Chapter 10
Expression Signature

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Abstract The prostate gland can be the site of multiple neoplastic transformation events, many of which give rise only to latent prostate cancer that does not progress to clinically detectable disease.

While evidence of major subtypes of prostate cancer is lacking at the histopathological level, recent genomic analyses have provided increasing evidence for molecularly defined subtypes (Tomlins et al., Neoplasia 10(2):177–188, 2008; Palanisamy et al., Nat Med 16(7):793–798, 2010; Taylor et al., Cancer Cell 18(1):11–22, 2010) but expression profiling analyses of tumor specimens have not strictly defined molecular signatures associated with distinct subtypes that specifically correlate with disease outcome (Singh et al., J Androl 23(5):652–660, 2002a; Singh et al., Cancer Cell 1: 203–209, 2002b; Lapointe et al., Proc Natl Acad Sci USA 101(3):811–886, 2004; Tomlins et al., Nat Genet 39(1):41–51, 2007a; Tomlins et al., Nature 448(7153), 595–599, 2007b). However, oncogenomic pathway analyses that integrate analyses of gene expression, copy number alterations, and exon resequencing may provide a unified approach for distinguishing prostate cancer subtypes and stratifying patient outcome (Taylor et al., Cancer Cell 18(1):11–22, 2010).

Integrating "omics" analyses with epigenetics will probably allow the identification of true different subtypes of prostate cancers characterized by divergent biological behavior and/or response to therapy.

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This chapter aims to summarize the most exciting data emerging from recent genetic and translational studies on prostate cancer, potentially shedding new light on surprising aspects concerning its biology and extremely promising for the generation of more effective and safe new molecular therapies.

10.1 Advances in Prostate Cancer Genomics

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It is hard to summarize the spectacular advances made in cancer genomics in the last few years.

The emergence of Next Generation DNA and exome sequencing of malignant tumors is revealing thousands of mutations in every tumor type, many of which seem unique to each prostate cancer patient. This confirms that the word "cancer" is a figurative umbrella covering incredible spectra of diseases. This biological complexity justify the extraordinary hurdle to translate the results of basic research into real benefit for the single cancer patient (Barbieri et al. 2012).

A group of genes strongly correlates with prostate tumor differentiation stage, according to the Gleason score (Singh et al. 2002a). The gene expression data generated by DNA micro-arrays profiles predict with accuracy the patient evolution after prostatectomy. These data support the notion that the PCa clinical behavior is related to specific differences in gene expression profile that are detectable at the time of diagnosis.

This looks particularly promising also for the identification of new targets for therapy.

As an example, it has been found that the transmembrane serine protease called hepsin is specifically over-expressed in non-metastatic carcinoma cells, and PCa cell lines overexpressing hepsin show a dramatic reduction in growth and invasion, and increase of apoptosis. It has been then hypothesized that the decrease/loss of hepsin expression could be related with a poor prognosis of PCa and then hepsin could represent a potential target for prostate cancer gene therapy (Magee et al. 2001).

An integrated analysis of 218 primary and metastatic prostate cancers, 12 cell lines and xenografts, performed by assessment of DNA copy number, mRNA expression, and focused exon resequencing identified as expected, changes in the PI3K and androgen receptor (AR) pathways in nearly all metastatic samples and in a number of primary cancer tissue (Taylor et al. 2010).

Unexpectly, the nuclear receptor coactivator NCOA2 gene on the 8q13 was found mutated and acting as an oncogene in 11 % of primary tumors. NCOA2 and other regulators of nuclear receptor function such as NCOR2, are involved in AR pathway molecular signaling. This finding is of relevance, because it extends the potential

importance of AR pathway perturbation even to disease initiation, while AR gene amplification or mutation is generally restricted to metastatic, castration-resistant disease (Tomlins et al. 2007a, b).

Several other emerging candidate cancer genes are *SPTA1* and *ADAM18*. *ADAM18* encodes a disintegrin and metalloprotease domain family member involved in sperm function. ADAM proteins exert key cell–cell and cell–matrix interactions.

In addition, *HSPA2*, *HSPA5* and *HSP90AB1*, heat shock genes encoding Hsp70 and Hsp90 isoforms, which form a chaperone complex, and the potassium channel genes *KCNQ3* and *KCNT1, with putative negative* tumor cell growth regulating activity, have been found to harbor point-mutation in a percentage of prostate cancer. Their functional significance, however, is still to be determined (Barbieri et al. 2012).

Anyhow, it has emerged that overall somatic point mutations and protein-altering point mutations are uncommon in prostate cancer if compared with other malignant tumor types, such as glioblastoma, lung cancer and melanoma (Barbieri et al. 2012; Taylor et al. 2010; Kumar et al. 2011; Gimba and Barcinski 2003; Greenman et al. 2007; Pleasance et al. 2010a, b).

In addition, no single gene emerged as commonly mutated. TP53 and PTEN, which act as prostate cancer tumor suppressors (Dong 2006; Pourmand et al. 2007), showed preferentially copy-number loss rather than point mutation.

The genomic and clinical outcome data from one of this study population are made available as a public resource, with the aim that it may contribute to define clusters of low- and high-risk disease beyond Gleason score of tumors (Taylor et al. 2010).

Novel adaptive clinical trial designs, linking *oncogenomic* (genomic and proteomic) alterations to treatment response and survival, are needed to translate molecular advances into clinical practice.

Nowaday, they have already changed our understanding of prostate cancer, with a progressive shift to a omics-based disease stratification approach and to molecularly guided therapeutic intervention modalities.

Definition of genetic and translational context will provide the data sets required to derive new classification schemes and the generation of a "biological road map" of prostate cancer, favoring the formulation of treatments tailored on patient specific tumor biology (Johnston and Lawler 2012). The end-point of this process will be the transition from the poorly understood, clinically heterogeneous prostate cancer superfamily to a collection of homogeneous molecular subtypes with the development of biomarkers able to distinguishing aggressive from indolent disease (Barbieri et al. 2012).

This approach holds promise as a way to maximize the benefit of targeted treatments while minimizing unnecessary side effects, with a predictable positive implications also for health economics (Johnston and Lawler 2012).

10.2 Interplay Between Genetic and Epigenetic Events in Prostate Cancer

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The interplay between genetic and epigenetic events has a causative role in the development and progression of prostate cancer. In fact, loss or gains of several chromosomes have been reported at chromosomes 8p and 8q, loss at 5q, 6q,10q, 13q, 16q, 18 and gains at 1q, 3q, 7 and Xq12, as indicated in Fig. 10.1 (Ribeiro et al. 2006; Sun et al. 2007). Which genes might be affected by these genetic events on each chromosome is still object of investigation. For example gains and amplification at chromosome 8q may lead to overexpression of myc with increase in the proliferation of the epithelial prostate neoplastic cells. On the other hand loss of genes at 8p may determine the loss of the NKX3A gene whose activity consists in the regulation of prostate epithelial development (Fig. 10.1).

In the most aggressive histotypes, the loss of function of PTEN, RB1 and TP53 tumor suppressors, by allelic loss or mutation, has been found in advanced stage of the disease. Alterations of autocrine and paracrine growth factor signaling pathways are also very common, even if RAS mutations have been rarely reported, so far.

In more than half of the prostate cancers, chromosomal rearrangements involving oncogenic transcription factors of the ETS family have been reported (Kumar-Sinha et al. 2008; Tomlins et al 2005).

The major translocation reported involves chromosome 21 and creates a fusion gene, in which the androgen-responsive TMPRSS2 promoter induces the expression of the ERG transcription factor (Tomlins et al. 2005). Two different mechanisms, an internal deletion within the chromosome or a chromosomal rearrangement, in which a fragment of the chromosome 21, separating the two genes, is translocated elsewhere, could be envisaged at the basis of the translocation.

One of the genes involved in the chromosomal translocation, TMPRSS2 (androgen-regulated trans-membrane protease, serine 2), encodes for a serine

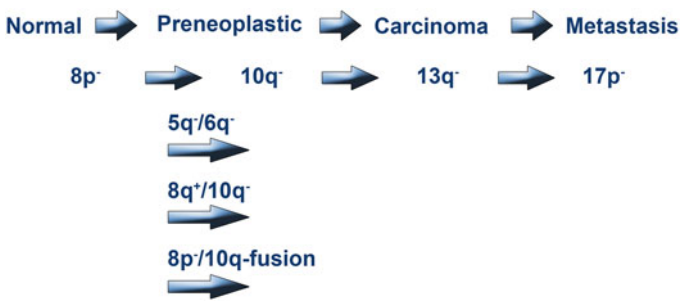

Fig. 10.1 Models of prostate cancer progression

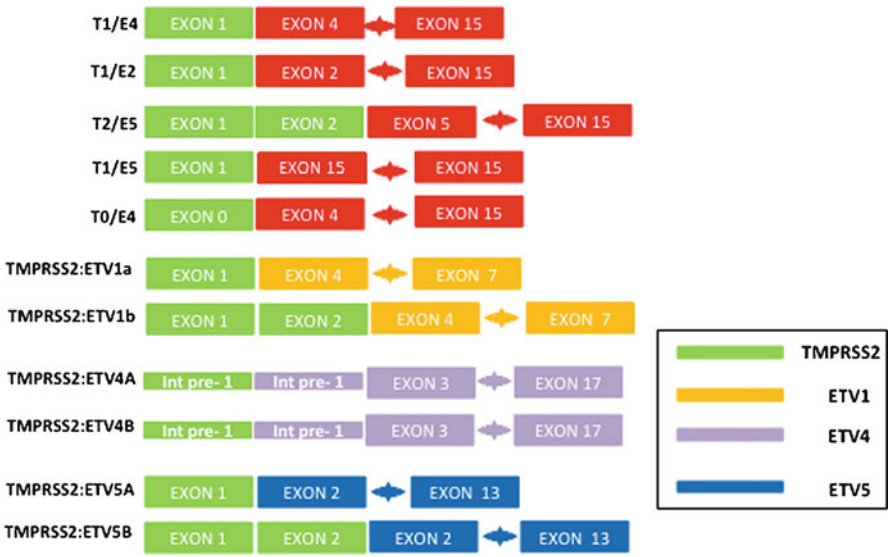

Fig. 10.2 Isoforms described to date of the TMRSS2-ERG fusion genes that give the idea of great instability of this rearrangement

protease secreted by prostate epithelial cells in an androgen-dependent manner (Afar et al. 2001), the other, ERG or ETV1, identified as member of the ETS family of oncogenes (Tomlins et al. 2005), has been previously classified as the most commonly overexpressed proto-oncogene in prostate cancer (72 % of all prostate cancer) (Petrovics et al. 2005). Both intra-chromosomal and inter-chromosomal genetic rearrangements create a fusion transcript involving ETS family members, whose activity is regulated by post-translational modifications.

The TMPRSS2 and ERG genes are roughly 3 megabases (Mb) distant on chromosome 21. In more than half of samples, fusion is the result of the deletion of the intervening DNA sequence, but fusion may also occur by a translocation (Yoshimoto et al. 2006; Tu et al. 2007). The exact points of DNA rupture, and the exons conserved in the fusion product, vary between patients and more than 20 TMPRSS2:ERG variants have been reported so far (Tomlins et al. 2005, 2006; Clark et al. 2007; Liu et al. 2007). Then, a nomenclature lists the variant transcripts, depending on which exons of the genes are involved (Clark et al. 2007). The most frequent variants result from the recombination between either exon 1 or exon 2 of TMPRSSR2 and exon 4 of ERG genes. Rarely, exons 2–5 have been reported. The fusion transcript including exon 1 of TMPRSS2 and exon 4 of ERG is one of the most described and identified as the T1/E4 following the above mentioned nomenclature (Clark et al. 2007) with a rate of up to 86 % among the reported fusions (Wang et al. 2006) (Fig. 10.2).

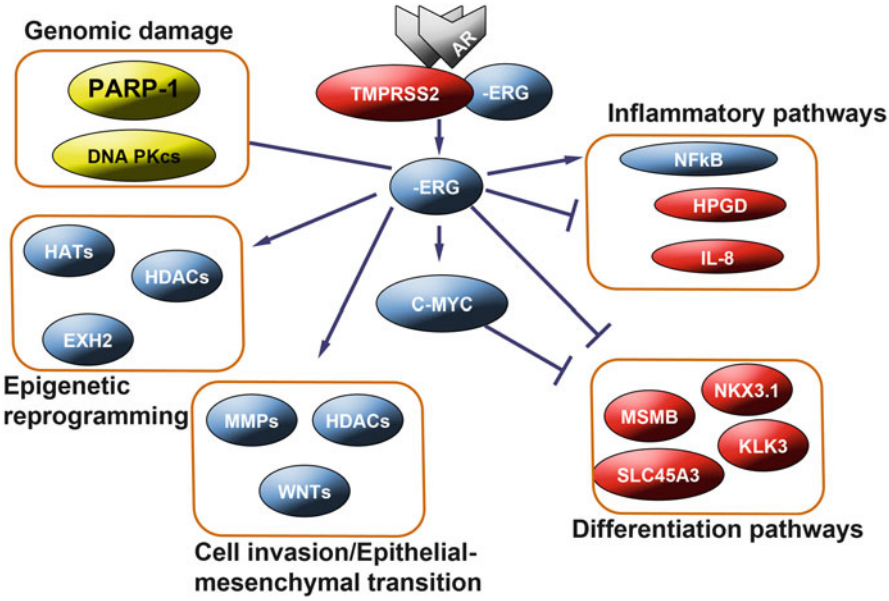

Fig. 10.3 ERG regulated prostate cancer pathways

The list of genes and the variants, involved in fusion transcripts, is continuously enlarging. In fact, new members of the ETS gene family (ETV4 and ETV5) have been reported in a few cases of prostate cancer (Tomlins et al. 2006; Helgeson et al. 2008). On the 5′ side of the translocation, new partners have also been described. A chimeric product derived from a variant isoform of TMPRSS2, which mapped 4 kb upstream of the more common start site has been reported (Lapointe et al. 2007). About 50 fusion partners for ETV1, comprising SLC5A3, HERV-K22q11.23, C15orf21, and HNRPA2B1 have been involved (Tomlins et al. 2007a, b; Helgeson et al. 2008). SLC5A3 recombine to ETV5, as well as to ETV1, but not to ERG (Tomlins et al. 2007a, b; Helgeson et al. 2008). Two additional fusion partners of ETV4 kallikrein 2 (KLK2) and calcium-activated nucleotidase 1 (CANT1) have been also reported (Hermans et al. 2008) (Fig. 10.3).

Overall, members of the ETS family are overexpressed in most prostate cancers and alternative mechanisms to gene fusions can be also envisaged. In fact, overexpression of ERG, in absence of fusion has been reported as well, but the underlying genetic mechanisms was not determined (Petrovics et al. 2005; Cai et al. 2007). Interestingly, androgen-dependent cases have been reported where the expression of androgen receptor and PSA levels are associated to the presence of TMPRSS2:ERG fusion transcript and to overexpression of the ERG gene. However, some androgen-independent cancers were found to harbour the TMPRSS2:ERG fusion transcript, in absence of the androgen receptor. Nevertheless, these tumors might have been

dependent from androgens at the beginning of the transformation process. FlI-1 and ETV4 have been found overexpressed in androgen-independent advanced prostate tumors.

Among the ETV1 fusion partners originally reported (Tomlins et al. 2007a, b) three of them, TMPRSS2, SLC5A3, and HERV-K22q11.23, appear to be androgen-responsive and two, C15orf21 and HNRPA2B1, drive the constitutive overexpression of ETV1 in the absence of androgen stimulation. In the next future, the interplay between clinical studies and the molecular biology understanding of the tumor should help to distinguish the course of the disease, in cases of cancer with different fusion proteins, and should help to correlate the response to androgen ablation treatments.

Fusion oncogenes of this type may explain how androgens come to drive cell proliferation in prostate cancers, instead of promoting cell differentiation, favouring cell survival and maintaining regulating secretory function as in the normal prostate gland.

Nevertheless, several parallel pathways of genetic alterations may exist in prostate cancer and key genetic changes may determine the aggressiveness of the single tumor. Even if it is true that prostate cancers develop through several steps, a better understanding of the sequential genetic events could help us to perform an early diagnosis and to select a personalized therapy.

10.2.1 Characterisation of TMPRSS2erg Protein

The TMPRSS2-ERG gene fusion generates a chimeric transcript that combine the prostate-specific promoter of the TMPRSS2 gene to the ERG oncogene open reading frame (ORF). Thus, the protein sequences have been predicted from the sequence of the fusion ORFs. Among the various fusion transcripts identified from the cDNA sequence, some are predicted to generate premature stop codons and to encode for a truncated protein, not functional. In some other cases, non-aminoacid sequence derived from TMPTSS2 is integrated in the hybrid ORF and therefore a fusion protein is not created (Clark et al. 2007).

10.2.2 Prevalence of Fusion Product Among Unselected Prostate Cancer Cases

The presence of a gene fusion product can be determined with different methods, like RT-PCR, that detect the level of RNA expression, like FISH, which measure the inappropriate juxtaposition of non-adjacent sequences or the breakage of a single gene and fusion to different chromosome sites, or like the array technology that

reveal the imbalance expression of individual exons. The assay used, the volume of cancer, the number of foci analysed and the number of chimeric variants studied in the screening panel may affect the rate and quality of the fusions reported so far. Moreover, a single cancer may have distinct foci that harbour different rearrangements involving separate genes, or no rearrangement at all. These data suggest that most of prostate cancers (more than 70 %) carry a fusion product (Hermans et al. 2006; Perner et al. 2006; Soller et al. 2006; Rajput et al. 2007; Tu et al. 2007; Nam et al. 2007). Since the number of variant species is continuously enlarging and the detection methods become always more sensitive, the proportion of prostate cancer samples containing more than one variant is predicted to increase progressively. Moreover, the heterogeneity of TMPRSS2:ERG gene fusion may account for the distinct foci of cancer that occur within a multifocal prostate cancer, which might represent different malignant clones and could, then, limit and delay the transfer to clinical use of the fusion products as putative biomarkers. Even if a complete characterization of the fusion products identified so far is still missing, an aggressive clinical behaviour has been reported together with the presence of blue-tinged mucin, a cribriform growth pattern, macronucleoli, intraductal tumor spread, and signet-ring cell features. Nevertheless, Gleason grade or stage, or PSA levels has not been associated with a particular type of fusion gene, yet (Perner et al. 2006; Wang et al. 2006; Lapointe et al. 2007; Rajput et al. 2007; Tu et al. 2007).

10.2.3 Clinical Significance of TMPRSS2:Erg Gene Fusion

Histologic grade (measured by the Gleason scoring system), tumor stage and PSA level at diagnosis are considered reliable prognostic factors for men with localised prostate cancer, so far. Men with tumors of higher grade (Gleason 8–10), stage (T3–T4), or PSA level (420 ng/ml) experience relatively high rates of progression to metastasis, when compared with men with tumors of lower grade, local stage, or low PSA level. Novel biomarkers are urgently needed in order to help to select specific treatments for individuals.

In conclusion, the original discovery by Tomlins et al. in 2005 of a frequent genetic event in prostate cancers has highlighted the role of chromosomal rearrangements in the aetiologies of common solid tumors. The importance of this genetic fusion have been confirmed and the classes of fusion genes, that are now considered among the most frequent recurrent rearrangements in cancer, have been enlarging. The consequence of the various chimeric transcripts is the overexpression of a member of the ETS family of oncogenes that tend to lose the androgen dependence in advanced disease after an initial phase of androgen control, lost later in advanced disease. The activation of this pathway may be causative to prostate carcinogenesis, but the clinical implication of the various fusion products is still under characterization. All the efforts are, in fact, now focalized to classify patients with different risk, identify a screening test and finally target the ETS family oncogene to open the way to novel molecular therapies.

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