapiro, K.K. Wong, K-ras activation generates an inflammatory response in lung tumors, Oncogene 25 (2006) 2105–2112.
[116] C. Lin, H. Song, C. Huang, E. Yao, R. Gacayan, S.M. Xu, P.T. Chuang, Alveolar type II cells possess the capability of initiating lung tumor development, PLoS One 7 (2012) e53817.
[117] M.J. Wilderman, S. Kim, C.T. Gillespie, J. Sun, V. Kapoor, A. Vachani, D.H. Sterman, L.R. Kaiser, S.M. Albelda, Blockade of TNF-alpha decreases both inflammation and efficacy of intrapulmonary Ad.IFNbeta immunotherapy in an orthotopic model of bronchogenic lung cancer, Mol. Ther. 13 (2006) 910–917.
[118] S. Lauber, The role of gp130 cytokines IL-6 and OSM on tumor development in mouse models for lung adenocarcinoma, Open Access Dissertations and Theses 7325, McMaster University, Hamilton, Ontario, 2012 (M.Sc).
[119] I.T. Chan, J.L. Kutok, I.R. Williams, S. Cohen, L. Kelly, H. Shigematsu, L. Johnson, K. Akashi, D.A. Tuveson, T. Jacks, D.G. Gilliland, Conditional expression of oncogenic K-ras from its endogenous promoter induces a myeloproliferative disease, J. Clin. Invest. 113 (2004) 528–538.
[120] V. Cortez-Retamozo, M. Etzrodt, A. Newton, P.J. Rauch, A. Chudnovskiy, C. Berger, R.J. Ryan, Y. Iwamoto, B. Marinelli, R. Gorbatov, R. Forghani, T.I. Novobrantseva, V. Koteliansky, J.L. Figueiredo, J.W. Chen, D.G. Anderson, M. Nahrendorf, F.K. Swirski, R. Weissleder, M.J. Pittet, Origins of tumor-associated macrophages and neutrophils, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 2491–2496.
[121] J.M. Fritz, L.D. Dwyer-Nield, A.M. Malkinson, Stimulation of neoplastic mouse lung cell proliferation by alveolar macrophage-derived, insulin-like growth factor-1 can be blocked by inhibiting MEK and PI3K activation, Mol. Cancer 10 (2011) 76.
[122] A.M. Houghton, Mechanistic links between COPD and lung cancer, Nat. Rev. Cancer 13 (2013) 233–245.
[123] H. Takahashi, H. Ogata, R. Nishigaki, D.H. Broide, M. Karin, Tobacco smoke promotes lung tumorigenesis by triggering IKKbeta- and JNK1-dependent inflammation, Cancer Cell 17 (2010) 89–97.
[124] J.E. Rundhaug, S.M. Fischer, Molecular mechanisms of mouse skin tumor promotion, Cancers (Basel) 2 (2010) 436–482.
[125] A.E. Winkler, J.J. Brotman, M.E. Pittman, N.P. Judd, J.S. Lewis Jr., R.D. Schreiber, R. Uppaluri, CXCR3 enhances a T-cell-dependent epidermal proliferative response and promotes skin tumorigenesis, Cancer Res. 71 (2011) 5707–5716.
[126] C. Gebhardt, A. Riehl, M. Durchdewald, J. Nemeth, G. Furstenberger, K. Muller-Decker, A. Enk, B. Arnold, A. Bierhaus, P.P. Nawroth, J. Hess, P. Angel, RAGE signaling sustains inflammation and promotes tumor development, J. Exp. Med. 205 (2008) 275–285.
[127] M. Salto-Tellez, B.K. Peh, K. Ito, S.H. Tan, P.Y. Chong, H.C. Han, K. Tada, W.Y. Ong, R. Soong, D.C. Voon, Y. Ito, RUNX3 protein is overexpressed in human basal cell carcinomas, Oncogene 25 (2006) 7646–7649.
[128] C. Guo, F. Yao, K. Wu, L. Yang, X. Zhang, J. Ding, Chromatin immunoprecipitation and association study revealed a possible role of Runt-related transcription factor 3 in the ulcerative colitis of Chinese population, Clin. Immunol. 135 (2010) 483–489.
[129] R.K. Weersma, L. Zhou, I.M. Nolte, G. van der Steege, H.M. van Dullemen, E. Oosterom, L. Bok, M.P. Peppelenbosch, K.N. Faber, J.H. Kleibeuker, G. Dijkstra, Runt-related transcription factor 3 is associated with ulcerative colitis and shows epistasis with solute carrier family 22, members 4 and 5, Inflamm. Bowel Dis. 14 (2008) 1615–1622.
[130] P.C. Dubois, G. Trynka, L. Franke, K.A. Hunt, J. Romanos, A. Curtotti, A. Zhernakova, G.A. Heap, R. Adany, A. Aromaa, M.T. Bardella, L.H. van den Berg, N.A. Bockett, E.G. de la Concha, B. Dema, R.S. Fehrmann, M. Fernandez-Arquero, S. Fiatal, E. Grandone, P.M. Green, H.J. Groen, R. Gwilliam, R.H. Houwen, S.E. Hunt, K. Kaukinen, D. Kelleher, I. Korponay-Szabo, K. Kurppa, P. MacMathuna, M. Maki, M.C. Mazzilli, O.T. McCann, M.L. Mearin, C.A. Mein, M.M. Mirza, V. Mistry, B. Mora, K.I. Morley, C.J. Mulder, J.A. Murray, C. Nunez, E. Oosterom, R.A. Ophoff, I. Polanco, L. Peltonen, M. Platteel, A. Rybak, V. Salomaa, J.J. Schweizer, M.P. Sperandeo, G.J. Tack, G. Turner, J.H. Veldink, W.H. Verbeek, R.K. Weersma, V.M. Wolters, E. Urcelay, B. Cukrowska, L. Greco, S.L. Neuhausen, R. McManus, D. Barisani, P. Deloukas, J.C. Barrett, P. Saavalainen, C. Wijmenga, D.A. van Heel, Multiple common variants for celiac disease influencing immune gene expression, Nat. Genet. 42 (2010) 295–302.
[131] D.M. Evans, C.C. Spencer, J.J. Pointon, Z. Su, D. Harvey, G. Kochan, U. Oppermann, A. Dilthey, M. Pirinen, M.A. Stone, L. Appleton, L. Moutsianas, S. Leslie, T. Wordsworth, T.J. Kenna, T. Karaderi, G.P. Thomas, M.M. Ward, M.H. Weisman, C. Farrar, L.A. Bradbury, P. Danoy, R.D. Inman, W. Maksymowych, D. Gladman, P. Rahman, A. Morgan, H. Marzo-Ortega, P. Bowness, K. Gaffney, J.S. Gaston, M. Smith, J. Bruges-Armas, A.R. Couto, R. Sorrentino, F. Paladini, M.A. Ferreira, H. Xu, Y. Liu, L. Jiang, C. Lopez-Larrea, R. Diaz-Pena, A. Lopez-Vazquez, T. Zayats, G. Band, C. Bellenguez, H. Blackburn, J.M. Blackwell, E. Bramon, S.J. Bumpstead, J.P. Casas, A. Corvin, N. Craddock, P. Deloukas, S. Dronov, A. Duncanson, S. Edkins, C. Freeman, M. Gillman, E. Gray, R. Gwilliam, N. Hammond, S.E. Hunt, J. Jankowski, A. Jayakumar, C. Langford, J. Liddle, H.S. Markus, C.G. Mathew, O.T. McCann, M.I. McCarthy, C.N. Palmer, L. Peltonen, R. Plomin, S.C. Potter, A. Rautanen, R. Ravindrarajah, M. Ricketts, N. Samani, S.J. Sawcer, A. Strange, R.C. Trembath, A.C. Viswanathan, M. Waller, P. Weston, P. Whittaker, S. Widaa, N.W. Wood, G. McVean, J.D. Reveille, B.P. Wordsworth, M.A. Brown, P. Donnelly, Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility, Nat. Genet. 43 (2011) 761–767.
[132] L.C. Tsoi, S.L. Spain, J. Knight, E. Ellinghaus, P.E. Stuart, F. Capon, J. Ding, Y. Li, T. Tejasvi, J.E. Gudjonsson, H.M. Kang, M.H. Allen, R. McManus, G. Novelli, L. Samuelsson, J. Schalkwijk, M. Stahle, A.D. Burden, C.H. Smith, M.J. Cork, X. Estivill, A.M. Bowcock, G.G. Krueger, W. Weger, J. Worthington, R. Tazi-Ahnini, F.O. Nestle, A. Hayday, P. Hoffmann, J. Winkelmann, C. Wijmenga, C. Langford, S. Edkins, R. Andrews, H. Blackburn, A. Strange, G. Band, R.D. Pearson, D. Vukcevic, C.C. Spencer, P. Deloukas, U. Mrowietz, S. Schreiber, S. Weidinger, S. Koks, K. Kingo, T. Esko, A. Metspalu, H.W. Lim, J.J. Voorhees, M. Weichenthal, H.E. Wichmann, V. Chandran, C.F. Rosen, P. Rahman, D.D. Gladman, C.E. Griffiths, A. Reis, J. Kere, K.C. Duffin, C. Helms, D. Goldgar, Y. Li, J. Paschall, M.J. Malloy, C.R. Pullinger, J.P. Kane, J. Gardner, A. Perlmutter, A. Miner, B.J. Feng, R. Hiremagalore, R.W. Ike, E. Christophers, T. Henseler, A. Ruether, S.J. Schrodi, S. Prahalad, S.L. Guthery, J. Fischer, W. Liao, P. Kwok, A. Menter, G.M. Lathrop, C. Wise, A.B. Begovich, A. Onoufriadis, M.E. Weale, A. Hofer, W. Salmhofer, P. Wolf, K. Kainu, U. Saarialho-Kere, S. Suomela, P. Badorf, U. Huffmeier, W. Kurrat, W. Kuster, J. Lascorz, R. Mossner, F. Schurmeier-Horst, M. Stander, H. Traupe, J.G. Bergboer, M.D. Heijer, P.C. van de Kerkhof, P.L. Zeeuwen, L. Barnes, L.E. Campbell, C. Cusack, C. Coleman, J. Conroy, S. Ennis, O. Fitzgerald, P. Gallagher, A.D. Irvine, B. Kirby, T. Markham, W.H. McLean, J. McPartlin, S.F. Rogers, A.W. Ryan, A. Zawirska, E. Giardina, T. Lepre, C. Perricone, G. Martin-Ezquerra, R.M. Pujol, E. Riveira-Munoz, A. Inerot, A.T. Naluai, L. Mallbris, K. Wolk, J. Leman, A. Barton, R.B. Warren, H.S. Young, I. Ricano-Ponce, G. Trynka, F.J. Pellett, A. Henschel, M. Aurand, B. Bebo, C. Gieger, T. Illig, S. Moebus, K.H. Jockel, R. Erbel, P. Donnelly, L. Peltonen, J.M. Blackwell, E. Bramon, M.A. Brown, J.P. Casas, A. Corvin, N. Craddock, A. Duncanson, J. Jankowski, H.S. Markus, C.G. Mathew, M.I. McCarthy, C.N. Palmer, R. Plomin, A. Rautanen, S.J. Sawcer, N. Samani, A.C. Viswanathan, N.W. Wood, C. Bellenguez, C. Freeman, G. Hellenthal, E. Giannoulatou, M. Pirinen, Z. Su, S.E. Hunt, R. Gwilliam, S.J. Bumpstead, S. Dronov, M. Gillman, E. Gray, N. Hammond, A. Jayakumar, O.T. McCann, J. Liddle, M.L. Perez, S.C. Potter, R. Ravindrarajah, M. Ricketts, M. Waller, P. Weston, S. Widaa, P. Whittaker, R.P. Nair, A. Franke, J.N. Barker, G.R. Abecasis, J.T. Elder, R.C. Trembath, Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity, Nat. Genet. 44 (2012) 1341–1348.

[133] J. Esparza-Gordillo, H. Schaarschmidt, L. Liang, W. Cookson, A. Bauerfeind, M.A. Lee-Kirsch, K. Nemat, J. Henderson, L. Paternoster, J.I. Harper, E. Mangold, M.M. Nothen, F. Ruschendorf, T. Kerscher, I. Marenholz, A. Matanovic, S. Lau, T. Keil, C.P. Bauer, M. Kurek, A. Ciechanowicz, M. Macek, A. Franke, M. Kabesch, N. Hubner, G. Abecasis, S. Weidinger, M. Moffatt, Y.A. Lee, A functional IL-6 receptor (IL6R) variant is a risk factor for persistent atopic dermatitis, J. Allergy Clin. Immunol. 132 (2013) 371–377.
[134] M. Apel, S. Uebe, J. Bowes, E. Giardina, E. Korendowych, K. Juneblad, F. Pasutto, A.B. Ekici, R. McManus, P. Ho, I.N. Bruce, A.W. Ryan, F. Behrens, B. Bohm, H. Traupe, J. Lohmann, C. Gieger, H.E. Wichmann, L. Padyukov, O. FitzGerald, G.M. Alenius, N.J. McHugh, G. Novelli, H. Burkhardt, A. Barton, A. Reis, U. Huffmeier, Variants in RUNX3 contribute to susceptibility to psoriatic arthritis, exhibiting further common ground with ankylosing spondylitis, Arthritis Rheum. 65 (2013) 1224–1231.
[135] C. Laprise, The Saguenay–Lac-Saint-Jean asthma familial collection: the genetics of asthma in a young founder population, Genes Immun. 15 (2014) 247–255.
[136] C. Helms, L. Cao, J.G. Krueger, E.M. Wijsman, F. Chamian, D. Gordon, M. Heffernan, J.A. Daw, J. Robarge, J. Ott, P.Y. Kwok, A. Menter, A.M. Bowcock, A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis, Nat. Genet. 35 (2003) 349–356.
[137] L. Prokunina, C. Castillejo-Lopez, F. Oberg, I. Gunnarsson, L. Berg, V. Magnusson, A.J. Brookes, D. Tentler, H. Kristjansdottir, G. Grondal, A.I. Bolstad, E. Svenungsson, I. Lundberg, G. Sturfelt, A. Jonssen, L. Truedsson, G. Lima, J. Alcocer-Varela, R. Jonsson, U.B. Gyllensten, J.B. Harley, D. Alarcon-Segovia, K. Steinsson, M.E. Alarcon-Riquelme, A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans, Nat. Genet. 32 (2002) 666–669.
[138] S. Tokuhiro, R. Yamada, X. Chang, A. Suzuki, Y. Kochi, T. Sawada, M. Suzuki, M. Nagasaki, M. Ohtsuki, M. Ono, H. Furukawa, M. Nagashima, S. Yoshino, A. Mabuchi, A. Sekine, S. Saito, A. Takahashi, T. Tsunoda, Y. Nakamura, K. Yamamoto, An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis, Nat. Genet. 35 (2003) 341–348.
[139] J. Dicken, A. Mildner, D. Leshlowitz, I.V. Touw, S. Hantisteanu, S. Jung, Y. Groner, Transcriptional reprogramming of CD11b+Esamhi dendritic cell identity and function by loss of Runx3, PLoS One 8 (2013) e77490.
[140] J. Lotem, D. Levanon, V. Negreanu, D. Leshkowitz, G. Friedlander, Y. Groner, Runx3-mediated transcriptional program in cytotoxic lymphocytes, PLoS One 8 (2013) e80467.
[141] G. Trynka, C. Wijmenga, D.A. van Heel, A genetic perspective on coeliac disease, Trends Mol. Med. 16 (2010) 537–550.
[142] A. Franke, D.P. McGovern, J.C. Barrett, K. Wang, G.L. Radford-Smith, T. Ahmad, C.W. Lees, T. Balschun, J. Lee, R. Roberts, C.A. Anderson, J.C. Bis, S. Bumpstead, D. Ellinghaus, E.M. Festen, M. Georges, T. Green, T. Haritunians, L. Jostins, A. Latiano, C.G. Mathew, G.W. Montgomery, N.J. Prescott, S. Raychaudhuri, J.I. Rotter, P. Schumm, Y. Sharma, L.A. Simms, K.D. Taylor, D. Whiteman, C. Wijmenga, R.N. Baldassano, M. Barclay, T.M. Bayless, S. Brand, C. Buning, A. Cohen, J.F. Colombel, M. Cottone, L. Stronati, T. Denson, M. De Vos, R. D'Inca, M. Dubinsky, C. Edwards, T. Florin, D. Franchimont, R. Gearry, J. Glas, A. Van Gossum, S.L. Guthery, J. Halfvarson, H.W. Verspaget, J.P. Hugot, A. Karban, D. Laukens, I. Lawrance, M. Lemann, A. Levine, C. Libioulle, E. Louis, C. Mowat, W. Newman, J. Panes, A. Phillips, D.D. Proctor, M. Regueiro, R. Russell, P. Rutgeerts, J. Sanderson, M. Sans, F. Seibold, A.H. Steinhart, P.C. Stokkers, L. Torkvist, G. Kullak-Ublick, D. Wilson, T. Walters, S.R. Targan, S.R. Brant, J.D. Rioux, M. D'Amato, R.K. Weersma, S. Kugathasan, A.M. Griffiths, J.C. Mansfield, S. Vermeire, R.H. Duerr, M.S. Silverberg, J. Satsangi, S. Schreiber, J.H. Cho, V. Annese, H. Hakonarson, M.J. Daly, M. Parkes, Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci, Nat. Genet. 42 (2010) 1118–1125.
[143] C.A. Anderson, G. Boucher, C.W. Lees, A. Franke, M. D'Amato, K.D. Taylor, J.C. Lee, P. Goyette, M. Imielinski, A. Latiano, C. Lagace, R. Scott, L. Amininejad, S. Bumpstead, L. Baidoo, R.N. Baldassano, M. Barclay, T.M. Bayless, S. Brand, C. Buning, J.F. Colombel, L.A. Denson, M. De Vos, M. Dubinsky, C. Edwards, D. Ellinghaus, R.S. Fehrmann, J.A. Floyd, T. Florin, D. Franchimont, L. Franke, M. Georges, J. Glas, N.L. Glazer, S.L. Guthery, T. Haritunians, N.K. Hayward, J.P. Hugot, G. Jobin, D. Laukens, I. Lawrance, M. Lemann, A. Levine, C. Libioulle, E. Louis, D.P. McGovern, M. Milla, G.W. Montgomery, K.I. Morley, C. Mowat, A. Ng, W. Newman, R.A. Ophoff, L. Papi, O. Palmieri, L. Peyrin-Biroulet, J. Panes, A. Phillips, N.J. Prescott, D.D. Proctor, R. Roberts, R. Russell, P. Rutgeerts, J. Sanderson, M. Sans, P. Schumm, F. Seibold, Y. Sharma, L.A. Simms, M. Seielstad, A.H. Steinhart, S.R. Targan, L.H. van den Berg, M. Vatn, H. Verspaget, T. Walters, C. Wijmenga, D.C. Wilson, H.J. Westra, R.J. Xavier, Z.Z. Zhao, C.Y. Ponsioen, V. Andersen, L. Torkvist, M. Gazouli, N.P. Anagnou, T.H. Karlsen, L. Kupcinskas, J. Sventoraityte, J.C. Mansfield, S. Kugathasan, M.S. Silverberg, J. Halfvarson, J.I. Rotter, C.G. Mathew, A.M. Griffiths, R. Gearry, T. Ahmad, S.R. Brant, M. Chamaillard, J. Satsangi, J.H. Cho, S. Schreiber, M.J. Daly, J.C. Barrett, M. Parkes, V. Annese, H. Hakonarson, G. Radford-Smith, R.H. Duerr, S. Vermeire, R.K. Weersma, J.D. Rioux, Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47, Nat. Genet. 43 (2011) 246–252.
[144] L. Jostins, S. Ripke, R.K. Weersma, R.H. Duerr, D.P. McGovern, K.Y. Hui, J.C. Lee, L.P. Schumm, Y. Sharma, C.A. Anderson, J. Essers, M. Mitrovic, K. Ning, I. Cleynen, E. Theatre, S.L. Spain, S. Raychaudhuri, P. Goyette, Z. Wei, C. Abraham, J.P. Achkar, T. Ahmad, L. Amininejad, A.N. Ananthakrishnan, V. Andersen, J.M. Andrews, L. Baidoo, T. Balschun, P.A. Bampton, A. Bitton, G. Boucher, S. Brand, C. Buning, A. Cohain, S. Cichon, M. D'Amato, D. De Jong, K.L. Devaney, M. Dubinsky, C. Edwards, D. Ellinghaus, L.R. Ferguson, D. Franchimont, K. Fransen, R. Gearry, M. Georges, C. Gieger, J. Glas, T. Haritunians, A. Hart, C. Hawkey, M. Hedl, X. Hu, T.H. Karlsen, L. Kupcinskas, S. Kugathasan, A. Latiano, D. Laukens, I.C. Lawrance, C.W. Lees, E. Louis, G. Mahy, J. Mansfield, A.R. Morgan, C. Mowat, W. Newman, O. Palmieri, C.Y. Ponsioen, U. Potocnik, N.J. Prescott, M. Regueiro, J.I. Rotter, R.K. Russell, J.D. Sanderson, M. Sans, J. Satsangi, S. Schreiber, L.A. Simms, J. Sventoraityte, S.R. Targan, K.D. Taylor, M. Tremelling, H.W. Verspaget, M. De Vos, C. Wijmenga, D.C. Wilson, J. Winkelmann, R.J. Xavier, S. Zeissig, B. Zhang, C.K. Zhang, H. Zhao, M.S. Silverberg, V. Annese, H. Hakonarson, S.R. Brant, G. Radford-Smith, C.G. Mathew, J.D. Rioux, E.E. Schadt, M.J. Daly, A. Franke, M. Parkes, S. Vermeire, J.C. Barrett, J.H. Cho, Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease, Nature 491 (2012) 119–124.
[145] B.R. Achyut, D.A. Bader, A.I. Robles, D. Wangsa, C.C. Harris, T. Ried, L. Yang, Inflammation-mediated genetic and epigenetic alterations drive cancer development in the neighboring epithelium upon stromal abrogation of TGF-beta signaling, PLoS Genet. 9 (2013) e1003251.
[146] T. Valencia, J.Y. Kim, S. Abu-Baker, J. Moscat-Pardos, C.S. Ahn, M. Reina-Campos, A. Duran, E.A. Castilla, C.M. Metallo, M.T. Diaz-Meco, J. Moscat, Metabolic reprogramming of stromal fibroblasts through p62-mTORC1 signaling promotes inflammation and tumorigenesis, Cancer Cell 26 (2014) 121–135.
[147] A. Duran, R. Amanchy, J.F. Linares, J. Joshi, S. Abu-Baker, A. Porollo, M. Hansen, J. Moscat, M.T. Diaz-Meco, p62 is a key regulator of nutrient sensing in the mTORC1 pathway, Mol. Cell 44 (2011) 134–146.
[148] S. Banerji, K. Cibulskis, C. Rangel-Escareno, K.K. Brown, S.L. Carter, A.M. Frederick, M.S. Lawrence, A.Y. Sivachenko, C. Sougnez, L. Zou, M.L. Cortes, J.C. Fernandez-Lopez, S. Peng, K.G. Ardlie, D. Auclair, V. Bautista-Pina, F. Duke, J. Francis, J. Jung, A. Maffuz-Aziz, R.C. Onofrio, M. Parkin, N.H. Pho, V. Quintanar-Jurado, A.H. Ramos, R. Rebollar-Vega, S. Rodriguez-Cuevas, S.L. Romero-Cordoba, S.E. Schumacher, N. Stransky, K.M. Thompson, L. Uribe-Figueroa, J. Baselga, R. Beroukhim, K. Polyak, D.C. Sgroi, A.L. Richardson, G. Jimenez-Sanchez, E.S. Lander, S.B. Gabriel, L.A. Garraway, T.R. Golub, J. Melendez-Zajgla, A. Toker, G. Getz, A. Hidalgo-Miranda, M. Meyerson, Sequence analysis of mutations and translocations across breast cancer subtypes, Nature 486 (2012) 405–409.
[149] I. Taniuchi, M. Osato, Y. Ito, Runx1: no longer just for leukemia, EMBO J. 31 (2012) 4098–4099.
[150] R.J. Fijneman, R.A. Anderson, E. Richards, J. Liu, M. Tijssen, G.A. Meijer, J. Anderson, A. Rod, M.G. O'Sullivan, P.M. Scott, R.T. Cormier, Runx1 is a tumor suppressor gene in the mouse gastrointestinal tract, Cancer Sci. 103 (2012) 593–599.