

From Normal Cells to Malignancy: Distinct Role of Pro-inflammatory Factors and Cellular Redox Mechanisms

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Abstract

The genesis of many solid cancers is a complex, multistep process that includes cellular neoplastic transformation, resistance to apoptosis, loss of control of cell cycle, angiogenesis and acquisition of invasive properties. Among a number of factors, the simultaneous existence of chronic inflammatory mechanism and down-regulation of antioxidant defense mechanism of cells are emerging as major causes of neoplastic transformation and the progression of many solid cancers. The longer the inflammation persists, higher the risk of developing many ages related malignancies such as organs of colon, stomach and prostate the Concurrent occurrence of these processes that may affect DNA mutations in cells by excessive generation of free radicals, Reactive Oxygen Species (ROS) and other active intermediates that exceed the limit of the cells ability to neutralize it. Chronic inflammatory conditions may activate a variety of pro-tumorigenic activities, such as stimulation of proliferative pathway, chemotactic activity, increased invasive potential of cells and angiogenesis. However, many of the antioxidants or cellular redox molecules play a crucial role in maintaining cellular homeostasis and response to oxidative damage but down-regulation of some of the cellular molecules of this process may lead to malignant transformation. We provide an overview of the possible mechanism(s) of interaction of pro-inflammatory factors in down-regulating the antioxidant and cellular redox mechanism(s) making cells susceptible to carcinogenesis. The elucidation of specific effects and interactions of these factors may provide the opportunity for the identification of new target molecules at the early stage of human malignancies.

Keywords: Inflammation; Antioxidant; Cellular redox; Nuclear factor-kappaB; Malignant transformation; Chemokines and chemokine-receptors

Introduction

Many human organs can take several years to turn malignant and have many causes. Cancer is more common in many industrialized nations, but there has been a growth in cancer rates in developing countries too, particularly as these nations adopt the diet and lifestyle habits of industrialized countries [1]. Over one million people in the United States get cancer every year. Anyone can get cancer at any age; however, about 80 percent of all cancers occur in people over the age of fifty-five and above [2]. The four most common cancers that account for over 50 percent of total cancer cases in the United States are: lung, colon/rectum, breast and prostate cancers [2].

Several factors both inside and outside of the body may contribute to the development of many cancer types. Many of these solid cancers were initially thought to be genetic diseases but research in the last decade has proven that cancer is predominantly an environmental disease with 80-90% of cases due to environmental and lifestyle factors, where as only 5-10% are caused by genetics alterations [3]. Some common environmental factors that lead to cancer that includes: tobacco (25-30%) [4], diet and obesity (30-35%) [5], infections, radiation and direct exposure to other environmental pollutants (15-20%) [6-8].

The progression human malignancies involve multistep processes and are accomplished by the combined effects of alterations of many physiological and pathological signaling processes [9]. Among a number of different biochemical events, the existence of chronic inflammation persistence in development of cancer has been gaining much attention in the case of stomach, colon as well as prostate

cancers [10,11]. Prolonged exposure to environmental factors generates excessive expression of pro-inflammatory genes that leads to alteration of the expression and function of oncogenes and/or tumor suppressor genes either due to epigenetic mutations or loss of expression of antioxidant molecules [12-16]. Constitutive activation of some common inflammatory mediators including chemokines, IL-8, IL-6, reactive oxygen species nitrogen species (RONS), cyclooxygenase-2 (COX-2) and nuclear factor (NF)- κ B are known to maintain cellular conditions favorable for malignant progression [17-19]. In many established solid cancers, the tumor microenvironment is well maintained by these inflammatory factors for tumor cell proliferation, survival and metastasis. Much of the published literature has highlighted the important role of inflammatory molecules in progression of these malignancies, whereas present literature related to the cellular redox sensitive mechanism in malignant transformation are not clearly explained yet. Although present literature has shown that down regulation of some of these factors in a number of solid malignancies and supplementation of chemo-preventive agents or antioxidant agents reduced the tumor burden [20,21]. In this review, we

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further provide an uncovered connection of the specific inflammatory and oxidant damage mechanism in recent development role of micro-RNAs in malignant transformation. The elucidation of specific effects and interactions of these various factors may provide the opportunity to identify new target molecules that leads to improve a diagnosis and treatment of many types of cancers.

Role of ROS in carcinogenesis

Reactive oxygen species (ROS) and reactive nitrogen species (collectively RONS) are highly reactive radicals which play an important role in the innate immune system [22]. The main feature of many cancer cells is a persistent to the oxidative state that leads to activation of intrinsic oxidative stress signaling [22]. Cancer cells have higher levels of reactive oxygen species than normal cells, and ROS are responsible for the maintenance of the many age related cancer phenotypes such as prostate and colon cancers [23-24]. Persistent ROS stress may induce adaptive stress responses, enabling cancer cells to survive with high levels of ROS and maintain cellular viability [25]. Although precise cancer cell survival mechanism is not yet known and how ROS acts as a “Double-Edged Sword”. Since the innate immune system comprises the cells to defend the host from infection or damage, in a non-specific manner. This means, cells of the innate system recognize and respond to host in a generic way, but unlike the adaptive immune system, it does not confer long-lasting or protective immunity to the infection [26]. Innate immune systems provide immediate defense, and are found in all classes of plant and animal life. In response to a stimulus, for example phagocytic cells release RONS and non-phagocytic cells produces RONS by pro-inflammatory cytokines and chemokines such as IFN γ , TNF α and IL1 β [26]. Such induction occurs at the transcriptional level through the activation of many transcription factors. The cytotoxic effects of NO (nitric oxide) are partly due to the production of peroxynitrite, a reactive oxidant formed by the rapid reaction of NO and superoxide [27]. The production of RONS by phagocytes induces cell death by phagocytic destruction and apoptosis, for instance oxidative stress induces p53 protein accumulation in prostate cancer cells directing them to die by apoptosis [29,30]. On the other hand, up-regulation of RONS, increased oxidative stress that may contribute to carcinogenesis [30]. RONS expression and its activity are up-regulated in several experimental models [31]. In fact, RONS activation is increased and its expression correlates with dysregulation of cellular redox potential and the degree of malignancy [32].

Increased expression of RONS was more pronounced in high-grade tumors in both the tumor vasculature and in peri-tumoral areas [33,34]. RONS activity up-regulated in prostate and colon cancers are well known, and lead to DNA damage and aberrant DNA cross-linking, thereby causing genomic instability such as inhibition of p53 protein transcriptional activity [35,36]. It is therefore conceivable that with prolonged exposure of cells to higher concentrations of RONS leads to chronic inflammatory process, and oncogenic progression in age related malignancies [36]. For example, epidermal growth factor receptor (EGFR), Akt and ERK activation are well known regulator of ROS-dependent cell proliferation and anti-apoptotic pathways [37,38]. RONS can post-translationally modify and inactivate the retinoblastoma1 tumor suppressor protein and thus lead to support tumor cell proliferation [39]. Furthermore, elevated RONS can increase angiogenesis and transcriptional activation of oncogenes [40]. Noticeably, a wide range of *in-vitro* and *in-vivo* models showed that RONS signaling can induce COX-2 and MAPK signaling, which itself is a potential link between inflammation and cancer [41]. A possible

mechanism mediated by environmental factors in oncogenic response is shown in Figure 1.

Molecular link of Inflammation and cancer related risk factors

In the last several years efforts have been made to shed new light on molecular and cellular signaling circuits linking inflammation and cancer [42]. Two major pathways have been well identified. (A) The Intrinsic pathway, in which genetic events cause neoplasia initiate the expression of inflammation-related molecules which would guide the construction of an inflammatory microenvironment. (B) In the extrinsic pathway inflammatory conditions facilitate cancer development [43]. The triggers of chronic inflammation increase cancer risk or progression include infections (e.g. *H. pylori* for gastric cancer and mucosal lymphoma; papilloma virus and hepatitis viruses for cervical and liver carcinoma, respectively), autoimmune diseases (e.g. inflammatory bowel disease for colon cancer) and inflammatory conditions of uncertain origins (e.g. prostatitis and prostatic intraepithelial precursor for prostate cancer) [44-47]. In both the above pathways, orchestrators of many molecules including, transcription factors and several pro-inflammatory factors such as IL-8, IL-6 and SDF-1, cause cancer related inflammation and tumor progression [48-52].

Contributions of potential genetic and environmental risk factors for the onset of cancer are identified at the molecular level. Moreover the distribution and rise prevention of the disease have been identified in several animal studies and did not give a final outcome of the connection of these mechanism. Some genome-wide studies identified the genes that were involved in the common process of inflammatory responses. However they do not correlate their molecular links in malignant transformation [53]. Examining the impact of inflammation and cancer related risk factot in malignant transformation remains a challenge for scientists due to the lack of appropriate animal models. A possible signaling mechanism in activation of pro-inflammatory mediators in development of cancer is described in Figure 2.

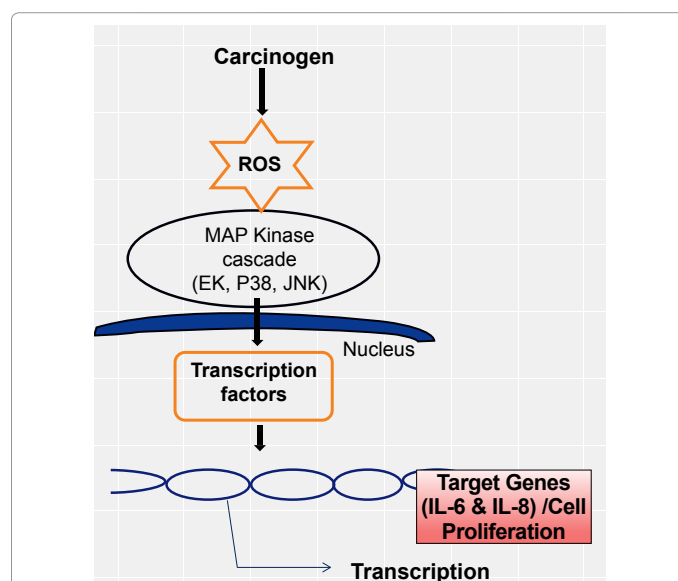


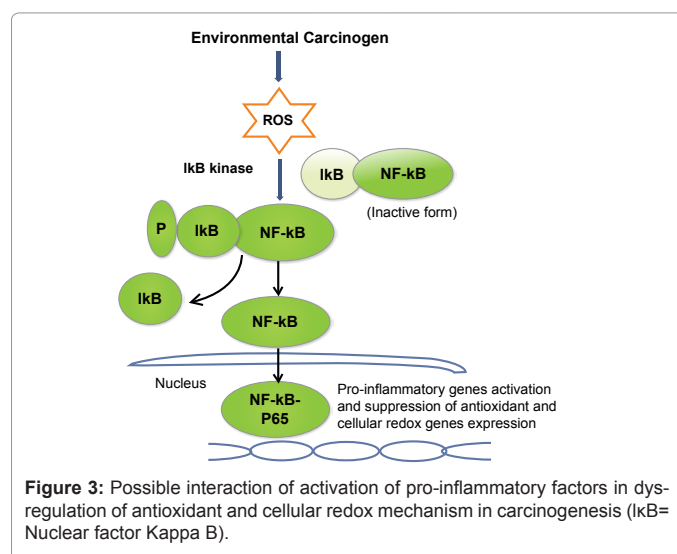
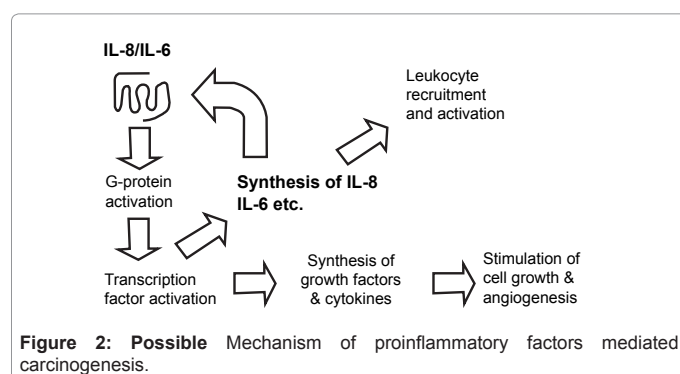
Figure 1: A possible interaction between environmental factors and ROS in activation of proinflammatory factors in carcinogenesis.

The link between pro-inflammatory pathway and cellular redox balance: New dilemma of nuclear factor- κ B (NF- κ B) pathway in this mechanism

The epithelium is a major target not only as an inert barrier, but it is also a major participant in signaling mechanisms during development and patho-physiological conditions [54]. Therefore, any damage caused to the epithelium can adversely affect its normal physiology and signaling processes. The major functions of the epithelium include: (i) it is a dynamic physiological barrier to diffusion and osmotic processes; (ii) it provides an integral metabolic function by synthesizing and degrading chemical components either endogenously produced or exogenously introduced; and (iii) it possesses a secretory property to produce chemokines, hormones, growth factors and enzymes [55,56]. This underlines the significance of a physiologically competent of the epithelium, because metabolic failure or noxious damage by many external factors would lead to abnormalities in normal development and disease progression [55,56]. The transition mechanism from the epithelium to other compartments are controlled by redox-sensitive transcription factors including activation of apoptotic signaling and pro-inflammatory cytokines and chemokines [55,56].

Rel/NF- κ B is a family of dimeric transcription factors that control the expression of numerous genes involved in the inflammatory process and other physiological responses of cells [57]. Many genes including TNF α , IL-1 β , IL-6, IL-8, IL-12 cell adhesion molecules (vascular cell adhesion molecule-1 and intercellular cell adhesion molecule-1), iNOS, and COX-2 have been known to be regulated via the NF- κ B transcription factor [58,59]. Activation of many of these genes is involved in cell growth, differentiation, regulation of apoptosis, chemotaxis and metastasis progression in prostate and other solid cancers (Figure 2) [60,61]. These factors become activated by exposure to pro-inflammatory stimuli or activation of inflammatory responsive gene element that controls cellular redox balance mechanism [62,63], such as activation of oxygen-evoked sensitive HIF-1 α and NF- κ B. These two factors closely coupled with intracellular redox state or redox equilibrium and responsive to expression and trans-activation of many genes. So the differential regulation of HIF-1 α and NF- κ B by oxygen-sensitive and redox-dependent pathways may play a role in inflammation related diseases [64] (Figure 3).

Concerning prostate cancer, present literature provides strong evidence confirming that HIF-1 α and NF- κ B factors are playing prominent role in proliferation and survival of tumor cells [62,63]. It was further reported that in many studies NF- κ B activation in response to chemotherapeutic agents and radiation somewhat protected many tumor cells *in-vitro*. We recently found the presence of constitutive expression of IL-8 in prostate cancer cells enhanced the activation of NF- κ B and enhanced the effectiveness of chemo-therapy drugs [64,65].



The increased NF- κ B- transcriptional activity reported in many malignancies [51]. However the mechanism of oncogenic response in the activation of that pro-inflammatory factors in de-regulation of antioxidant and cellular redox mechanism in carcinogenesis is not known. Mechanism proposed in Figure 3.

Recently these factors have been shown to control anti-apoptotic proteins Bcl-2 and Bcl.xL expressions in prostate cancer. Bcl-2 expression was altered when expression of IL-8 was down-regulated in prostate cancer cells (PC-3 and DU145) [48]. The down-regulation of IL-8 by siRNA increases the apoptosis and sensitized the response of cancer cells to chemotherapeutic drugs Docetaxel and Staurosporine [48]. The over-expression of IL-8 is associated through activation of two cognate cell surface receptors CXCR1 and CXCR2 that may be mediated through NF- κ B activation (65). In many experimental models, it has been demonstrated that there is an activation of NF- κ B in intestinal and prostate tumor macrophages, where the constitutive production of chemokines, particularly IL-6 and IL-8, are required to drive the proliferation of premalignants intestinal epithelial cells [48,49]. IL-6 is also known to exert its proliferatives effect on the many epithelial cells, through the activation of another transcription factor called signal transducer and activators of transcription-3 (STAT3), which further synergizes with NF- κ B to increase the expression of many survival genes responsive to cancer cell survival in the cancer cells [50].

Many factors secreted by monocytes and macrophages contribute to chronic inflammation. Many of the inflammatory gene promoters have specific binding sites for transcriptional modulators, and up-regulation occurs in the setting of synergistic interaction of transcriptional factors, especially during oxidative stress or hypoxia/anoxia stimulation. IL-8 exerts its function through linkage with three different kind of G-protein-coupled chemokine receptors, CXCR1, CXCR2 that is known to be associated with G-protein signaling and Duffy antigen receptor (DARC). Recently, we have shown that IL-8 also interact with CXCR7 and exert major signaling pathway for cell survival [66]. Thus pro-inflammatory mediators play a significant role in autocrine and paracrine mechanism(s) in response to tissue stress that promotes the development of neoplasia.

Micro RNA as regulatory molecules in inflammation and cancer

MicroRNAs (miRNAs) are recently discovered a class of small,

evolutionarily conserved RNA molecules, which is known to negatively regulate gene expression at the post-transcriptional level [67]. miRNAs consist of 18 to 25 nucleotides that are modulating gene expression via the RNA interference (RNAi) pathway. RNAi is a post-transcriptional silencing mechanism present in most eukaryotic organisms, in which exposure to double-stranded RNA induces the sequence specific degradation of homologous messenger RNAs (mRNA) [68]. miRNAs act by base-pairing with their target mRNAs through perfect or near perfect complementarity, particularly at the 3' untranslated regions (UTRs) of the target mRNAs, that leads to their translational repression and/or direct cleavage [69]. Many of microRNAs may play a role in the tumorigenesis and progression of cancer [70]. Recently, researchers demonstrated that miR-15a and miR-16-1 expression was inversely correlated to Bcl-2 expression in Chronic Lymphocytic Lymphoma (CLL) and both these miRNAs negatively regulate Bcl-2 at a post-transcriptional level [71]. Furthermore, the Bcl-2 repression by these miRNAs was induced apoptosis in a leukemic cell lines [72,73]. The molecular mechanism(s) played by micro RNA of the inflammatory process is regulated by miRNAs an entirely novel level of regulatory control.

Increased levels of miR-21 have also been found in several chronic inflammatory diseases [74]. Extensive research has explored miRNA involvement in the development and fate of immune cells and in both the innate and adaptive immune responses. Whereas strong evidence links between miRNA expression to signaling pathways and receptors with critical roles in the inflammatory response such as NF- κ B and toll-like receptors are reported [74]. The elevated levels of miR-21 were observed in cancer tissues that may be in part responsible for inflammation-associated with colon cancer progression [75]. MiR-21 targets a number of tumor suppressor genes including programmed cell death-4 (PDCD4) and increased miR-21 expression can increase cell proliferation and inhibit apoptosis, stimulates invasion, intravasation and metastasis in colorectal cancers [75]. Inflammatory stimuli can increase the expression of miR-21 and 181b-1 via PTEN and CYLD which are part of the epigenetic switch linking inflammation to cancer [76-77]. The EGFR pathway has also been shown to increase miR-21 expression that regulates anti-apoptotic pathway in lung cancer [78]. Understanding the role of miRNAs in modulation of gene expressions, that leads to sustain chronic inflammation is important for the development of new therapies for cancer progression.

Conclusions

We have learned much about the role of inflammation, inflammatory processes and inflammation mediators in the pathogenesis of age related disease cancer. Present evidence suggested that genetic alteration or environmental exposure is linked to prostate, and other site malignancies may be due to early loss of cellular protection to oxidative damage, that participate in the increase of chronic inflammatory responses. The activation of inflammatory mediators including cytokines, chemokines, RONS, COX-2 and NF- κ B can create cellular conditions favorable to malignant transformation due to loss or imbalance of cellular redox and antioxidant signaling. Perturbation of antioxidant or cellular redox mechanisms may be required in order to enhance the tumor associated environment of many cells. Understanding these pathways in animal and other models may enhance potential health benefits of a number of antioxidants or anti-inflammatory agents, and maintenance of the cellular redox status crucial for optimal cellular function.

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