Virchows Arch (1998) 432:389–406
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REVIEW ARTICLE

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Genetic aspects of prostate cancer

Received: 24 October 1997 / Accepted: 16 January 1998

Abstract Despite its high incidence and mortality rate, the molecular mechanisms underlying the oncogenesis and progression of prostate cancer are still unclear. This review, based on recently published data, surveys the current state of knowledge of human prostate oncogenesis, dealing with genetic predisposition in familial clusters of prostate cancer, providing new information on the somatic genetic alterations, which have been approached in four ways (measurement of DNA content, cytogenetic analysis, in situ hybridization, and molecular analysis), and investigating the problems of androgen independence and intratumour heterogeneity in prostate tumours. Lastly, the potential clinical applications of the genetic alterations, which may become important in the near future, are addressed.

Key words Prostate cancer · Oncogenes · Tumour suppressor gene · Loss of heterozygosity · Fluorescence in situ hybridization · Comparative genomic hybridization

Introduction

Prostatic carcinoma is one of the most common male cancers, and its incidence is increasing alarmingly. It exhibits a wide variety of biological behaviour, arising from a complex aetiology that involves both exogenous (including socio-economic situation, diet, geography, etc.) and endogenous (hormonal imbalance, epithelium/stroma interactions, family history) factors.

The prognosis depends on the stage of disease at diagnosis: only localized prostate cancer can be cured by radical treatment. However, despite attempts at early detection, a large proportion of patients have advanced disease at diagnosis: about 28% of patients have extraprostatic involvement, and 25% have bone metastases [101]. Moreover, it is currently impossible to determine the extension of the cancer accurately preoperatively, and advanced-stage prostate carcinomas are often undetectable. Imaging modalities such as radionuclide bone scan, computed tomography and magnetic resonance imaging are not sufficiently sensitive to detect microscopic extension of the tumour beyond the prostatic capsule; indeed, 30% of patients with clinically localized disease at the time of surgery will have tumour recurrences caused by occult micrometastatic dissemination. Histological grade, pathological stage, and tumour extent are the most discriminatory prognosticators at present, but these markers only indicate the likely outcome and major efforts must be made to develop additional prognostic indicators for prostatic carcinoma.

Androgen ablation is the treatment of choice for patients with locally advanced and/or metastatic disease. However, approximately 20% of men receiving hormonal manipulation fail to respond. Futhermore, most patients who show an initial therapeutic response relapse within 3 years, with an androgen-independent carcinoma that is rapidly fatal. Understanding the mechanisms by which a hormone-sensitive tumour escapes hormonal control is a challenge for clinicians and scientists alike.

The recent discovery of “cancer genes” and the application of recombinant DNA techniques have helped to refine tumour characterization. Modern biology is revealing the molecular bases of numerous diseases, with the most striking results in hereditary diseases and neoplasms. Tumour initiation and progression result, at least in part, from the successive accumulation in a given cell of constitutional and somatic genetic events that convert proto-oncogenes into activated oncogenes, or inactivate tumour-suppressor genes.

Unlike leukaemia, in which specific translocations are observed, prostate cancers involve a complex set of recurrent genetic anomalies. Analysis of the constituted genome of prostate cancer patients may identify different susceptibility genes and, hence, individuals at risk in families with a history of prostate cancer.

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Detection of the most common somatic genetic alterations will enhance our understanding of the molecular mechanisms of prostate oncogenesis and should lead to the discovery of new prognostic variables to guide therapeutic options.

Constitutional mutations: genetic predisposition

The notion of genetic predisposition to cancer is underpinned by the recent discovery of genes conferring susceptibility to certain cancers or to syndromes associated with cancers (*VHL*, *APC*, *RET*, *WT1*, *RB1*, *TP53*, *NF1*, *NF2*, *BRCA1*) [113]. It is generally believed that most adult human tumours arise following an accumulation of mutations targeting multiple growth-regulating genes. Persons who inherit one of these mutations are at increased risk of developing specific cancers at an early age. This model also implies that every cell in the relevant tissues of genetically susceptible individuals is at increased risk of neoplastic transformation, in contrast to the situation with sporadic cancer. Predictably, many hereditary cancers have multifocal precursor lesions and a tendency towards multifocal tumours. Through the use of genotypic markers (restriction fragment length polymorphisms, microsatellite polymorphisms), segregation analysis in high-risk families now offers the possibility of detecting predisposing genes involved in different hereditary cancers.

Numerous studies have provided evidence of familial clustering of prostate cancer in about 20% of cases [6, 108]. Segregation analysis of familial prostate cancer suggests the existence of at least one dominant susceptibility locus [32]. Linkage analysis is the cornerstone of efforts to map inherited prostate cancer genes, and many groups are now carrying out a genome-wide search in selected prostate cancer families. National advertising, media events, and mail shots directed at support groups and urologists are used to recruit families into such studies. The families are selected on the basis of the number of first-degree relatives diagnosed with prostate cancer, early onset of disease, and the number of living affected members from whom samples can be obtained for typing.

The location of the first prostate cancer susceptibility gene was recently determined by Isaacs's group, who established genetic linkage to 1q24-25 in families with an increased incidence of prostate cancer [190]. The *HPC1* (hereditary prostate cancer 1) gene has not been cloned, and its functions are unknown. Candidate genes in this region include the *SKI*, *ABL2*, and *TRK* oncogenes, and also *LAMC2*, which encodes an isoform subunit of laminin. Smith et al. estimate that the gene they are homing in on is involved in about a third of hereditary prostate cancers. As not all prostate cancer-prone families are linked to *HPC1* [149], studies are in progress to identify other potential prostate cancer susceptibility genes.

Another investigational approach exploits information on known genes. The excess risk of prostate cancer observed in men with affected brothers in comparison with those with affected fathers is consistent with an X-linked model of inheritance [152], and the androgen receptor (*AR*) gene is an interesting candidate [36]. The transactivation activity of *AR* is encoded by exon 1, which contains polymorphic CAG and GGC repeats; a smaller size of these repeats is associated with a higher level of receptor transactivation function, resulting in a higher risk of prostate cancer [72]. However, genetic variation in the androgen receptor does not seem to be involved in prostate cancer susceptibility [197].

There are striking differences in prostate cancer incidence rates among racial and ethnic groups, with African-American men having the highest incidence and Japanese and Chinese men the lowest. These differences might be determined by different levels of testosterone, and particularly its intraprostatic metabolite dihydrotestosterone (DHT). Genetic variants of the *SRD5A2* gene, which encodes the type II isoenzyme of steroid 5α-reductase, may explain the molecular genetic basis of the substantial racial/ethnic variability in risk. A specific polymorphism of *SRD5A2* is observed in high-risk populations [176]; indeed, these 5α-reductase enzyme variants may result in an elevation of the enzyme activity, resulting in an increased prostatic level of DHT. High levels of this hormone would then increase the risk of developing prostate cancer.

Prostate cancer mortality rates correlate well with ambient levels of UV radiation, giving rise to the hypothesis that low UV exposure may be a risk factor for prostate cancer. Most of the body's supply of vitamin D is synthesized in the skin in response to UV radiation, and a recent study showed that the vitamin D receptor (VDR) genotype is an important determinant of the risk of prostate cancer [202].

As genes predisposing to breast cancer also increased the risk of prostate cancer [7, 209], the *BRCA2* gene, which is responsible for inherited breast cancer, is an interesting candidate [231].

Somatic genetic alterations

The contemporary view of cancer is that a detectable tumour arises from cell transformation, loss of contact inhibition and acquisition of invasive capacity as the result of successive mutations. A cell that acquires a specific genetic alteration may develop a proliferative advantage. Clonal expansion of this cell, driven by successive mutations, can lead to tumour progression. Molecular studies strongly support the idea that multiple genetic changes are required for oncogenesis. The coordinated action of both classes of gene (proto-oncogenes and tumour-suppressor genes) seems to be required for tumour development. An archetypal example is the genetic model of colorectal tumourigenesis proposed by Vogelstein, which requires genetic alterations on several chromosomes [57].

Somatic genetic anomalies have been studied in three ways:

Cytogenetic analysis, which identifies karyotype anomalies (loss and/or gain of chromosomes, structural anomalies).

In situ hybridization techniques, which identify chromosomal anomalies. Comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) have refined the analysis of chromosomal anomalies through the use of molecular probes.

Molecular biology techniques, which detect molecular anomalies and mutations of oncogenes or tumour-suppressor genes.

Cytogenetic analysis

Solid tumours are more difficult to analyse and interpret cytogenetically than are leukaemias. At first sight, karyotyping of a solid tumour reveals a complicated set of chromosomal anomalies, which appear to reflect nonspecific alterations. However, some of these anomalies seem to recur in certain types of cancer, thus providing valuable information on the location of pathogenetically important genes.

Initial studies focused on established cell lines derived from prostate tumours (see references in [8]) in order to identify consistent chromosome changes. Later, fresh tumours or paraffin-embedded material were used for cytogenetic evaluation. However, fewer than 350 primary tumours and metastases have been examined cytogenetically. Although cytogenetic analysis of prostate tumour cells often reveals complex karyotypes, the most common changes observed are nonrandom loss of chromosome Y and gain of chromosome 7 [23, 151]. Gain of chromosome 7 is one of the most frequently recurrent structural aberrations, but chromosome arm 7q deletions are also frequent [8, 141]. Other consistent findings include losses of chromosomal material from 8p and 10q, with structural aberrations at bands 8p22 and 10q24 [141], structural rearrangements of chromosome 1, and gain of 8q [8]. Other abnormalities have also been reported, mostly in complex karyotypes, indicating that they are secondary in nature. The most conspicuous secondary changes include gains of chromosomes 12, 14, 17, 18, 20, 22 and monosomies 2, 4, 5, and 19 [8, 141, 151].

Double minutes and homogeneously staining regions, two cytogenetic phenomena associated with oncogene amplification in neoplastic cells, have rarely been observed in prostate tumour cells [136, 141]. Later studies using CGH showed amplified regions in which amplified oncogenes had not been identified by molecular studies.

Cytogenetic data show that the karyotype is normal in approximately 50% of tumours and that clonal abnormalities represent 30% of alterations. Numerical chromosomal aberrations in prostate cancer coincide with disease progression, aggressive tumour behaviour, unfavourable outcome and shorter survival [8, 82, 83, 141], whereas clonal karyotypic abnormalities are rarely observed in locally confined prostate tumours [23]. Although cytogenetic analysis reveals only gross abnormalities, these provides important indicators for molecular studies.

In situ hybridization

The difference in resolution between cytogenetic analysis and molecular analysis is narrowing with the development of new in situ hybridization techniques (FISH and CGH). These techniques also avoid the main drawback of cytogenetics: the need for cell culture, which is a source of a selection bias towards tumour cells with a high mitotic index.

FISH can be used to detect, locate and quantify specific nucleotide sequences (DNA or RNA) in tissue sections, isolated cells or chromosome preparations. Recent experiments using double labelling show that FISH resolutions of better than 5 kb should be feasible in the near future. FISH data are in agreement with previous cytogenetic studies regarding abnormalities of chromosomes 7, 8, 10 and Y [2, 26, 173, 218], but also show frequent losses of chromosome arms 17q and 18q [24, 102]. FISH studies show few simple monosomic tumours but frequent partial chromosome losses in DNA polysomic tumours, in keeping with the cytogenetic evolution concept of Shackney et al. [184]. The significance of chromosome 7 aneusomy, which is one of the most frequent events observed in high-stage prostate cancer [9, 199] and might be a marker of poor prognosis [1], is still unclear; trisomy 7 may be due to the presence of tumour infiltrating lymphocytes [100].

CGH analyses, which are designed to reveal regions that are amplified or lost in a genome [106], confirm that chromosome deletions are more frequent than chromosome gains in prostatic tumours. Although most of the abnormalities observed by means of CGH had previously been detected by cytogenetic methods or FISH, CGH has identified some new alterations, including deletions on chromosome arms 6q, 9p and 22q [33, 104, 219] and a new amplified region at 8q24 [215], pointing to the presence of genes involved in prostate carcinogenesis.

However, in view of the currently poor precision of this new technique, it should be coupled with FISH to confirm and quantify the observed genetic alterations.

Molecular analysis

The first molecular studies focused on oncogene activation (*MYC, ERBB2, RAS*), growth factors and their receptors, and the androgen receptor. However, as already suggested by in situ hybridization studies, the most frequently observed genetic anomalies in prostate cancer are deletions affecting several chromosome arms, which might inactivate tumour-suppressor genes. Microsatellite instability, which has recently been demonstrated in tumours of subjects with hereditary nonpolyposis colorectal cancer (HNPCC) and in sporadic colorectal and other

cancers (endometrium, stomach and pancreas), is debated in prostate cancer.

Proto-oncogenes in prostate cancer

The MYC proto-oncogene. MYC (located at 8q24) and the *MYCL1* and *MYCN* genes form the *MYC* family. *MYC* is commonly amplified in solid tumours (breast cancer, small-cell lung carcinoma, cervical carcinoma) and is rearranged in haematological malignancies (Burkitt's lymphoma, T cell acute lymphocytic leukaemia). The gene encodes a 59- to 62-kDa nuclear protein involved in the control of normal growth, differentiation and apoptosis, and its expression is regulated by a complex mechanism involving *cis*- and *trans*-activators. Myc protein appears to act as a transcription factor and contains the helix–loop–helix and leucine zipper domains, which are involved in the formation of DNA-binding protein complexes. The transcriptional activity of Myc requires binding to Max protein and may be regulated by two newly identified proteins, Mad and Mxi1, which compete with Myc for Max [73].

Significantly high rates of *MYC* expression have been reported in prostatic adenocarcinomas [30, 59]. *MYC* amplifications and *MYC* rearrangements have been observed in prostatic cancer cell lines [65, 159], but these alterations could arise as an adaptive change in culture, as they have not been confirmed by molecular studies on prostate cancer tissues [60, 127]; this suggests that *MYC* activation is due to mechanisms other than amplification.

Proto-oncogene ERB-B2. The *ERB-B2* proto-oncogene belongs to the *ERB-B* family, the first identified member of which (*ERB-B1*) encodes the EGF (epidermal growth factor) receptor. Overexpression in human tumours occurs either through gene amplification or through transcriptional or post-transcriptional deregulation. Two other genes of the *ERB-B* family have been identified by sequence homology: *ERB-B3* [121] and *ERB-B4* [170]. This multigene family encodes transmembrane receptors with tyrosine kinase activity.

Higher levels of ERB-B2 oncoprotein were observed in prostatic tumours than in normal tissues [62, 123]. However, molecular studies show that *ERB-B2* amplification is infrequent in prostate tumours [60, 127, 142, 235], suggesting that ERB-B2 activation is not due to gene amplification. The value of *ERB-B2* expression as a prognostic indicator in prostate cancer is controversial [62, 123].

RAS Proto-oncogene family. The *RAS* gene family, consisting of *HRAS*, *KRAS* and *NRAS*, encodes highly related G (for GTP-binding) proteins with molecular weights of approximately 21,000 ($p21^{RAS}$). *RAS* genes are essential for the transduction of extracellular signals that induce proliferation and differentiation. $p21^{RAS}$ is a membrane-located guanine nucleotide-binding protein that is active in the GTP-bound state. Activating mutations in *RAS* genes result in constitutive signalling to downstream elements and are frequent in a wide variety of tumours.

Although the specificity of the primary antibody used in these studies (RAP-5) has been challenged, immunohistochemical assays indicate a high level of $p21^{RAS}$ in prostate tumours [196, 216]. $p21^{RAS}$ overexpression seems to correlate with prostate cancer progression [78] and could be associated with the emergence of bone metastases [56]. However, immunostaining for $p21^{RAS}$ seems to have little value in the diagnosis or grading of prostate cancer [27]. Results of molecular studies of point mutations in *RAS* genes, leading to constitutive activation, are controversial [4, 76, 116, 156] as discrepancies could be due to ethnic differences [118, 225].

Other amplified genes. The 11q13 band is amplified in a wide variety of human tumours, and there are several genes of importance in this region (*INT2/FGF3*, *HST/FGF4, CCND1*, *EMS1*). Molecular studies, using *INT2/FGF3* as a marker of the amplification unit in 11q13, suggest that amplification of this band is infrequent in prostate cancer [60, 127].

The *PTI-1* gene, which contains a sequence analogous to the human elongation factor EF-1α, might be a member of a class of oncogenes that could contribute to the development of human prostate carcinoma [185].

Human papillomavirus

The human papillomavirus (HPV) family is made up of approximately 65 different types. An aetiological role for some high-risk HPVs (for example HPV16 and 18) has been suggested, especially in anogenital cancer. More than 70% of uterine cervical cancers contain integrated HPV16 and HPV18 DNA in genomic DNA. Experimental observations that HVP E6 and E7 oncoproteins can bind to cellular tumour-suppressor proteins p53 and pRb [48, 228] clearly indicate the importance of endogenous events that might arise from HPV infection.

The role of HPV in prostate cancer is controversial [50, 150, 157, 182]. The observed HPV viral sequences in prostate tumours could be due to contamination by urethral cells, which form a reservoir for HPV [229].

Polypeptide growth factors and their receptors

Peptide growth factors with common structural properties and functions have been grouped into superfamilies. This review will focus on four major families of peptide growth factor: epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF), and transforming growth factor-β (TGFβ), and their role in normal and malignant prostate tissue. Polypeptide growth factors may use either autocrine or paracrine pathways to signal cells in the microenvironment. The role of growth factors in prostatic adenocarcinoma has been reviewed by Steiner [195].

Epidermal growth factor family of peptides and receptors. A family of epidermal growth factor-like peptide growth factors currently includes EGF, TGFα, amphiregulin, heparin-biding EGF and *cripto*. All of these molecules signal through the same transmembrane glycoprotein receptor and tyrosine kinase; EGF receptor (EGFR) encodes by the *ERB-B1* gene. EGF and TGFα are virtually identical in their ability to bind EGFR and have similar biological properties.

The paracrine interaction of EGF and TGFα on the EGFR has been implicated in prostate cancer cell growth and proliferation [35, 61, 210]. Moreover, there may be an autocrine relationship between EGFR, TGFα and EGF and the potential for autocrine stimulation in prostate cancer cell lines [137, 145], primary tumours [37], and androgen-independent metastatic tumours [183]. Although the expression pattern and functional analysis of EGFR and its ligands suggest that EGFR is involved in several cell functions [205], particularly the regulation of epithelial proliferation and differentiation [186], EGFR expression in prostatic diseases is still controversial [88, 144, 210].

Fibroblast growth factor family of peptides and receptors. The FGF family (also known as the heparin-binding growth factor family) has at least nine members, including acidic and basic FGF (FGF1 and FGF2), INT2 (FGF3), HST (FGF4), keratinocyte growth factor (KGF; FGF7), androgen-induced growth factor (AIGF; FGF8) and GAF (FGF-9). The biological effects of FGFs are tranduced through four specific high-affinity cell surface area receptors with tyrosine kinase activity, including FGFR1 (FLG) and FGFR2 (BEK).

To date only FGF1, 2, 3, 7 and 8 have been detected in prostate tissue. FGF family members have biological properties that could contribute to the transformed phenotype, but their exact role in prostate cancer is unclear. Prostatic stromal cells are the exclusive source of FGF7 and the major FGF mRNA expressed in the human prostate [232]. FGF7 may act in a paracrine fashion in human prostate cancer, and significant up-regulation of FGF7 expression is observed in hormone-refractory prostate carcinomas [134]. Over-expression of FGF8 has been observed in prostate tumours, and the level of its expression was related to grade [133].

Insulin-like growth factor family of peptides and receptors. The insulin-like growth factor (IGF) family is made up of insulin growth factors I and II, and relaxin. IGFs are thought to be involved in various functions, including cell growth and cell division, and apoptosis [103]. IGF may signal via the insulin-like growth factor I and II receptors, and it is interesting that the IGFIIR/*Man-6-P* gene functions as a tumour-suppressor gene in human liver carcinogenesis [45].

IGF-II has an important role in the adult prostate, as a paracrine and an autocrine regulator of cell proliferation. It appears that androgen-insensitive prostate cancer cell lines secrete IGF-II and over-express IGF-IR, setting up an autocrine stimulation loop that maintains uncontrolled proliferation. Bi-allelic expression of the *IGFII* gene, which normally demonstrates imprinting, has been observed in prostate carcinoma, suggesting that the loss of imprinting may be linked to the development of abnormal growth states in prostate tissue [98].

Transforming growth factor family of peptides and receptors. The TGFβ family consists of five isoforms, but only types 1–3 have been detected in mammals. TGFβ may be a stimulator or inhibitor of cell growth, depending on the cell type and state of differentiation. TGFβ also acts as a regulator of cell cycle kinetics; it inhibits pRb phosphorylation and *MYC* transcription [3], and regulates CDI (cyclin-dependent kinase inhibitor) activity, especially p15INK4B/MTS2 and p27Kip1 (79, 171). Type I, II and III receptors are the best-characterized among the eight polypeptides known to be linked to TGFβ.

TGFβ is a potent inhibitor of the proliferation of normal prostate epithelial cells. Prostate tumours frequently lose the expression of TGFβ type I and/or II receptors, which would lead them to escape the growth-inhibiting effect of TGFβ and thereby acquire a more malignant phenotype [109]. TGFβ1 might affect mobility, even in vivo, and contribute to tumour aggressiveness [153]. Moreover, the plasma TGFβ1 concentration is a potential new tumour marker attributed to the presence of invasive cells, that may also be used in the prognostic analysis of prostate cancer [97]. High-level TGFβ expression has been observed, both in vivo and in vitro, in tumour cells exposed to drugs, suggesting that TGFβ might also play a role in apoptosis [125]. Loss of TGFβ1 type I and II receptor expression correlates with tumour grade, providing a potential mechanism for prostate cancer cells to escape the growth-inhibiting effect of TGFβ [110].

Other growth factors. HGF (hepatocyte growth factor) and its receptor, encoded by the proto-oncogene *MET*, are upregulated in prostate cancer (especially lymph node and bone metastases) and its expression seems to be associated with tumours that progress to androgen-independent growth [87, 169].

PDGF (platelet-derived growth factor) consists of two polypeptide chains (PDGF-A and PDGF-B) linked by disulfide bonds. PDGF-A and its receptor are upregulated in prostate adenocarcinomas [64]. The PDGF-B polypeptide chain, encoded by the proto-oncogene *SIS*, is also over-expressed in androgen-independent prostate cancer cell lines [189] and poorly differentiated tumours [166]. However, further studies are required to assess the role of PDGF in prostate oncogenesis.

NGF (nerve growth factor) belongs to the neurotrophin family, which includes brain-derived neutrophic factor (BDNF) and neutrophins 3, 4 and 5 (NT 3, NT 4 and NT 5). The glycoprotein $gp75^{NGFR}$ is the low-affinity NGF receptor and Trk_j the high-affinity receptor. NGF and NGF receptors have been detected in human prostate cancer and normal tissues by molecular biology methods

[147]. A negative correlation between p75$^{NGF\text{-}R}$ expression and the progression of human prostate cancer has been observed [165]. NGF-R is involved in apoptosis of neural cells, and the observed mutations of p75$^{NGF\text{-}R}$ in prostate cancer cell lines [163] might prevent p75$^{NGF\text{-}R}$ from inducing apoptosis.

Lastly, the haematopoeitic factor interleukin 6 (IL-6) is of particular interest. IL-6 is a pleiotropic cytokine produced in substantial amounts in semen. IL-6 receptor has been detected in prostate carcinoma and prostate cancer cell lines, most of which also secrete IL-6 [187, 188]. IL-6 is a candidate mediator of human prostate cancer morbidity [211].

Inactivation of tumour suppressor genes

In recent years another class of "cancer gene", the tumour-suppressor genes (TSGs), has been added to the oncogenes. These are negative regulators of cell growth that appear to act in recessive manner; that is to say they are only inactivated when both alleles are altered. Two successive steps are therefore necessary. The first event may be somatic (sporadic cancer) or germinal (hereditary cancer). As tumour-suppressor genes are affected by recessive damage, an indirect strategy based on the detection of allelic losses (or LOH) is used to locate and identify them. The size of a chromosomal deletion (which may be infra-cytogenetic) can be determined by studying the LOH of several neighbouring loci on a given chromosome. Efforts are being made to detect deletions in many types of cancers, first to discover links between a given type of tumour and a specific loss of genetic material, and second to identify candidate tumour-suppressor genes in this genomic region. This approach has proved extremely fruitful in the case of retinoblastoma, in which evidence of LOH in 13q14 led to the identification of the first tumour-suppressor gene *RB1* [63, 132]. Later, multiple losses of genetic material were described in other cancers, suggesting that several tumour-suppressor genes are involved in tumour development [57].

Prostate cancer allelotyping for LOH description. It now seems that the most consistent genetic alterations in adenocarcinoma of the prostate are LOH involving certain regions corresponding to chromosomal arms 7q, 8p, 10q, 13q, 16q, 17, and 18q (Table 1). Moreover, the arms of the most frequently deleted chromosomes have recently been studied by using numerous, regularly spaced polymorphic probes. Several deleted regions on a single arm have been identified in this way, thus further complicating the identification of tumour-suppressor genes in prostate cancer. For example, three deleted regions have been found on chromosome arm 8p. Most of the altered regions are common to prostate and other cancers [179]. This suggests that a single suppressor gene may play a part in the genesis of different cancers, but possibly at different stages of tumour progression, or that there are several genes in a given region, each with a particular function in one type of cancer. Indeed, certain deleted regions in prostate cancer are located in known suppressor genes (*RB1*, *CDH1*, *DCC*, etc.), although the involvement of these genes in this cancer has not been demonstrated.

Chromosome arm 13q losses and *RB1*

Chromosome 13q is often deleted in prostate cancer [22, 167], and the retinoblastoma susceptibility gene (*RB1*) is a candidate suppressor gene at this region. *RB1* encodes a nuclear phosphoprotein which plays an important role in the negative regulation of cell proliferation [227]. In-

Table 1 Loss of heterozygosity (*LOH*) in human prostate cancer and candidate genes. Most references concerning each chromosome alteration are listed; all references not cited specifically here are cited in [42]

	Average LOH (%)	Range (%)	References	Number of tumors studied	Common deleted regions	Candidate genes
5q	24	10–43	[21, 42, 130, 212]	101	5q21	*APC, CTNNA1*
6q	28	33	[39, 42]	107	6q13–q22	?
7q	32	0–75	[31, 42, 124, 129]	199	7q31	?
8p	66	10–90	[41, 42, 54, 95, 105, 124, 130, 148, 222]	800	8p22, 8p21.3 8p12	*N33, NKX3.1*
10p	20	0–57	[42, 95, 115, 124, 126, 208]	212	10p11.2	?
10q	33	0–62	[31, 42, 95, 115, 124, 126, 130, 208]	336	10q23.3 10q24	*PTEN/MMAC1* *MXI1*
13q	26	10–67	[22, 31, 40, 42, 96, 124, 130, 167, 207]	301	13q14.1	*RB1*
16q	42	14–53	[31, 42, 53, 93, 124, 131, 198]	348	16q22.1 16q23.2–q24.1 16q24.3-qter	*CDH1* *CDH13, BCAR1* *BBC*
17p	16	5–38	[21, 42, 93, 95, 212]	206	17p13.1	*TP53*
17q	15	4–52	[42, 95, 130, 230]	198	17q21	*BRCA1, NME1, NME2*
18q	29	17–43	[21, 31, 41, 42, 67, 124, 128]	179	18q21.3–q23	*DCC, MADR2, DPC4*

activation of the growth-inhibitory functions of $p110^{RB1}$, by phosphorylation in late G1, is accompanied by the release of certain bound transcription factors prerequisite for the activation of S-phase genes, notably the E2F family. Phosphorylation of $p110^{RB1}$ appears to be mediated by the kinase activities of CDK4/6-cyclin D.

The observation of a homozygous deletion within the *RB1* promoter region in a prostatic carcinoma [16], and the phenotypic reversion of the human carcinoma cell line DU145 when normal *RB1* expression is restored by retrovirus-mediated gene transfer [17], suggest that *RB1* inactivation could play a significant role in prostate oncogenesis. Mutations [122] and frequent LOHs of the *RB1* gene were observed in later studies [22, 167]. However, some data indicate no correlation between $p110^{RB1}$ nuclear staining and LOH at the *RB1* locus [40, 207], and the role of *RB1* in prostate cancer thus remains to be determined.

Chromosome arm 16q losses and *CDH1*

One of the most frequently recurrent aberrations in prostate tumours involves chromosome arm 16q [31, 130]. The *CDH1* gene, which encodes the epithelial cell adhesion E-cadherin, might be the target of the observed LOH on this chromosome arm. The *CDH1* gene is of particular interest, because it can function as an invasion-suppressor gene [221]. Initial data on the *CDH1* gene showed that loss of *CDH1* correlates in vivo with invasive behaviour and/or metastatic capacity [29]. The reduced expression of E-cadherin in high-grade prostate tumours was subsequently confirmed [213] and may be a phenomenon associated with a poor prognosis and a lower survival rate in patients with prostate cancer [177, 214]. The recent positional cloning of *CDH1* [14] will allow more detailed study of this gene, which can also be silenced by DNA hypermethylation [74]. Chromosome arm 16q might harbour other TSGs involved in prostate carcinogenesis, as recent reports have pointed to other novel sites of deletion on 16q [131, 198].

Chromosome arm 17p losses and *TP53* inactivation

LOH at the *TP53* locus, and physical deletions of 17p, have been observed in only a few prostate tumours [25]. However, *TP53* is the most thoroughly studied gene on this chromosome arm in prostate cancer, as *TP53* alterations are some of the most common genetic changes in solid tumours. *TP53* encodes a 53-kDa nuclear phosphoprotein whose principal physiological role seems to be the regulation of the cell cycle, contributing to the maintenance of DNA integrity [75]. If DNA is damaged, p53 levels increase and the cell cycle is arrested in G1 to allow for repairs. Several studies have shown that *TP53* can induce apoptosis [233]. *TP53* is regarded as a tumour-suppressor gene. In numerous human tumours, two copies of *TP53* are inactivated successively, in line with the hypothesis formulated by Knudson [113]. The alterations in *TP53* are the most commonly observed genetic anomaly in human cancers, be they hereditary or sporadic [75]. Mutation of *TP53* often increases the half-life of p53 protein, rendering it detectable by immunohistochemistry.

In prostate cancer both molecular and immunohistochemical assays indicate that *TP53* alteration is a late event. *p53* abnormalities seem to be associated with the progression of prostate tumours [18, 51] and loss of differentiation [80]. They are also associated with metastatic tumours, and *TP53* ought to be viewed as a putative anti-metastasis gene in prostate cancer [193]. Moreover, accumulation of mutated p53 is associated with hormone-refractory tumours [5, 80], active cell proliferation and poor outcome in terms of progression and survival [204, 217].

Chromosome arm 18q losses and the *DCC* gene

The *DCC* (deleted in colorectal carcinomas) tumour-suppressor gene, which suppresses the malignant phenotype of transformed human epithelial cells [112], is frequently altered in colorectal cancer [57]. In prostate cancer, LOHs on chromosome arm 18q have often been observed [124], especially in the *DCC* region [128]. The target gene of the observed 18q LOHs seems to be involved in prostate cancer progression [130]; *DCC* is a good candidate gene, as loss of expression (86%) and loss of heterozygosity (45%) have often been observed in human prostate carcinomas [67].

Other chromosomal regions undergoing losses

Deleted regions have been described in chromosomal regions not containing putative tumour-suppressor genes (Table 1). While the target gene of these deletion is unknown, the smallest commonly deleted regions have been defined on the more frequently affected chromosome arms, including 7q, 8p, and 10q [115, 129, 148]. Although the first molecular studies provided valuable data on the location of suppressor genes potentially involved in prostate oncogenesis, the results are in no way definitive. There may be much smaller deletions detectable only by more refined and thorough molecular techniques than those currently available. Numerous deleted regions (and therefore potential suppressor genes) clearly remain to be described in prostate and other cancers. It seems increasingly clear that most suppressor genes are not specific to a single cancer but are relatively common [179], and studies of other tumours should therefore provide insight into the molecular analysis of prostate cancer. In the same way, it would be useful to analyse chromosomes or chromosome segments involved in the suppression of phenotypic characteristics of tumour cells (oncogenicity, invasiveness, metastatic activity and immortalization) by cell fusion analysis (Table 2). This approach has proved extremely fruitful in the case of *KAI1* (see below).

Table 2 Chromosome segments and chromosomes involved in the suppression of different phenotypic characteristics of prostate tumour cells by cell fusion analysis

Chromosome arms and chromosomes	Phenotype suppression[a]
1p	*KREV* (inhibition of cell growth) [28]
5q	5q21, *CTNNA1* (tumorigenicity) [55]
7q	7q31 (tumorigenicity) [234]
8	Chromosome 8 (metastatic activity) [90]
	8p21-p12 (metastatic activity) [160]
10	Chromosome 10 (tumorigenicity) [92]
	10q (metastatic activity) [161]
	10pter-q11, *PAC* (tumorigenicity; apoptosis) [181]
11p	11p11.2-p13 (metastatic activity) [89]
	11p13, CD44 (tumorigenicity, metastatic activity) [71]
12	12pter-q13 (tumorigenicity) [13]
13q	*RB1* (tumorigenicity) [17]
17	Chromosome 17 (tumorigenicity) [19]
	17pter-q23 (metastatic activity) [178]
	17q12-q22 (tumorigenicity) [158]

[a] Microcell-mediated chromosome segment or chromosome transfer into prostate cancer cells results in suppression of growth rate, tumorigenicity, metastatic ability or induction of apoptosis of hybrid cells

Molecular exploration of the genome of prostate cancer cells should be pursued with more informative markers (such as microsatellite polymorphisms) combined with new in situ hybridization techniques (CGH and high-resolution FISH). It is also important to re-examine the chromosome arms that did not initially show allelic losses when they were analysed at a single locus. However, not all the deletions observed in prostate cancer necessarily lead to the discovery of tumour-suppressor genes. It may be that certain deletions deregulate the expression of one or several neighbouring genes simply by a gene dosage effect.

Other candidate tumour-suppressor genes in prostate cancer. Dong et al. [46] identified the metastasis-suppressor gene *KAI1* on chromosome 11p11.2. The *KAI1* gene belongs to a family of membrane glycoproteins and is assumed to function in cell–cell interactions and possibly cell migration. *KAI1* expression is reduced in human cancer cell lines derived from metastatic prostate cancer, but whether its down-regulation causes metastasis of human prostate cancer in vivo is unknown. Interestingly, down-regulation of *KAI1* during the progression of human prostate cancer rarely involves gene mutation or allele loss [47].

CD44 forms a group of transmembranous glycoproteins formed by alternative splicing of a single mRNA. Loss of expression of CD44 standard form (CD44s) correlates with a poor prognosis independent of stage and grade and may serve as a useful marker for predicting the metastatic ability of prostatic cancer cells [71, 162].

Thymosin β15, a positive regulator of prostate cancer cell mobility in the Dunning rat tumour model, should provide the much-needed positive marker of the metastatic potential of prostate cancer [10], being up-regulated in human prostate cancer with increasing Gleason grades and metastatic potential.

The putative protein tyrosine phosphatase gene (*PTEN* or *MMAC1*) recently mapped at 10q23 [135, 194] is a strong candidate tumour suppressor gene for prostate cancer.

HIC-1 (hypermethylated in cancer), a new zinc-finger transcription factor gene at 17p13.3, and a potential downstream target of p53, is a candidate tumour suppressor gene for prostate cancer [223]. Indeed, silenced gene transcription associated with hypermethylation has been put forward as one mechanism for TSG inactivation, and *HIC-1* span a region which is aberrantly hypermethylated in certain types of human cancer [94, 168], including prostate cancer [155].

The *CTNNA1* gene at 5q31, which encodes α-catenin protein, is of particular interest. α-Catenin, a cytoplasmic protein, acts inside the cell to couple the E-cadherin molecule to the microfilament cytoskeleton, and homozygous deletion of *CTNNA1* is one mechanism responsible for the loss of normal cell–cell adhesion in prostate cancer [154].

The *RAS*-related gene *KREV* at 1p13, which induces partial suppression of the malignant phenotype of human prostate cancer cell lines containing actived *RAS* oncogene [28], is a potential tumour-suppressor gene in prostate oncogenesis.

CDKN2 (also known as *MTS1* or *INK4a*), a gene that encodes the cell cycle-regulatory protein cyclin-dependent kinase-4 inhibitor (p16INK4a) involved in a wide variety of human cancers [107], is another candidate TSG for prostate cancer. Genetic alterations of *CDKN2* have been observed in the human prostate cancer cell line DU145 [114].

Although *CDKN2A* mutations are infrequent in prostatic carcinomas [143, 164, 200], gene deletion and methylation could combine to inactivate *CDKN2A* in a subset of tumours [99]. The identification of *CDKN2A*, which is involved in a wide variety of human cancers, shows how important it is to study proteins involved in the cell cycle, where relations with cancer are increasingly evident.

NME1 and *NME2* (also known as *nm23-H1* and *nm23-H2*), coding for the A and B subunits of a human nucleoside diphosphate kinase (NDPK), respectively, lie in tandem array 4 kb apart on chromosome 17q, around bands 21.3–22. Genetic alterations of *NME1* are infrequent in prostate cancer [21], and the involvement of Nme-1 protein in the metastatic process is controversial [91, 117]. Decreased expression of Nme-2 protein, a transcriptional activator of *MYC* [172], correlated with increasing stage of prostate tumours [58], suggesting a role in the metastatic phenotype.

Lastly, *WAF*1 at 6p22.1 is an interesting candidate, as somatic mutations of this gene have been observed in prostate tumours [69]. Clearly, additional studies are required to determine the role of these genes in prostate oncogenesis.

Microsatellite instability due to inactivation of DNA repair system genes

Many findings point to genomic instability as critical in the acquisition of multiple alterations during the multistage process that characterizes prostate cancer and other malignancies. Particular attention has been paid to microsatellite instability, which results in the replication error phenotype (RER) originally described in hereditary nonpolyposis colorectal families. Mutations (constitutional and/or acquired) in the *MSH2*, *MLH1*, *PMS1* and *PMS2* genes, which are the human counterparts of genes involved in repairing base mismatches in yeast and bacterial DNA, may be responsible for widespread and multiple alterations in microsatellites of tumour cells [139]. At present it seems that these genes are tumour-suppressor genes [81]. Alteration of the genes of the DNA repair system may constitute a new oncogenic mechanism responsible for a "mutator phenotype", which is revealed by alterations in microsatellites of the genome (repetitions of mono-, di-, tri- and tetranucleotides) and which appears to be responsible for the appearance of specific oncogenic mutations. These microsatellite instabilities have also been identified in sporadic colorectal and other cancers, such as cancers of the endometrium, stomach and pancreas (references in [139]). In sporadic colorectal cancers, microsatellite instabilities are specific to proximal colon tumours, which have low LOH frequencies [140]. Microsatellite instability, therefore, seems to be one alternative to LOH in the genesis of certain types of cancer.

Microsatellite instabilities have been observed in the human prostate cancer cell line DU145 and coincided with somatic mutations of DNA mismatch repair genes of the *MLH1* and *PMS2* categories [20]. RER data on prostate cancer tissues have shown prevalences ranging from 5% to 70% [68, 203, 212]. Egawa et al. [52] pointed out racial differences in genetic alterations during oncogenesis in prostate glands with distinct variations in the frequency of microsatellite instability. Regarding the overall evaluation of RER at the tumour level, there is no international consensus as to when a tumour should be labelled RER^+ or RER^-. It is important to distinguish between tumours demonstrating a low frequency of alterations and those having instability at multiple loci [42], and an accepted definition is highly desirable for practical purposes. RER might be related to a growth advantage phenotype in clinical postatate cancers [226] and be associated with high-grade [203] and poorly differentiated tumours [52].

Telomerase and telomere shortening

Telomeres are specialized structures at the ends of eukaryotic chromosomes and are involved in the protection and replication of chromosomes [15]. In humans they are composed of a sequence of six nucleotides (TTAGGG) repeated from a few to a thousand times. These sequences are synthesized by telomerase, a ribonucleoprotein enzyme. The extension of telomeres by telomerase is required to counter the normal shrinkage of chromosomes that occurs after each round of DNA replication. The length of a telomere is thus determined by the balance between the number of cell divisions and the activity of telomerase. Germline cells and most developing fetal cells have high telomerase activity. In normal adult somatic cells, telomere shortening is thought to be the controlling factor, or mitotic clock, that determines senescence. In normal somatic cells, the activity of telomerase seems to be below the detection limit, whereas malignant tumours often contain measurable telomerase activity, which may immortalize cells and allow unlimited proliferation [44].

Both tissues and cell lines of prostate cancer exhibit telomerase activity, whereas normal prostate cell lines, BPH, and normal prostate tissues do not [111, 138, 192]. Telomerase activity might therefore be a diagnostic marker for malignant prostate tissues [192] and an index of the malignant potential of prostate cancer (metastasis and outcome) [138]. It would be interesting to extend telomerase activity studies to prostatic needle biopsies.

Technical problems related to intratumour heterogeneity

Molecular analyses remain difficult to interpret owing to the cellular heterogeneity of tissue specimens. In the case of LOH, an allele is rarely completely lacking, not only because of the frequent contamination by normal cells but also because tissue specimens contain several subpopulations of tumour cells. In prostate cancer, in addition to dominant cancer nodules, separate smaller tumour foci often exhibit a different histological grade. This heterogeneity in prostate neoplasias is reflected at the molecular level, and LOH often differs considerably among morphologically defined areas of a given tumour [54]. The alterations observed most probably arise from an ancestral cell already present in the tumour, which became the founder of particular subclones identified by molecular tags. It is conceivable that alterations are underestimated in a significant number of cases, when the percentage of tumour cells bearing the genetic alteration is small or when there are two clones bearing genetic alterations that cancel each other out (such as monosomy and trisomy of the same chromosome).

The second problem is that certain regions of the genome previously identified as exhibiting allelic losses could, in fact, be the target of allelic gains. Such errors of interpretation might focus attention on a chromosome region that does not bear a tumour-suppressor gene. Indeed, the distinction between allelic gain and loss remains problematic, to the point that certain authors prefer to speak of allelic imbalance, without seeking to specify gain or loss of genetic material.

In order to interpret molecular analyses with as little ambiguity as possible, it is necessary to distinguish between normal and tumour cells and between subclones of tumour cells. In addition, it appears preferable to com-

pare the results obtained by means of classical molecular techniques with those yielded by other methods such as FISH. The latter can distinguish unambiguously between losses and gains of genetic material. As each nucleus is analysed individually, this method overcomes the problems of sample heterogeneity. However, even FISH has its limits. For example, if LOH at a given locus involves two alleles inherited from the same parent (mitotic recombination or deletion followed by reduplication of the remaining allele), the genetic alteration will only be revealed by methods detecting allelic loss, and not by FISH.

The different normal and tumour cell subpopulations can be distinguished morphologically or by means of biological techniques (DNA content, S-phase, or subpopulation-specific oncoprotein antigens). For example, the detection of allelic loss, using PCR-based microsatellite polymorphisms, can be done on morphologically different tissue microsamples from an archival tumour tissue section. In the same way, the separation of aneuploid and diploid subpopulations by flow cytometry could reveal full allelic loss in the aneuploid subpopulation.

Androgen-independent prostate cancer

The predominant systemic treatment for patients with metastatic disease is hormonal or androgen-ablative therapy. Although an initial response to hormone therapy is observed in 70–80% of patients with advanced disease, most tumours progress rapidly to androgen-independent growth and only 10–20% of patients are alive 5 years after diagnosis. The failure of endocrine therapy is one of the most important problems in the management of prostate cancer.

One of the most specific genetic changes detected by means of CGH in hormone-refractory prostate carcinomas is the gain of 8q [34], and especially the 8q24-qter region [215, 219]. One possible target gene at 8q24 is the *MYC* gene, whose high-level amplification is very rarely seen in primary tumours. There may be other, currently unknown, target genes at the distal 8q locus, whose increased copy number is selected for during endocrine therapy.

Another specific genetic alteration frequently observed in hormone-refractory tumours is the gain of Xq [219]; the target gene of amplification is likely to be the androgen receptor (*AR*) gene at Xq12; indeed, amplification of *AR* was detected in 30% of recurrent tumours but in none of the primary tumours taken from the same patient prior to therapy [220], in addition, *AR* amplification leads to increased mRNA expression [119]. Finally, high-level expression of *AR* was observed in hormone-refractory tumours [84, 180, 201]. Mutation is another mechanism by which *AR* may be involved in hormone resistance.

Mutations of *AR* are rare in primary tumours and are principally found in hormone-independent carcinomas [180]. Mutations are found either in the transactivator domain [206], or in the hormone-binding domain [66], leading to transactivation of the receptor by other steroids such as oestrogen and progesterone [201]. Failure of conventional androgen-deprivation therapy in prostate cancer may be caused by clonal expansion of tumour cells that are able to continue androgen-dependent growth despite the low serum concentrations of androgens; and the increased expression of the *AR* gene may have a key role in this process.

The effect of androgen ablation results principally from the induction of apoptosis in the tumour cells. Another explanation for the emergence of androgen-independent prostate cancer is the selection of cells that fail to activate the programmed cell death cascade in response to androgen withdrawal. The molecular basis for androgen independence could involve the expression of genes such as *BCL2* that override programmed cell death. Elevated expression of Bcl-2 has proved to be highly protective against a wide variety of apoptotic stimuli [175] and Bcl-2 oncoprotein could play a part in hormone-resistant human prostate cancer [38, 146].

Bcl-2 is normally expressed in the basal cells of the prostatic glandular epithelium [85]. Over-expression of Bcl-2 can protect human prostate cancer cells from apoptotic stimuli in vitro and might be a factor enabling cells to survive in an androgen-deprived environment in vivo [174]. It is of interest that treatment of prostate cancer cell lines expressing Bcl-2 with taxol induces Bcl-2 phosphorylation and programmed cell death [77]. However, *BCL2* belongs to an expanding family of apoptosis-regulating genes, and *BCLX-L* and *MCL1*, which block cell death, might be also involved in the progression of prostate cancers [120].

The proliferation of metastatic prostate cancer cells is remarkably slow, which explains the limited value of anti-proliferative chemotherapy [11]; spermine, an endogenous inhibitor which can repress prostatic carcinoma cell growth in the prostate [191], could explain this slow growth.

A genetic model of prostate oncogenesis

Is there a particular order of alterations in prostate carcinogenesis, and how would such an order influence the prostate tumour phenotype? Vogelstein's group argues that it is the gradual accumulation of changes, rather than their order of occurrence, that is likely to be most important in colorectal tumorigenesis [57]. Nonetheless, it may be that certain events occur more specifically in the early or late stages of a given type of cancer. A sequence of oncogenic stages has been proposed in colorectal carcinoma [57], melanoma [224] and bladder cancer [43], but these are malignancies in which biopsy material is easily obtained at different tumour stages. It is not yet possible to envisage a specific sequence in prostatic oncogenesis, but short sequences have been suggested [93]. Figure 1 gives a summary of genetic alterations associated with progression of prostate cancer. In fact, it is questionable whether there is a single genetic

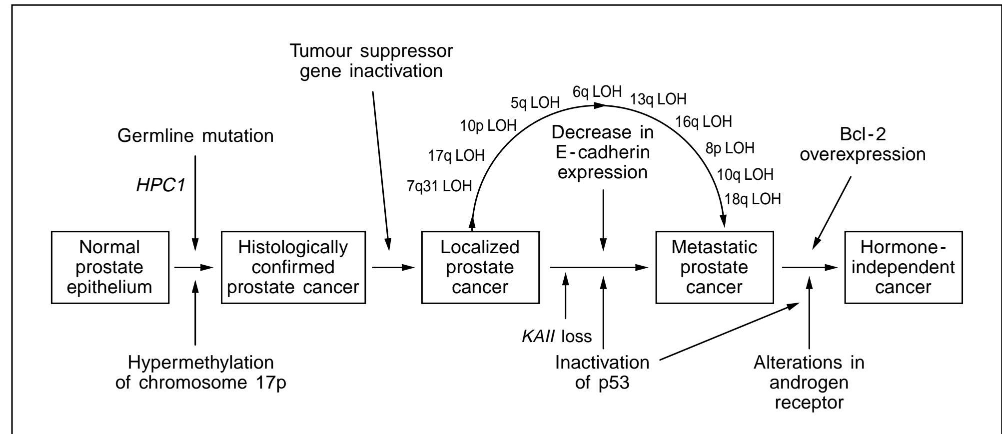

Fig. 1 Genetic alterations associated with progression of prostate cancer

model for prostate oncogenesis, given the biochemical, histological, clinical and geographic heterogeneity of this cancer.

Nevertheless, the different genetic alterations could quickly be fitted into place in this hypothetical scheme, if it is correct, by applying the polymerase chain reaction (PCR) technique to different morphological areas of paraffin-embedded tumour sections. This would allow the successive stages of prostatic tumourgenesis to be studied [12]. The phenotype of each cell is the result of interactions between its genetic potential and the environment, and genetic alterations are therefore necessary, but not sufficient, to account for the malignant phenotype of a cell. This is where the molecular model reaches its limits.

It is equally important to consider epigenetic phenomena in the development of cancer, as the state of neighbouring cells and the hormonal status of the patient also seem to be crucial in oncogenesis. The development of the prostate is closely regulated by multiple hormones and peptide growth factors, and the complex paracrine interactions between the epithelial and stromal cells involved are known to play a crucial role in the development of prostatic adenocarcinoma.

Genetic alterations and clinical applications

Clinical applications are currently limited but may become important in the near future.

Screening of subjects at risk

Identification of prostate cancer susceptibility genes will open up a new field of clinical applications, by allowing early diagnosis in “high-risk” individuals and improving the prognosis.

Identification of a specific group of patients

Prostate cancers are highly heterogeneous. The use of molecular markers to identify subgroups should open up a new approach to the diagnosis of cancers considered clinically and histologically equivalent but whose outcome is different. Molecular markers should also prove useful in medical decision-making when histopathological analysis is inconclusive at certain stages of tumour progression (principally in the early stages of oncogenesis). When used in tandem with recognized pathological characteristics, these new biological markers should help in screening for benign prostate lesions with a high risk of malignant transformation. In the near future screening for genetic alterations induced by unidentified specific prostate carcinogens may allow the identification of subpopulations at risk and lead to preventive measures, such as avoidance of exposure to the carcinogen by subjects at risk.

Prognosis

Prostate cancer exhibits a wide range of biological behaviour. Histological grade and disease extension are at present the most frequently used prognostic indicators. PSA related to tumour volume has a relative statistical predictive value for histological stage, but PSA alone cannot optimize the therapeutic choice. The prognostic variables used in prostate cancer cannot be used to predict the outcome of individual patients, or to optimize the treatment. Indeed, treatment depends mainly on the stage of the disease at the time of diagnosis and on potential for development, and new biological prognostic markers are needed to increase predictive reliability. In recent years, several additional biological tumour markers have been linked to prostate tumour prognosis. Potential prognostic variables have been reviewed by Gao et al. [70], and a number warrant further investigation. However, there is no general agreement on the best combination of these prognostic factors.

Cytogenetic and molecular biology techniques should soon allow us to correlate acquired or inborn alterations of the genome directly with the risk of tumour progression.

Results diverge in terms of both the frequencies of these alterations and their prognostic value. These discrepancies may result from the clinical, histological and ethnic heterogeneity of prostate cancer and hence imply differences in the characteristics of the tumours included in the different studies. Technical conditions and patient follow-up may also hinder comparability. It is therefore necessary to standardize, as far as possible, the methods of sampling and analysis of DNA, RNA and protein when assessing the prognostic value of certain alterations. The study population should also be large, and strictly defined, to permit between-study comparisons and data analysis in well-defined subgroups. Investigators should heed the outcome itself (relapse rate, overall survival, metastasis-free survival) rather than the combination of conventional factors of poor prognosis (histoprognostic grade and tumour stage). The need is for multiparametric, multivariate, and prospective studies with several years of follow-up.

Therapeutic prospects

Advances in our understanding of the molecular basis of cancers should yield novel therapeutic strategies. Following on from the discovery and characterization of genes whose products deregulate normal cells, it is reasonable to suppose that cancer therapy will one day involve "re-education" rather than elimination of the tumour cell.

Cancer gene therapy approaches can be divided into two types. One area of investigation involves ex vivo gene transfer to mediate tumour cell expression of immunostimulatory proteins. The second involves direct gene transfer into tumour cells in situ. Targetting strategies use a variety of delivery systems including retrovirus producer cells and adenovirus supernatants, under specific promoter control (PSA for the prostate), for the expression of cytotoxic gene products. The lack of specificity of conventional chemotherapy might be palliated by means of immunotherapy using drugs coupled to antibodies, and gene therapy using drug-activating genes (suicide genes) controlled by a specific tumour promoter. Transfection of the tumour suppressor gene *RB1* in in vitro tumour models and subsequent reimplantation in nude mice has shown that malignancy can effectively be reversed by means of gene therapy [18]. Therapeutic trials in prostate cancer are under way and promising results have been obtained [49, 86]. However, it is difficult to predict the feasibility and efficacy of these techniques in clinical practice. The consequences of normalizing the regulation of a genetic alteration (even one that occurs early) in a genetically and epigenetically deregulated patient remain to be determined.

Acknowledgements This work was supported by the Ligue Nationale de Lutte Contre le Cancer (LNCC); the Comités Régionaux des Hauts de Seine, du Val d'Oise et des Yvelines; and the Association pour la Recherche sur les Tumeurs Prostatiques (ARTP).

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