Chapter 2
Molecular Determinants of Cancer-Related Inflammation

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Abstract Tumor cells communicate with the cells of their microenvironment via a series of molecular and cellular interactions to aid their progression to a malignant state and ultimately their metastatic spread. Of the cells in the microenvironment with a key role in cancer development, tumor associated macrophages (TAMs) are among the most notable. Tumor cells release a range of chemokines, cytokines and growth factors to attract macrophages, and these in turn release numerous factors (e.g. VEGF, MMP-9 and EGF) that are implicated in invasion-promoting processes such as tumor cell growth, flicking of the angiogenic switch and immunosuppression (Rogers and Holen, J Transl Med 9:177, 2011).

2.1 Background and Aims

A long time ago, Virchow hypothesized the existence of an interplay between inflammation and cancer (Balkwill and Mantovani 2001). Nowadays, i*t has been accepted* that at least 20 % of all human cancers (Vykhovanets et al. 2011) share a common causative *inflammatory* background, and chronic inflammatory states are emerging as having a relevant role also in prostate carcinogenesis. Histology has confirmed the strong association between morphological evidence of chronic inflammation, pre-malignant, and malignant changes in the prostatic epithelium (MacLennan et al. 2006). Chronic inflammatory cells as lymphocytes, tumor-associated macrophages (TAM), mast cells, dendritic cells, natural killer (NK) cells, exert their defensive activity via a plethora of molecules, comprising pro-inflammatory cytokines, growth factors, reactive oxygen species, interferons (IFNs)

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and proteases, membrane perforating agents, matrix metalloproteinase (MMP), and enzymes like as cyclooxygenase-2 (COX-2). They in turn interact with transcription factors as Nuclear Factor κB (NF-κB) (Vendramini-Costa and Carvalho 2012). The hyperactivation of NF-κB maintains an inflammatory status in the prostate(Vykhovanets et al. 2008), and is considered a potential molecular bridge between inflammation and prostate cancer (Karin 2006).

Besides the underlying causative environmental and endogenous factors, the stable umbalance of proinflammatory pathways active in chronic inflammation may lead to the establishment of prostatic regenerative lesions ending to a peculiar type of atrophy, defined as "proliferative inflammatory atrophy (PIA)", which is thought to contribute to the rise of risk for prostate cancer. The relationship between prostate cancer onset and progression and inflammation is being explored at genetic and epigenetic level (Vykhovanets et al. 2011).

Research in this area at present is particularly active, considering its possible beneficial fall-out on population: as an example, we could imagine that the administration of specific anti-inflammatory agents in men may reduce the risk of prostate cancer development.

This chapter will present an overview of the recent knowledge on the role of chronic inflammation in the pathogenesis and/or therapy outcome of prostate preneoplastic lesions and prostate cancer.

Chronic inflammation is associated with the development of several cases of head&neck, esophagus, stomach, colon, liver and urinary bladder cancer (Sugar 2006; Coghill et al. 2011). Besides its initiating causes (either infectious or non-infectious inflammatory diseases, and/or environmental/epigenetic factors), inflammation enhances cellular turnover of the injured cells, as the result of tissue repair processes.

Epidemiological, genetic and molecular findings accumulating from more than a decade, indicate that chronical prostatitis correlate with an increased risk of prostate cancer (PCa), supporting the hypothesis that inflammation may be a cause of neoplastic transformation also for prostatic tissue (Sfanos and De Marzo 2012).

Prostatitis is actually classified into four distinct entities (Murphy et al. 2009).

Category I: acute bacterial prostatitis, due to a uropathogen, often with systemic symptoms.

Category II: chronic bacterial prostatitis due to recurrent episodes of documented infections with the same uropathogen.

Category III: chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), lacking a documented infection from uropathogens, ending with neurological injury with or without pelvic floor dysfunction.

Category IV: asymptomatic inflammatory prostatitis, of uncertain clinical and biological significance.

Acute prostatitis is infrequent; sometimes (in about 10 % of cases) it may result in a chronic bacterial prostatitis and further 10 % into chronic pelvic pain syndrome (Wagenlehner et al. 2013).

Viruses, fungi, mycobacteria and parasites may cause prostatitis (De Marzo et al. 2007), but the microbial agents responsible of most cases of bacterial prostatitis are represented by *Escherichia coli*, coagulase-negative *Enterococcus* spp. (de Kleijn et al. 1997; Arnow and Flaherty 1997) and Corynebacterium glucuronolyticum.

Chronic non-bacterial prostatitis is much more frequent. They are underdiagnosed with respect to the infectious ones, so that an "histological prostatitis" represents an accidental finding on biopsy for prostate cancer (Stimac et al. 2009; Gui-zhong et al. 2011; Ugurlu et al. 2010; Fujita et al. 2011) or benign prostatic hyperplasia (BPH) (Nickel et al. 1999; De Marzo et al. 2007).

The manifold non-infectious causes of prostate chronic inflammation encompass (De Marzo et al. 2007; Sfanos and De Marzo 2012) hormonal alterations, that may lead to architectural alterations predisposing prostatic tissue to inflammation and physical trauma, particularly related to corpora amylacea, that are thought to represent remnants of past acute inflammatory events, and are composed of organic matrix comprising proteins involved in acute inflammation, such as lactoferrin, myeloperoxidase and α-defensins. These proteins, in turn, may induce the overexpression of stress-proteins by prostate cells (Sfanos et al. 2009).

Other inducers of chronic inflammation are several urine metabolites, which overactivate inflammatory cells in prostate tissue of patients suffering for urine reflux, and dietary and/or environmental carcinogens, reaching the prostate through urine reflux and/or blood.

Interestingly, racial and geographical difference in the incidence of prostatitis have been reported and they paralleled those observed for prostate cancer, with the highest prevalence in African American men and the lesser in Asian men. This, further support the hypothesis of a causative role of inflammation in prostate cancer pathogenesis (Wallace et al. 2008).

Indeed, bacterial and non-infectious chronic prostatitis may lead to prostate cell hyperproliferation, and this event seems to be correlated with the emergence of benign prostatic hyperplasia (BPH) (Nickel 2008).

Chronic inflammation is thought to induce the antigen-presenting capacity of prostatic stromal cells, via the overproduction of the prostate growth-promoting chemokine IL-8 induced by Th1 and Th17 cell-derived inflammatory cytokines (Steiner et al. 2003).

Th17 cells belong to a $CD4^+$ effector T cell lineage which develops through distinct cytokine signals [specifically interleukin (IL)-23] and produce IL-17.

Th17 cells mediate a number of autoimmune diseases, and seem to have a role in inflammation-associated cancer (Weaver et al. 2006; Bettelli et al. 2007).

Long-lasting inflammation induces also the up-regulation of the vitamin D receptor (VDR), which agonizes intra-prostatic androgen signalling by exerting immunostimulating and co-inflammatory effects. BPH stromal cells express high levels of VDR, further supporting the role of chronic inflammation in BPH pathogenesis and their usefulness as therapeutic targets for pharmacological treatment of BPH.

Moreover, chronic inflammation is responsible for the condition termed "Proliferative inflammatory atrophy (PIA)".

Long-standing PIA gradually lost the function of cellular detoxification, by silencing of glutathione-S transferase. This favor an increased susceptibility of prostatic epithelial cells to genomic damage by inflammatory oxidants or nutritional carcinogens, assisted by several other inflammation-induced proteins, as the macrophage scavenger receptor 1 and Toll-like receptor-4.

Prostatitis-derived PIA, then, may gradually transitate to prostatic intraepithelial neoplasia, and take a part in the multifactorial background leading to prostate cancer (Wagenlehner et al. 2007).

PIA, is morphologically characterized by the presence of atrophic-regenerating epithelial cells (De Marzo et al. 1999) that may occupy large regions of the prostate. In these areas, it is frequent the finding of high-grade PIN, (De Marzo et al. 2007; Nelson et al. 2003; Putzi and De Marzo 2000), with variable degree of transitions between PIA, PIN and true prostate cancer (Putzi and De Marzo 2000; Wang et al. 2009b).

PIA has some of the hallmark gene expression changes found in prostate cancer and PIN. For example, two genes which are highly expressed in normal prostate epithelium and frequently down-regulated or absent in PIN and prostate cancer, NKX3.1 and p27, are down-regulated in prostate atrophy (De Marzo et al. 1999, 2007; Bethel et al. 2006), showing, in turn, increased immunostaining for p53, Ki-67, COX-2 and glutathione *S*-transferase-π (GSTP1), particularly in areas adjacent to inflammation (Wang et al. 2009a).

As atrophy/PIA is highly prevalent in the peripheral zone of the prostate, it is possible that a proportion of PIN and/or prostate cancer may originate in these areas (Nakayama et al. 2003).

Recently it has been reported that chronic inflammation in benign tissue was predictive of a higher risk for prostate cancer diagnosis and, specifically, with higher-grade (Gleason score 7–10) disease. The risk of prostate cancer and high-grade prostate cancer also increased with the number of biopsies that were found to contain chronic inflammation

Moreover, several lines of evidence indicate that inflammation in and around prostate cancer is associated with worse disease outcome (Karja et al. 2005; Nonomura et al. 2011).

Among the major effectors of the dangerous potential of inflammation on cancer predisposition are cytokines.

Besides many protean roles in immune system, hematopoiesis, and key biological functions (Sun et al. 2007), these low-molecular weight molecules interact with several types of cells and proteins within the tumor environment (De Marzo et al. 2007; Coussens and Werb 2002), *and* have been associated from long time with the biology and prognosis of several cancer.

As an example, the production of cyclooxygenase (COX) enzymes due to inflammation may alter the environment of precancerous tissues (Mantovani et al. 2008; Coussens and Werb 2002), being important in the pathogenesis of prostate cancer (Wang and Dubois 2006).

Interleukin-4 (IL-4), IL-6 and IL-10 are frequently elevated in blood of prostate cancer patients and, increased levels of transforming growth factor beta (TGFβ), have been detected in serum and in primary and metastatic prostate cancer tissue samples (Perry et al. 1997).

Whereas in normal cells, TGFβ stops cell proliferation, induces differentiation, and/or apoptosis; in cancer cells, mutations of the TGFβ pathway confer resistance to growth inhibition by TGFβ, resulting in uncontrolled cell proliferation. The increase of TGFβ production in cancer cells also stimulates angiogenesis and suppresses the activities of infiltrating immune cells, thereby facilitating the tumor to escape from immunosurveillance. On the other hand, prostate epithelial cancer cells show loss-of-expression of T cell cytolytic promoting IL-7. This causes a severe depletion of prostate-associated lymphocytes (Tang et al. 1997). As an antagonistic relationship has been hypothesized between TGF β and IL-7, it has hypothesized that their level of expression may be used in combination with Gleason score and pre-treatment PSA level to predict prognosis of prostate cancer patients (Tang et al. 1997; Dubinett et al. 1995).

The preliminary results indicate that this addition, at least, doubled the prognostic predictive ability in respect to the use of the sole Gleason score and pre-treatment PSA (Dubinett et al. 1995; Schroten et al. 2012).

Several additional studies have focused, instead, on the specific targeting of the IL-6 as alternative/adjunctive therapy in aggressive, therapy-resistant prostate cancers.

IL-6 is a multifunctional cytokine produced by multiple cell types, including macrophages, endothelial cells and T lymphocytes; it is involved in innate and adaptive inflammatory processes, including acute-phase inflammatory response (Hirano 1992).

When deregulated, IL-6 intervenes in multiple disease processes, including autoimmune disorders, rheumatoid arthritis, osteoporosis, psoriasis, diabetes, atherosclerosis and cancer (Ishihara and Hirano 2002; Kishimoto 2005).

In prostate cells, IL-6 contributes to the activation of androgen receptor (AR) (Culig and Puhr 2012) High-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer cells (Hobisch et al. 2000) overexpress IL-6 and its receptor IL6-R and, patients suffering from metastatic and hormone-refractory prostate cancers, show high IL-6 plasmatic levels (Smith et al. 2001). The linking between IL-6 and prostate cancer morbidity (Twillie et al. 1995), could reside on the stabilization of an ‘epigenetic transformed’ state of prostate cancer cells, due to the cooperative action of inflammation/IL-6 production, STAT3 and NF-κB activation (Iliopoulos et al. 2009).

Recently, 6 mg/kg anti-IL-6 antibody CNTO328 were administered i.v. every 2 weeks for 12 cycles to 53 patients with castration-resistant prostate cancer pre-treated with taxane chemotherapy. Tumor response was assessed after every three cycles. Primary end- point was PSA response rate defined as a 50 % reduction. Declining C-reactive protein levels during treatment may reflect biological activity.

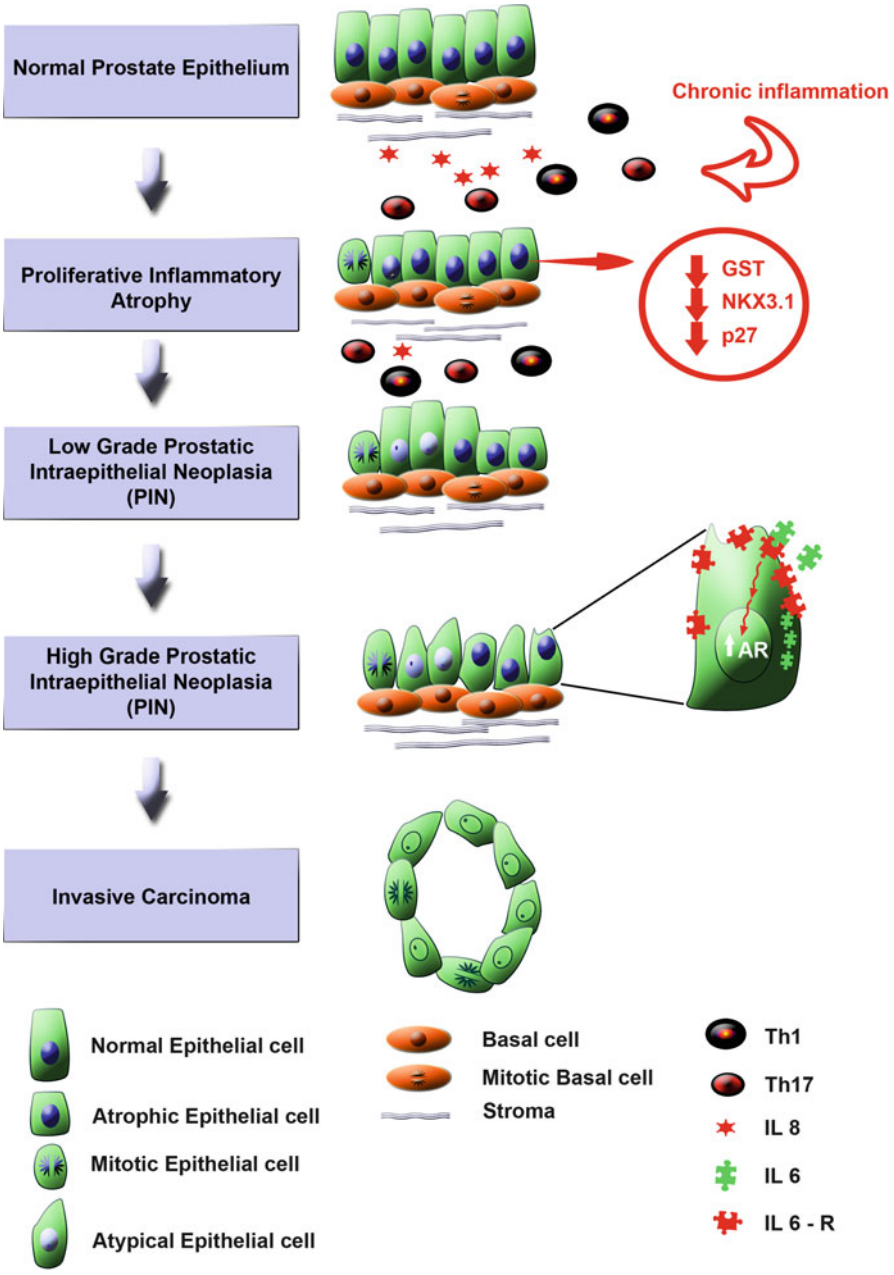

Fig. 2.1 Inflammatory background in prostate carcinogenesis. Chronic inflammation is considered to influence the antigen-presenting capacity of prostatic stromal cells, by the overproduction of the prostate growth promoting chemokine IL8, induced by Th1 and Th17 cells. The stable unbalance of proinflammatory pathways activated in chronic inflammation may lead to the formation of prostatic regenerative lesions, such as a peculiar type of atrophy, defined as

Despite evidence of CNTO-mediated IL-6 inhibition, elevated baseline IL-6 levels portended a poor prognosis (Sfanos and De Marzo 2012). These represent only preliminary data but, considering the potential contribution of IL-6 to therapy for progressing prostate cancers, this cytokine is actually regarded with particular interest for applied prostate cancer research.

Interestingly, it has been found that serum concentrations of IL-6-family cytokines were reduced significantly in animals fed with a tomato-enriched diet. As well, the anti-inflammatory omega 3 PUFA has been associated with a decreased risk of PC (Fradet et al. 2009).

Another inflammatory cytokine of possible significance, as potential mediator between prostatic inflammation pathways and prostate carcinogenesis, is the macrophage inhibitory cytokine 1 (MIC-1), which belongs to the transforming growth factor-β (TGF-β) superfamily (Bootcov et al. 1997).

MIC-1, also known as prostate-derived factor (PDF) or growth differentiation factor-15 (GDF-15), was first identified in activated macrophages (Bootcov et al. 1997) and has been associated with the progression of various types of diseases (Fig. 2.1).

In cancer, macrophages migrate from the circulation into the tissue, and return to the bloodstream or lymphatic system after having phagocytated tumor debris (Faber et al. 2012).

Macrophages are essential in the processes of migration, invasion and tumor metastasis (Stewart et al. 2004; Condeelis and Pollard 2006; Roorda et al. 2009).

As for IL-6, the increased expression of MIC-1 has been associated with a variety of tumors, including breast, gastric, colorectal (Senapati et al. 2010; Breit et al. 2011) and prostate cancer and, high serum levels of MIC-1, have shown to predict poor prognosis of prostate cancer patients (Nakamura et al. 2003; Cheung et al. 2004; Brown et al. 2009).

The MIC-1 gene has emerged as an ideal key candidate to explain the link between macrophage-linked inflammation and prostate cancer pathogenesis (Karan et al. 2009).

The expression of MIC-1 has been reported in conjunction of infiltrating lymphocytes in non-neoplastic human prostate tissues (Paralkar et al. 1998; Bostwick et al. 2003). This has to be considered an early response to inflammation in prostate, which, in the long-time, may enhance cell proliferation (Bootcov et al. 1997; Chen et al. 2007).

Fig. 2.1 (continued) "proliferative inflammatory atrophy (PIA)", that shows an increased susceptibility of prostatic epithelial cells to genomic damage by inflammatory oxidants or nutritional carcinogens, linked to the lost of cellular detoxification, caused by the silencing of glutathione S transferase. Moreover, PIA shows the same gene expression changes found in prostate cancer and PIN, such as downregulation of NKX3.1 and p27. Therefore, PIA gradually transitates to prostatic intraepithelial neoplasia, and take part in the background leading to prostate cancer. Inflammation influences cancer predisposition by production of cytokines. In particular, IL-6 regulates positively the expression of androgen receptor (AR) and is overexpressed in PIN and prostate cancer cells

Macrophages were identified in both epithelium and the stromal area of inflammation-associated to human benign prostatic hyperplasia (BPH) tissues, suggesting that they might play roles in BPH development. Yet the underlying mechanisms remain unclear. New insights for alternative therapeutic approach to counteract BPH via inflammatory signaling pathways (Lu et al. 2012), may thus be provided.

The finding of an autocrine-paracrine positive loop between MIC-1, IL-1β and TNF-α in the human LNCaP prostate cancer cell line, has suggested that MIC-1 overexpression could play a critical role also in the in the early stages of prostate cancer development (Bootcov et al. 1997). The glandular and peri-glandular CD68+ macrophages accumulation in PIA lesions strength the link between the macrophage-rich inflammatory microenvironment and prostate cancer development (Vykhovanets et al. 2008).

This is further supported by the observation that (De Marzo et al. 2007; Platz and De Marzo 2004) prostate cancer is frequently associated with an increased prostate tissue susceptibility to inflammatory injury/infections.

Of additional interest, the overexpression of MIC-1 has been also described during the progression to androgen-independent and metastatic prostate cancers, associated with a poor outcome of patients. In PC3 cells, high levels of MIC-1 were associated with the acquisition of epithelial-mesenchymal transition, higher invasive capacity and docetaxel resistance. These phenomena were in large extent reversed through MIC-1, which proved also effective in promoting the docetaxel-induced cytotoxic effects both on the stem cell-like side population and the non-side population, thus suggesting a promising improving effect of MIC-1 downregulation on the efficacy of current chemotherapies for aggressive prostate cancer (Mimeault et al. 2013).

Moreover, in model studies, macrophages have shown to be sensitive to bis-phosphonates, as do osteoclasts, which belong to the same cell lineage, reversing their phenotype from pro-tumoral CD204(+) M2 to tumoricidal CD68(+) M1 upon treatment with zoledronic acid (Rogers and Holen 2011; Fujii et al. 2013).

These exciting results necessitate of further validation on large series of cases. Nevertheless, they indicate that also in prostate cancer, as it is progressively being shown in most of solid cancers (Stewart et al. 2004), stromal cells and their products are determinant for epithelial neoplastic transformation (Pupa et al. 2002). The alteration of the tumor microenvironment homeostasis has a determinant impact on tissue architecture, adhesion, apoptosis and cell proliferation regulation, favoring the shifting toward oncogenic change (Stewart et al. 2004) and conditioning the response to cytotoxic therapies and prognosis of patients.

The reciprocal interaction between the multiple effectors of inflammation could be considered "the epigenetic framework for tumor progression" (Huang and Ingber 2006) and, as such, it represents a potentially modifiable scenario.

Dietary or medicinal intake of anti-inflammatory compounds, as NSAID (Jafari et al. 2009), soy and green tea, are being increasingly proposed to reduce prostate cancer risk by human epidemiology studies and in animal studies (Hsu et al. 2010).

Similarly, in prostate cancer cell lines, the treatment with phytoestrogens genistein and daidzein resulted in demethylation of GSTP1 and ephrin B2 (EPHB2) promoter regions (Vardi et al. 2010) confirming that the protective effects of soy in prostate cancer prevention may involve epigenetic modifications to DNA.

The promise that the malignant phenotype can be reversed through the correction of tumor microenvironment features (Kenny and Bissell 2003), make this one of the most promising and innovative experimental fields on prostate cancer treatment and, the emerging data at this regard, could provide us with a more comprehensive view of prostate cancerogenesis.

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