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Keeping up NF-κB appearances: Epigenetic control of immunity or inflammation-triggered epigenetics

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ABSTRACT

Controlled expression of cytokine genes is an essential component of an immune response and is crucial for homeostasis. In order to generate an appropriate response to an infectious condition, the type of cytokine, as well as the cell type, dose range and the kinetics of its expression are of critical importance. The nuclear factor-κB (NF-κB) family of transcription factors has a crucial role in rapid responses to stress and pathogens (innate immunity), as well as in development and differentiation of immune cells (acquired immunity). Although quite a number of genes contain NF-κB-responsive elements in their regulatory regions, their expression pattern can significantly vary from both a kinetic and quantitative point of view, reflecting the impact of environmental and differentiative cues. At the transcription level, selectivity is conferred by the expression of specific NF-κB subunits and their respective posttranslational modifications, and by combinatorial interactions between NF-κB and other transcription factors and coactivators, that form specific enhanceosome complexes in association with particular promoters. These enhanceosome complexes represent another level of signaling integration, whereby the activities of multiple upstream pathways converge to impress a distinct pattern of gene expression upon the NF-κB-dependent transcriptional network. Today, several pieces of evidence suggest that the chromatin structure and epigenetic settings are the ultimate integration sites of both environmental and differentiative inputs, determining proper expression of each NF-κB-dependent gene. We will therefore discuss in this review the multilayered interplay of NF-κB signaling and epigenome dynamics, in achieving appropriate gene expression responses and transcriptional activity.

1. IKK/IκB-dependent tuning of NF-κB/DNA-binding dynamics

Proinflammatory stimuli and stress conditions quickly activate the transcription factor NF-κB, which subsequently induces transcription from several genes, including those encoding inflammatory cytokines, chemokines, adhesion molecules, cytoprotective proteins and immediate early genes [1–8]. NF-κB is the generic name of a family of transcription factors, that share a Rel homology domain, function as dimers, but which are sequestered in the cytoplasm through physical interaction with inhibitors of the IκB (inhibitor of κB) family. The most classical NF-κB dimer consists of a p50 subunit (processing product of a 105 kDa precursor protein) and the transactivating subunit p65 (or relA), but other variants, like homodimers of the former

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subunits or combinations with c-Rel, also do occur. Following cell stimulation with Notch1 or with proinflammatory cytokines like TNF-α, IL1, etc., or triggers of Toll-like receptors (TLRs) such as lipopolysaccharide (LPS), or following engagement of the antigen receptors of B- and T-cells, the cytoplasmic IκB kinase (IKK) complex becomes activated and phosphorylates the IκB molecules, leading to their degradation through the ubiquitin-proteasome pathway. This cascade of events is usually indicated as the 'canonical' NF-κB activation pathway. Signaling to NF-κB thus involves its release from IκB in the cytosol, followed by translocation into the nucleus. The IKK complex encompasses three known subunits: two protein kinases (IKKα and IKKβ) and a structural/regulatory subunit (called NF-κB essential modulator (NEMO) or IKKγ).

Recently, a so-called 'non-canonical' pathway has also been uncovered, which causes NF-κB activation in response to a specific set of stimuli, including B-cell-activating factor (BAFF), lymphotoxin β (LTβ), CD40 ligand (CD40L) [9] or Notch3 [6,10]. This 'non-canonical' pathway seems to be more specifically involved in lymphoid organ formation and B- or T-cell maturation, whereas the classical ('canonical') pathway is involved in the response of multiple cell types to inflammatory stimuli. The 'non-canonical' pathway is IKKβ- and IKKγ-independent and targets p100. p100 is a member of the cytoplasmic NF-κB inhibitors and the precursor of the NF-κB family member p52, which retains NF-κB subunits, such as relB, in the cytoplasm. Following cell stimulation, p100 is partially degraded via an NF-κB-inducing kinase (NIK)- and IKKα-dependent manner, thereby liberating p52/relB com-

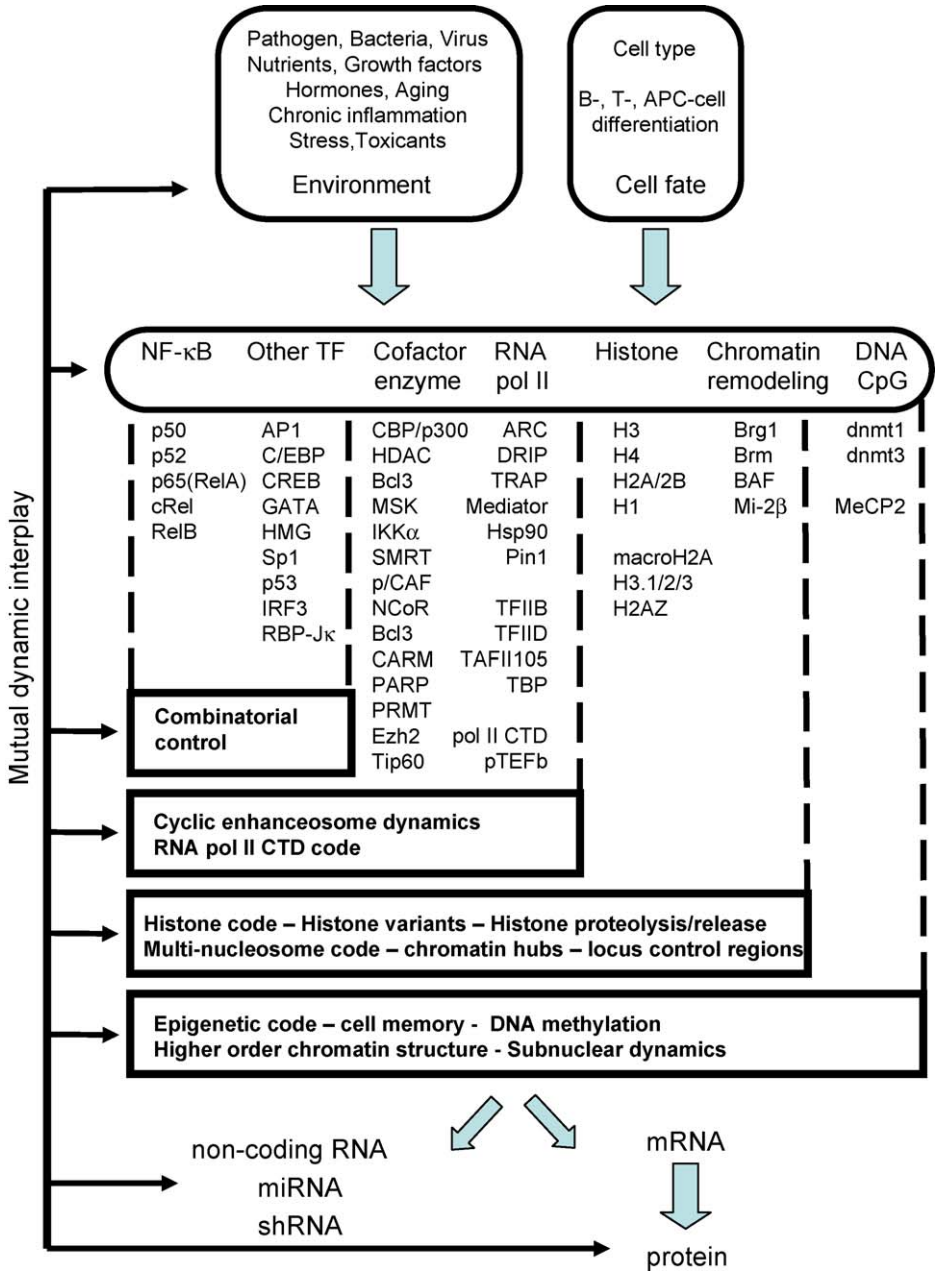

Fig. 1 – Multi-faceted interplay of NF-κB signaling with the epigenetic network.

plexes, which can differentially activate NF-κB-dependent target genes [4].

Previously, a primary goal has been to identify signaling-responsive transcription factors that specifically regulate immune gene expression [11]. In this perspective, different labs have succeeded to correlate clusters of inflammatory gene expression (''inflammatory signature'') according to their respective promoter organization and the presence of transcription factor-binding elements, by means of appropriate computational approaches [12–16]. Interestingly, different inflammatory triggers (TNF, IL1, various TLR ligands) were found to activate different subsets of NF-κB target genes with different kinetic profiles [17,18]. Based on simplifying reductions of the IKK/IκB/NF-κB-signaling module, various computational gene expression models were designed that describe the temporal control of NF-κB activation by the coordinated activation of the IKK complex and the degradation/synthesis of IκB proteins. NF-κB regulation of IκBα gene transcription represents a delayed negative feedback loop that drives oscillations in NF-κB translocation and subsequently in gene transcription events [17–23]. At another level, time-dependent crosstalk of synergistic or antagonistic autocrine inflammatory circuits, i.e. via direct receptor activation or release of various growth factors and/or cytokines further imposes intracellular variation in NF-κB-driven gene expression [6,7,24]. Indeed, as NF-κB is part of a complicated signaling network, combinatorial interactions between differentially activated signaling pathways may elicit different IKK activation kinetics and turnover of IκB members, which thus create time-dependent variation (early-late, transient-sustained, oscillatory-stable, ...) in the gene expression dynamics [1,2,25–29]. Actually, signal transduction pathways are modular composites of functionally interdependent sets of proteins that act in a coordinated fashion to transform environmental information into a phenotypic response [29–31]. Inflammation is essentially integration of information: signals from the environment are transferred by signaling networks to the genome, where they are interpreted to start or stop only those cellular functions that give the appropriate response [32] (Fig. 1). Today, integrated systems biology approaches, comprising tandem affinity purification, liquid-chromatography tandem mass spectrometry, proteomics, network analysis and functional perturbation studies using genetic approaches or genomewide RNAi screens provide important insight into the logic of the NF-κB-signaling pathway [30,31,33–36] (see also Table 1).

2. Synergistic and combinatorial control of NF-κB enhanceosomes

Another level of specificity may originate from the expression and DNA-binding of specific NF-κB subunits on subsets of promoters. From a genomewide location analysis aiming to identify targets of all five NF-κB proteins (p50, p52, crel, RelB, p65) before and after stimulation of monocytic cells with bacterial lipopolysaccharide (LPS), it was concluded that genes which became bound by multiple NF-κB subunits were the most likely to show increases in RNA polymerase II occupancy and gene expression [37]. Although the apparent consensus sequence of DNA-binding sites for NF-κB (κB sites) are highly diverse, they show a remarkable conservation during evolution [38]. However, although different dimers display differences in affinity for any given κB site, no typical consensus motifs can be deduced for each κB dimer pair [39,40]. Furthermore, dimers can be exchanged at NF-κB motifs in gene promoters over time [41]. Nevertheless, genetic evidence from mutant mice and cells reveals that specific gene activation requires specific combinations of NF-κB proteins [28,36]. This indicates that NF-κB family member specificity for endogenous promoters is not solely encoded by the κB site sequence itself, but may also depend on allosteric conformational changes that codetermine which bound NF-κB dimers will form transcription-productive interactions [42,43]. In addition, posttranslational modifications of NF-κB members (phosphorylation, acetylation, ...) may codetermine DNA-binding specificity directly via changed dimer composition, cooperative effects with distal or proximal bound factors, or indirectly via change of its subcellular distribution (or gradient) [44–50].

Further, a higher selectivity can be reached via combinatorial interactions between NF-κB and other transcription factors which may define so-called ''regulatory codes'' for subsets of genes (for example different subclasses of immunity genes), that share regulatory DNA enhancer properties

Table 1 – Experimental approaches to study NF-κB function

Description	Example references
Mathematical models of NF-κB signaling dynamics	
Computational approaches	[23,28]
NF-κB-dependent gene expression networks	
Arraytechnology (cDNA, oligo)	[12,16]
ChIP on chip	[15,85]
NF-κB-dependent protein networks	
TAP-tagging, MALDI-TOF, LCMS, RNAi	[30,31]
Single cell phospho-proteomics by FACS	[35]
Bimolecular fluorescence (BiFc)	[400]
NF-κB chromatin studies	
Chromatin immunoprecipitation, RNAi	[41,141,156,175, 176,183,401]
DNase, MNase accessability assays	[222,225–228, 402,403]
CHART-PCR	[189,229]
Genomic footprinting	[403]
Functional NF-κB studies	
Genetic knockout/knockin	[36]
Genomewide RNAi library screen	[34,404]
Antisense oligodeoxynucleotides (ODN)	[405,406]
Decoy ODN	[407,408]
Biochemical inhibitors	[3,274,409–413]
Antagonistic antibodies	[414,415]
NF-κB imaging studies	
Realtime imaging FRET/FRAP	[19,50,100]
Luciferase reporter gene mice (as readout for NF-κB-driven promoter activity)	[416]
IκB-luciferase reporter protein mice (as readout for IKK-activity)	[417]

with constrained organizational features and cofactor affinities thus forming specific ''enhanceosome'' complexes [51–59]. Today, various examples exist of synergistic interactions between NF-κB and partner transcription factors (HMG, C/EBP, ATF/CREB, GATA, IRF3, AP1, STAT, Sp1, p53, RBP-Jκ, ...) which add extra specificity to the NF-κB response in a stimulus-dependent and tissue-specific fashion or restrict sensitivity to negative regulators of the pathway [56,60–86]. Advanced usage of gene expression profiling and chromatin immunoprecipitation applications (''ChIP on chip'') allows to further elucidate combinatorial control of NF-κB-driven gene expression on a genomewide scale [14,37,61,85]. The time-dependent profile of TF binding renders a dynamic scaffold platform to recruit bridging cofactors, which further link TF transactivation domains to RNA polymerase II function. These coregulator (corepressor/coactivator) complexes possess ''sensing'' and ''adaptor'' activities required for interpretation of multiple signaling pathways. This strategy imposes a temporal order for modifying programs of transcriptional regulation in response to the cellular milieu, which is used to mediate developmental, homeostatic and pathological events [87]. The cyclic nature of cofactor recruitment within enhanceosomes may reflect changes in affinity and turnover, due to a dynamic TF-binding profile, different sets of posttranslational modifications (P, Ac, ...) of TF and/or cofactors (also considered as ''TF/cofactor code'') and fine-tuned proteasomal activities [88–96]. The timing of transcriptional activation and the ordered recruitment of transcription factors (TFs) to promoters are the engines which, at the right moment and for the right time period, drive the transcriptional regulation of each gene throughout the life of a cell [97,98]. However, the highly dynamic nature of TF binding (timescale of seconds) observed in kinetic imaging assays (FRAP) and the slower dynamics of transcription complex (dis)assembly (timescale of minutes to hours) detected in chromatin immunoprecipitation (ChIP) assays, seem at first sight incompatible within one transcription model: are enhanceosomes native existing biochemical complexes at the single cell level (which can be immunopurified and characterized by proteomic approaches) or rather artificial experimental snapshots (reflecting a crosslinked average response of factor recruitment in a cell population) [99]? Enhanceosomes may appear when stochastic binding of multiple TF/cofactors reaches an equilibrium with its nucleoplasmic partner concentrations (comparable with stable appearance of a water fountain in which water molecules are continously replaced), but its physical existence still needs to be proven at the single cell level [100,101]. Nevertheless, the dynamic enhanceosome model allows flexible feedback options when environmental conditions change, as fluctuations in signal intensity and factor concentrations can immediately be sensed due to continuous factor sampling in the nucleoplasm [23,87,99,100,102–104]. Interestingly, IKK/IκB-signaling dynamics, responsable for the nuclear localization of NF-κB, seems also involved in nucleocytoplasmic shuttling of cofactors (i.e. SMRT, NCoR, ...) [105–111], as well as in cofactor (SRC, SMRT) phosphorylation [108,109,112,113]. Altogether, the enhanceosome complexes, as discussed above, represent another level of signaling integration converging on NF-κB-driven promoters [51,114–116].

3. Chromatin code and NF-κB-driven gene expression: a recipee for transcription speed, specificity or quantity?

Whereas cytoplasmic activation of NF-κB leads to nuclear import of the factor and dynamic binding to a great variety of gene promoters, the importance of additional mechanisms controlling the nuclear activities of NF-κB is nowadays generally accepted [45,117–120]. More and more evidence is accumulating that regulatory networks are controlled by ''epigenetic'' (defines a potentially heritable alteration in gene expression without an accompanying change in primary DNA sequence) mechanisms superposed on the primary genetic code, which require dynamic crosstalk of promoter enhanceosomes with the local chromatin environment and DNA methylation events [104,120–125].

Today, there has been a growing appreciation of the role of chromatin structure in gene regulation. Before most activators of a gene access their DNA-binding sites, a transition from a condensed (''solenoid-like fiber'') to a decondensed (''beads on a string'') chromatin structure appears to take place. Conversely, the acquisition of a more condensed chromatin structure is often associated with gene silencing [126,127]. This structural restriction of chromatin on gene expression can be overcome by multi-subunit enzymatic cofactor complexes which reversibly modify (acetylation, phosphorylation, ubiquitylation, glycosylation, sumoylation) amino-terminal histone tails, more particularly on K,R,S,T residu's. In general, DNA is wrapped around nucleosomes, which are arranged as regularly spaced beads (146 bp DNA/nucleosome) along the DNA. Typically, nucleosomes consist of a histone octamer of histones H2A/B, H3 and H4. Since the discovery of histone-modifying enzymes, N-terminal histone tails protruding from nucleosomes were found to be 'velcro patches' for (de)acetylases, (de)methylases, ubiquitin(SUMO)ligases, kinases, phosphatases, glycosylases, which together establish specific histone modification patterns involved in transcription [87]. There is now a large body of evidence showing that modifications of the histone tails provide signals (''binary switches'') that are recognized by specific binding proteins that can in turn influence gene expression and other chromatin functions [104,128,129]. Specific sets of histone modifications and/or variants are associated with genes that are actively transcribed or are repressed, a phenomenon defined as the ''histone code'' [121,129–138]. Furthermore, as histone marks were found to gradually change along the gene locus from 5′ to 3′ orientation, this is consistent with a redundant histone code to indicate gene activity [139]. Alternatively, as nucleosomes can be replaced as part of the transcriptional process, coordinated histone patterns at active genes might result from turnover during transcriptional initiation and elongation [124,130]. As such, turnover speed rather than absolute histone modification patterns were found to correlate with gene activity [140,141]. These histone marks may be related to changes in nucleosome densities along the DNA (acetylation is known to convert silenced heterochromatin-DNA fibers into relaxed euchromatic nucleosome beads on a DNA string) due to interference with nucleosome mobility (positioning) [142], nucleosome depletion (proteolysis) [143–146] and/or nucleosome composition (i.e. histone eviction or

exchange by specialized histone variants such as H3.3, H2AZ, macroH2A) [147–151]. Histone tail modifications may also affect enhanceosome half-life (periodic cofactor recruitment) [89,90,152–155] or trigger recruitment of specialized chromatin-remodeling factors (i.e. Brg, Brm, ...) [156,157]. The spatial and time-dependent combinations of histone modifications further increase the complexity of information contained in chromatin [104,130,132–134,158,159]. Of special note, ''histone code'' may only become biologically meaningful at the level of the chromatin fiber (''chromatin regulatory code'') which, upon integration of conformations of multiple nucleosomes, translates allosteric changes into specific gene (cluster) activities, in order to establish specific regulatory programs at the genome level [159–162]. In analogy to allosteric control of enzymes, specific gene activity may be determined by the spatial organization (compartmentalization in discrete territories) and structural landscape (three-dimensional structure) of a gene locus, by altering the higher order structure of chromatin (*cis* mechanism) or by generating a binding platform for effector proteins (*trans* mechanisms) [87,163–169].

Since NF-κB binds very poorly or not at all to nucleosomal DNA, its activation must be coordinated to that of enzymatic chromatin-remodeling complexes [120,149,170]. Transcription factors can be classified into two categories depending on how they gain access to their cognate sites in chromatin: (1) factors which are able to bind to their target sites in nucleosomes and (2) factors which require nucleosome remodeling before they can bind to nucleosomally organized DNA [171–174]. Using chromatin immunoprecipitation it was nicely demonstrated that, upon cell stimulation by inflammatory stimuli, different target genes can recruit NF-κB with different kinetics (fast, slow), depending on constitutive (immediately accessible) or inducible (late accessable) H4 acetylation modifications in their chromatin structure [175]. Similarly, we and others found that inflammatory stimuli induce phosphoacetylation of histone H3 (K9-S10) at a subset of cytokine and chemokine genes to enhance the accessibility of the cryptic NF-κB-binding sites and to mark promoters for increased NF-κB recruitment [94,176–178]. Furthermore, reductions in H3 Lys 9 methylation, concomitantly with increasing H3/H4 acetylation strongly correlate with RNA polymerase II recruitment, generating a window of time in which transcription is permitted in specific NF-κB-inducible inflammatory genes [129,179]. This pattern is characterized by relatively low levels of H3 Lys 9 methylation that are erased upon activation and again restored concurrently with postinduction transcriptional repression [179]. Finally, incorporation of the unusual histone variant macroH2A, which has been associated with repression of transcription, was found to interfere with the binding of the transcription factor NF-κB and to impede SWI/SNF-dependent remodeling [149].

During the last years, NF-κB-driven gene expression was found to involve various cofactors, including kinases (PKAc, MSK, IKKα, NIK) [1,44,92,94,108,109,180], poly(ADP-ribose) polymerase (PARP) [181,182], methylases (CARM, PRMT) [183–185], prolyl isomerase (Pin1) [186], (de)acetylases (CBP/p300, p/CAF, Tip160, HDACs 1–6, SIRT) [91,92,107,115,187], SWI/SNF (Brg1) [126,156,188,189], etc. Posttranslational modifications (P, Ac, SUMO, Ub, Me, ...) of either NF-κB or cofactor complexes were found to affect cofactor complex associations and activities [190,191], dynamics of nucleocytoplasmic shuttling [192–196], nucleolar sequestration [48] or association with chaperone proteins (HMG, IκB, hsp, 14-3-3) [70,74,76–79,197,198] and/or with subcellular structures (i.e. nuclear lamins, nuclear pore complex, actin skeleton, speckles, transcription factories, PML bodies, nucleoli) [167,168,199–208]. However, as various cofactors (MSK, IKKα, CBP, HDAC) regulate NF-κB as well as chromatin components, we are faced with a chicken and egg problem: is NF-κB the driving force for chromatin relaxation or does chromatin relaxation happen prior to NF-κB-binding? If NF-κB recruitment is highly determined by the preset chromatin environment, then NF-κB itself (or the corresponding established NF-κB/cofactor complex) cannot be the driving force for chromatin relaxation as it joins a predetermined chromatin condition (Hoya-Arias R, et al., in preparation). On the other hand, NF-κB mutants with impaired cofactor association capacity, clearly show defects in gene induction properties [46,92,94,118,178,186,209]. Interestingly, TF with distinct posttranslational modifications (P, Ac, ...) demonstrate different affinities for a preset chromatin-DNA environment [100]. Kinetic imaging studies (FRAP), which measured chromatin residence time of wt NF-κB p65, revealed complete NF-κB turnover on active chromatin in less than 30 s, in dynamic equilibrium with nucleoplasmic dimers and independently of promoter occupancy by other sequence-specific transcription factors, suggesting that promoters sample nucleoplasmic levels of NF-κB over a timescale of seconds, thus rapidly re-tuning their activity. Remarkably, an NF-κB p65 S536A phosphomutant with strongly impaired proteasomal degradation properties, reveals a prolonged residence time and suggests that NF-κB recruitment on chromatin is highly susceptible to catabolic processes [93,100,152–154]. Of further interest to the chicken-egg paradox, cyclic NF-κB recruitment did not translate into cyclic histone acetylation waves but did rather coincide with cyclic RNA pol II recruitment which triggers gene activation [100]. Along the same line, NF-κB may catalyze RNA pol II transcription–elongation activity upon corecruitment of TFIIB, TFIID, TAF105, TBP, ARC/DRIP/TRAP/mediator cofactors and the elongation factor pTEFb, which results in hyperphosphorylation of its carboxy terminal domain (also considered as RNA pol II ''CTD code'') [210–221]. In contrast, AP1 and C/EBP may serve distinct roles (such as modulating histone acetylation levels or chromatin opening), as they reveal different occupancy profiles and remain bound between two cycles of NF-κB occupancy. At the nucleosome level, various chromatin studies of NF-κB-driven promoters (HIV, IFNβ, TLR2, GM-CSF, IL2, IL6, IL12, IκB, TNFSF6L, ...) have also pointed to hierarchic roles of constitutive TF (Sp1, AP1, CREB, C/EBP, GATA3, ...) versus inducible TF (NF-κB) in initiating chromatin opening versus triggering gene activation (Ndlovu MN', in preparation) [65,66,155,173,189,222–232]. Interestingly, prebound enhancer transcription factors were found to initiate chromatin opening events without the need of chromatin remodeling factors, by histone fold contacts of their C-terminal transactivation domain with histone H3 and H4 [233,234]. How patterns of prebound enhancer factors are established during cell fate development is less well understood and is a major hot topic in the epigenetic field today [235–245].

4. Epigenetic code: cellular memory versus transcription memory

Cells of multicellular organisms are genetically identical, but structurally and functionally heterogenous due to differential patterns of gene expression. Many of these differences arise during development and are subsequently retained through cell proliferation (mitosis). Stable alterations of this kind are said to be epigenetic, because they are heritable in the short term but do not involve mutations of the DNA itself and are therefore potentially reversible. Epigenetic changes can also arise in adults either by random change or under the effect of the environment [246–250]: aging [251–256], chronic inflammation [126,257–260], stress [261–264], viral/bacterial infections [265–269] diet (Dijsselbloem N, et al., in preparation) [178,249,253,270–277], hormones [278,279], toxicants [280–283] and endocrine disruptors [284–288] are considered as important factors which impact on epigenetic settings. Interestingly, hsp90, a key protein in the heat shock response pathways, has recently been characterized as an epigenetic gatekeeper (''capacitor'') that interfaces with the environment and may ultimately determine whether particular (epi)genetic settings will succeed in achieving phenotypic expression, presumably via hsp90 interactions with the chromatin machinery [289–293]. Epigenetic regulation might explain the phenotypic discordance often observed among monozygotic twins, differences in age of onset of disease (multiple sclerosis, diabetes, asthma, ...), fluctations in disease severity, sex effects, parent-of-origin effects and sporadic cases of disease [294,295]. Of special interest, NF-κB induced interleukin-6 (IL6) gene expression, which is criticially involved in acute inflammatory stress responses (innate immunity), acquired immune responses (haematopoiesis, differentiation of B, T, APC cells) and neuronal stem cell differentiation, was found to elicit epigenetic changes via regulation of DNA-methyltransferases (dnmts) [296–298] and histonemethyltransferases (Ezh2) [299]. This suggests that epigenetic regulators themselves are susceptable to inflammatory control. Reciprocally, impaired DNA methylation was found to increase IL6 levels too [300,301]. As strongly elevated IL6 levels have been implicated in chronic inflammatory disorders, haematological malignancies, cancer progression (renal cell carcinoma, breast, lung, colon, ovarian and gut cancer, multiple myeloma), neurodegeneration and aging frailty [302–304], it will be interesting to further explore how IL6-triggered epigenetic events may affect onset of disease, disease progression or disease severity [296–298,305–308]. As an example, DNA methylation of the NF-κB-responsive element in the Fas (CD95, Apo-1, TNFRSF6) gene promoter, was found to silence its expression in metastatic prostate carcinoma; whether anti-IL6 or epigenetic therapies may relieve Fas silencing and sensitize for apoptosis awaits further study [123,249,309,310].

Today, it is believed that two layers of epigenetic code are superposed, i.e. first a ''cellular memory'' layer (mitotically heritable or imprinted cell fates), which preserves a window of ''transcription potency'' throughout the cell cycle, and a second ''transcription memory'' layer, which dynamically translates environmental signals in effective gene transcription profiles within the transcription frame established through the first layer [159,247,311–314].

Briefly, in mammalian cells there are three interconnected molecular mechanisms of epigenetic regulation: DNA methylation, histone modifications, and RNA interference [125,158,242,264,311,313,315–319]. Hypermethylation of CpG-rich promoters triggers local histone code modifications resulting in a cellular camouflage mechanism that sequesters gene promoters away from transcription factors and results in stable silencing [159]. DNA methylation at CpG dinucleotides (5′-CG-3′) occurs upon transfer of S-adenosylmethionine on cytosine by DNA-methyltransferases (dnmt). Whereas dnmt3a/b are responsible for DNA methylation during development (differentiation), dnmt1 is in charge of maintaining DNA methylation patterns in DNA replication during cell division. In mammalian cells, the fidelity of maintenance of methylation is 97–99.9% per mitosis, whereas de novo methylation is as high as 3–5% per mitosis, thus creating possibilities for epigenetic changes [247]. Interestingly, DNA methylation marks are recognized by DNA methyl-binding proteins (MBD) which can interact with corepressor-associated enzymes (i.e. HDACs, Ezh2, ...), thus further linking DNA methylation and chromatin regulation [125]. There is good evidence that RNA also regulates chromatin architecture [317,320–323]. DNA methylation can thus be RNA-directed. Functional non-coding RNAs which affect chromatin modifications have been shown to control gene expression from a single locus (Tsix RNA), from chromosomal regions (Air RNA) and from entire chromosomes (roX and Xist). Interestingly, a conserved chromatin-binding chromodomain, which occurs in Polycomb proteins as well as heterochromatin protein HP1, as the histone acetyltransferase MOF, are RNA-binding modules, which have important roles in position effect variegation, heterochromatin spreading and X chromosome dosage compensation [324–326]. Finally, non-coding RNAs were found to act as steroid coactivators, during hormone-dependent chromatin remodeling [327]. Despite the exponential increase in identification of non-coding RNAs in higher eukaryotes which affect cell fate [319,328–331], the functional links with epigenetic control of NF-κB signaling just start to be unraveled [332–334].

Besides the role of NF-κB in acute innate immune responses discussed sofar, NF-κB has also been recognized to be crucial for the development (survival and differentiation) of several mammalian haematopoietic cell lineages [335–339]. During their development from progenitors, lymphocytes make a series of cell fate decisions. These decisions reflect and require changes in overall programs of cytokine gene expression. To maintain cellular identity, programs of gene expression must be iterated through mitosis in a heritable manner by epigenetic processes, which include DNA methylation, histone and transcription factor modifications and conservation of higher order chromatin structure. Interesting experimental evidence shows that the cytokine gene expression profile and histone code, studied in a T-cell model primed under T-helper type I (Th1) or Th2 conditions, give rise to 'polarized' cytokine gene expression and histone acetylation patterns (cell fate memory); in this model, a subset of Th2 cells failed to express particular cytokines upon exposure to Th1 conditions [340–342]. Although important regulatory roles of various non-coding RNAs have also been proposed during haematopoiesis, it awaits further investigation how these RNA molecules may

impact on NF-κB-dependent epigenetic networks and/or haematological malignancies [259,332,338,343–347].

Along the same line, in a model of myofibroblast transdifferentiation, NF-κB-driven IκB gene expression was shown to be counteracted by a methyl-CpG-dependent mechanism, involving recruitment of a MeCP2-CBF1(RBP-Jκ) corepression complex at the NF-κB motif [348]. Whether this mechanism can be generalized to other CBF1-sensitive NF-κB-regulated target genes, awaits further investigation [69,349].

In another context, as an example of transcription memory, interleukin-2 promoter demethylation was demonstrated prior to TF binding; upon withdrawal of the stimulus, TF binding remains in absence of the DNA methylation signal, which allows a faster and stronger gene response during the second stimulation [338,350]. Finally, anti-inflammatory glucocorticoid hormones were found to regulate DNA demethylation within a key enhancer of the rat liver-specific tyrosine aminotransferase (Tat) gene. As a stronger subsequent glucocorticoid response is observed, demethylation appears to provide memory of the first stimulation. During development, this demethylation occurs before birth, at a stage where the Tat gene is not yet inducible, and it could thus prepare the enhancer for subsequent stimulation by hypoglycemia at birth. In this respect, demethylation appears to contribute to the fine-tuning of the enhancer and to the memorization of a regulatory event during development [279].

5. NF-κB: from Igκ light chain-binding nuclear factor to epigenetic trigger of monoallelic B cell receptor editing

Investigation of NF-κB in regulating V(D)J recombination complexes begun nearly 20 years ago, when NF-κB was first discovered based on its ablity to bind to κB sites within the Igk intronic enhancer [351]. Based on correlations between its activation and increased κ rearrangement in pre-B-cell lines, it was believed to be a controlling factor in recombination of that locus [352]. The development of mature B- and T-cells in the lymphoid systems involves a series of molecular decisions that culminate in the expression of a 'single antigen receptor' on the cell surface, which depends on restriction of VDJ rearrangement to only one allele in each cell, a process called ''allelic exclusion'' [339,353,354]. For a diploid organism such as man, the epigenetic code instructs whether two alleles of a particular gene can be expressed at different levels due to X chromosome inactivation, gene imprinting, difference in local promoter activity (polymorphism), or mRNA stability. As such, disruption of the balance of epigenetic networks (loss of imprinting (LOI), either biallelic expression or complete silencing of imprinted genes, or imbalanced allelic expression) can cause severe malignancies [123,250,355–360]. Epigenetic mechanisms involved in the establishment of allelic exclusion of the Igκ locus are mainly achieved by differential NF-κB-dependent DNA demethylation, asynchrous DNA replication, differential chromatin modifications, unequal nuclear localization and non-coding RNA [257,361–364]. Surprisingly, during gene targeting knockin experiments with the Igκ locus in which the κB motif was eliminated, it seemed that the κB site appeared to be unimportant for κ gene recombination [365,366]. However, in a new recent study it was demonstrated that NF-κB regulates Igκ rearrangement by coordinating recombinase activator gene (RAG) expression and Igκ accessability during B-cell receptor editing [367,368].

6. Future challenges

Today, most research efforts in unraveling specificity and dynamics of NF-κB-driven gene transcription have focused on signaling networks which converge on proximal promoter regions. However, upon unbiased mapping of in vivo binding sites of various TF (p53, Sp1, cmyc) by means of ChIP on Chip [369] or ChIP-PET [370] experiments, only 22% of transcription factor-binding regions are located at the 5′ termini of protein-coding genes while 36% lie within or immediately 3′ to well characterized genes and are significantly correlated with non-coding RNAs [370]. A significant number of these non-coding RNAs are also dynamically regulated and overlapping pairs of protein-coding and non-coding RNAs were found to be coregulated by common transcription factors and by common environmental signals [369]. These non-coding RNAs appear to comprise a hidden layer of internal signals that control various levels of gene expression in physiology and development, including chromatin architecture/epigenetic memory, transcription, RNA splicing, editing, translation and turnover [332–334,371–373]. Similarly, unbiased binding profiling experiments with NF-κB TF may unveil yet unexplored RNA regulatory networks too, involved in fine-tuning NF-κB immune biology [374].

Furthermore, as high confident TF binding loci were detected far away from proximal promoters of genes or found adjacent to inactive genes, it is possible that many binding sites function through long-distance interactions as enhancers or locus control regions (LCRs) to modulate gene expression [165,375]. As such, studying expression of specific NF-κB-driven genes within the context of chromatin hubs by chromosome conformation capture (3C) analysis approaches and RNA fluorescence may reveal novel regulatory perspectives with respect to euchromatin/heterochromatin spreading, insulator positions, inter/intragenic chromatin regulation, matrix attachment regions, intranuclear gene localization and subnuclear gene migration during innate or acquired immune physiological or pathological cellular responses [122,162–164,169,346,376–389].

In conclusion, the paradigm that persistent infections and chronic inflammation contribute via cytokine- and chemokine-mediated disbalanced immune responses to carcinogenesis becomes more and more attractive in cancer research [2,390]. Besides genetic factors, the epigenetics of impaired NF-κB cell signaling and signal transduction by proinflammatory cytokines and chemokines during carcinogenesis has recently gained much interest [279,359,391–399]. As such, it will be a challenge for future anti-inflammatory therapeutics and preventive cancer research to identify novel epigenetic targets which allow selective modulation of the NF-κB-signaling network.

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