

OXIDATIVE STRESS AND INFLAMMATION: "THE LESSER OF TWO EVILS" IN CARCINOGENESIS

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INTRODUCTION

Literature is replete with reports indicating the involvement of oxidative stress and inflammation in tumorigenesis. Reactive oxygen species (ROS) are by-products of various oxidized cellular metabolites that serve as the "business end" as well as the consequence of oxidative stress leading to DNA damage, mutagenesis, and destruction of diverse biological macromolecules. These events may eventually culminate in carcinogenesis- through varied mechanisms such as inhibition of apoptosis, increased cellular proliferation, angiogenesis, and disruption of DNA repair mechanism. Inflammation *per se* or as a ROS-dependent mediator is a connecting link between carcinogenesis and oxidative insult. Alternatively, chronic inflammation via the exacerbation of ROS and pro-inflammatory cytokines aids in carcinogenesis by providing an environment conducive for exponential growth of malignant cells. Understanding the mechanisms of carcinogenesis over the years indicates that oxidative stress and inflammation as two distinct but related processes form the basis for the establishment of cancer, and/or aggressiveness to foster tumor growth the main sources of cancer. Though, these critical mediators of carcinogenesis are interrelated to each other, it is still not clear which leads to the other and contributes more towards to pathophysiology of cancer and. In this review, we describe the role of these processes in the complex and multifaceted mechanism of carcinogenesis.

CARCINOGENESIS: CONCEPT AND CAUSES

In a "normal" homeostatic environment cells undergo constant self-renewal where they proliferate or die at a well-balanced rate. However, any disruption of this physiological balance may cause these cells to divide abnormally in an uncontrolled manner, which ultimately can lead to the formation of cell mass, often referred to as "tumors". Hence the term "carcinogenesis or tumorigenesis" implicates the process by which normal cells gets transformed into cancerous cells. Hanahan & Weinberg (Hanahan and Weinberg, 2000) have summarized this multistage process into the following six hallmarks: a) continuous proliferation, b) resist cell death, c) evade growth suppressors, d) attain immortality, e) induce angiogenesis and finally, f) trigger invasion and metastasis. Over the last several years, various concepts that have been put forward to delineate the complexities associated with carcinogenesis (Lichtenstein, 2009) leading to the development of the disease such as:

- a) Etiological factors
- b) Mutagenesis and epigenetic regulation
- c) Cancer stem cell theory

ETIOLOGICAL FACTORS:

Both genetic and environmental factors have been implicated in the development and progression of cancer (Belitskii, 2008, Gurtsevich, 2008). Utilizing advanced molecular techniques, numerous studies have been conducted on oncogenic viruses and

transformed genes to delineate the process and factors that cause the disease; however there is no single cause that can be identified, which leads to cancer. Previous reports suggest that genotoxic factors such as oncogenic viruses, chemical carcinogens, ultraviolet and ionizing radiations, chronic bacterial infections may be a few factors resulting in cancer (Bergsmedh et al., 2001, Thilly, 2003). However, recent insights suggest that- the cellular microenvironment too plays a pivotal role in carcinogenesis (Gatenby and Gillies, 2008). Any given cell can be considered as a “microprocessor” of multistage events, accumulates various mutagens such as reactive oxygen species (ROS) and DNA depurination / deamination products or mutagenic events such as chromosomal aberrations, which may sporadically influence the process of cancer development (Thilly, 2003, Bergsmedh et al., 2001). Earlier reports have suggested that a number of malignant tumors are of viral origin, which includes hepatitis and papillomas (Gurtsevich, 2008). The etiology and mechanism of infection-based cancers has been extensively studied with respect to human genetic variability in immune response and natural history of cancer risk in ethnic groups. These studies suggest that, in most cases, these infectious agents have co-evolved along with the host (humans) and have adapted to their environment. Such adaptations may include colonization and evasion of host immune system or use of host machinery for growth and multiplication by integration of viral genes in the host genome (e.g., human papillomavirus (HPV) (Chuang, 2012). However, in these cases the malignancies may be caused due to somatic mutations/selection of malignant clones as a resultant of chronic inflammatory responses, which may be induced in the infected tissues.

MUTAGENESIS AND EPIGENETIC REGULATION:

There is a wealth of literature to support the role of mutations and epigenetic events as lead causes of cancer. However presently, these views are intertwined and it appears that one or

more of these mechanisms namely, point mutations, chromosomal aberrations, histone modifications, methylation of tumor suppressor genes, or miRNA regulation, may play a pivotal role (Tomlinson et al., 1996, Wood et al., 2007, Lotem and Sachs, 2002, Baylin and Ohm, 2006, Feinberg, 2007, Hendrix et al., 2007, Ryazansky, 2008). Mutations being rare and random and more often monoclonal, lend credence to the idea that the epigenetic mechanisms involved in gene regulation from the early stages of embryogenesis to other subsequent stages of development play a vital role in carcinogenesis (Bird, 2007). Hence, some of the key epigenetic regulators described below may often promote the process of cancer transformation.

DNA methylation:

The DNA methylation is process of covalent addition of a methyl group to the 5' position of cytosine base in the DNA. Several perturbations in methylation have been reported in human malignancies (Tischoff et al., 2006, Valinluck and Sowers, 2007). The most dominant of these is hypermethylation that mostly occur in CpG islands located on the promoter regions of tumor suppressor genes such as E-cadherin (CDH1), p53, p57 and p73 that may result in gene silencing (Herceg, 2007, Murao et al., 2006, Ushiku et al., 2007). The hypermethylations may result in perturbations in cell cycle, DNA repair and apoptosis hence recognized as a critical mechanism in tumorigenesis (Tischoff et al., 2006). Conversely, hypomethylation in certain genes such as insulin-like growth factor-2 (IGF-2) has been reported to cause genomic instability and accelerating tumor transformation (Cui et al., 2002).

Histone modifications:

Chromatin remodeling mainly by histone modifications is well known mechanism in gene regulation. Two classes of enzymes namely, histone deacetylases (HDAC) and histone acetyltransferases (HAT) control the transcriptional

regulation in a variety of genes (Gray and Teh, 2001, Huang, 2006). Aberration in HDACs and HATs activation/inactivation has been implicated in carcinogenesis (Gray and Teh, 2001, Huang, 2006). For instance, activation of NF- κ B expression and release of IL8 due to proinflammatory response such as LPS was dependent on p38 mitogen activated protein (MAP) kinase and inhibitory kappa-B kinase (IKK) mediated phosphorylation of histone-3 (Saccani et al., 2002, Yamamoto et al., 2003). Hence inflammation induced histone modifications and upregulation of certain genes or enzymes, lead to disruption in cellular machinery thereby causing genetic instability causing carcinogenesis.

miRNA and cancer:

Certain reports suggest link between miRNA and inflammation with context to carcinogenesis (Schetter et al., 2010). For example, induction of let-7a miRNA in human malignant cholangiocytes when stably transfected with IL-6 leads to phosphorylation of STAT-3, a key molecule that associates inflammation with cancer (Meng et al., 2007). Another oncogenic micro RNA, MiR-155 is stimulated during inflammatory conditions (Faraoni et al., 2009). Inflammatory stimulus such as LPS treatment, bacterial or viral infection leads to increased miR-155 expression (Xiao et al., 2009, Motsch et al., 2007). Overexpression of miR-155 is known to cause repression of tumor p53 induced nuclear protein, which is downstream of p53 signaling and may be a likely mechanism for pro-carcinogenic mechanism that leads to the disease (Gironella et al., 2007). Thus deciphering the role of miRNA in cancer and its possible use as diagnostic marker appears to have promise for the future.

In summary epigenetic regulation is formed during early stages of embryogenesis which present themselves during subsequent life (Bernstein et al., 2006, Chang et al., 2007). In addition these events are inheritable and

polyclonal that emerges simultaneously in many cells (Bird, 2007, Feinberg et al., 2006). Hence, any epigenetic dysregulation that leads to the disease is considered as more severe and detrimental by nature (Baylin and Ohm, 2006, Jones and Baylin, 2007).

CANCER STEM CELL THEORY:

The identification of cancer stem cells (CSC) by Bonnet and Dick in the subpopulation of leukemia cells, has led to the transformation in the concept of carcinogenesis (Bonnet and Dick, 1997). The hypothesis of CSCs has been earlier related to the “embryonal rest” theory by Virchow and Cohnheim according to which the cancer originates from an embryonic cell present in dormant organisms that may be “activated” upon response to stress or inflammation (Balkwill and Mantovani, 2001, Coussens and Werb, 2002). The theory of CSC too suggests that they follow a hierarchical design as opposed to the common understanding that cancers are resultant of chaotic cell proliferation. These stem cells have the ability to self-renew and differentiate that result in parent and daughter populations. In addition, they also have supplementary properties like plasticity, capability for infinite division and ability to form *de novo* tumors (Hermann et al., 2008, Hermann et al., 2007). The concept of CSC may explain possible difficulties in chemotherapy and perhaps be a potential new target for cancer therapy (Abelev, 2008).

Although there is a lack of understanding about the causes, origin, and development of cancers, the process of carcinogenesis holds some common denominators. Free radical mediated oxidative stress and inflammation are two of such critical denominators, which are central not only to the initiation, promotion and metastasis of cancers, but also have secondary immuno-modulatory effects that are pivotal to tumorigenesis ((Reuter et al., 2010). Therefore, in this review our focus is to address the role of these components in carcinogenesis.

OXIDATIVE STRESS AND INFLAMMATION: THE UNTAMED ENEMIES WITHIN

Oxidative stress is the end result of an imbalance between the free radicals or reactive oxidants (reactive oxygen or nitrogen species-ROS/RNS) and the defense mechanism, predominantly antioxidants. These disturbances cause extensive cellular damage mainly through the production of free radicals, which are highly reactive and can damage the biomolecules besides disrupting the cellular signaling mechanism (Durackova, 2010). At the sub-cellular level, oxidative phosphorylation in the mitochondria is one of the major sources of ROS such as superoxide radicals ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2), which target diverse cellular lipids and proteins, besides acting as potential mutagens (Schraufstatter et al., 1988).

Oxidative stress has been associated with cancer where genomic instability, DNA mutations, and uncontrolled cell proliferation are observed (Visconti and Grieco, 2009). In cancer cells, ROS can induce increased metabolic activity, dysregulation in mitochondrial activity, enhanced activity in enzymes such as NADPH oxidase (NOX), cyclooxygenases (COX), or lipoxygenases (LOX) and uncontrolled release of growth factors (Storz, 2005, Babior, 1999, Chiarugi and Fiaschi, 2007). Beside these, ROS is also known to contribute in genetic control of cell invasion, epigenetic control in disease development, and induce resistance to chemotherapy (Feinberg et al., 2006, Fruehauf and Trapp, 2008). Moreover, recently it has been revealed that tumor micro-environment and metabolic re-programming in tandem with ROS lead cells to be more metastatic and invasive (Fiaschi and Chiarugi, 2012, Hanahan and Weinberg, 2011).

The ROS is mainly regulated by two different protein families namely, MAPK (mitogen activated protein kinase) and the redox sensitive kinases (Waris and Ahsan, 2006). MAPK are serine/threonine kinases that upon activation phosphorylate the serine or

threonine residues on substrate regulating the gene expression, proliferation, metabolism, and cell death. MAPK activation leads to increased proliferation of cells mediated by increased AP-1 activity, which in turn promotes the cyclin dependent kinases (cdks) enabling cell division (Wada and Penninger, 2004).

Similarly, chronic inflammation induced by various factors has been linked to increased risk of human cancers (Bartsch and Nair, 2006). During inflammation a respiratory burst is caused due to the recruitment of immune cells such as mast cells and leukocytes that result in increased accumulation of reactive oxygen and nitrogen species that can act as effectors of inflammation driven carcinogenesis (Hussain et al., 2003, Coussens and Werb, 2002). One of the plausible mechanism postulates that chronic inflammation in tissues and generation of free radicals cause DNA damage that lead to activation of oncogenes and/or inactivation of tumor suppressor genes initiating cancer. One such example is mutations in *ras* and *p53* genes that have been observed in many human cancers (Rajalingam et al., 2007, Strano et al., 2007). In addition inflammatory response leads to a cascade of transcription factor activation, for example hypoxia-inducible factor-1 α (HIF1- α), nuclear factor kappa B (NF- κ B), signal transducer and activator of transcription 3 (STAT3), which control stress response (Fig.1). Also abnormal expression of inflammatory cytokines (like TNF- α , IL-1 β) and differential expression in miRNAs have been reported to play vital role in ROS induced inflammation (Hussain and Harris, 2007). Disproportion in the redox homeostasis followed by a production of free radicals leads to the attenuation of antioxidant activities leading to oxidative stress.

Under normal conditions the cells respond to the stress by activation of apoptosis, a caspase-activated pathway induced programmed cell death. However under chronic conditions formation of mutated cells bypass the apoptosis leading to selective survival of cancerous cells. Hence alleviating inflammatory response has

been considered as a promising strategy for chemoprevention (Surh et al., 2005). However, it necessitates further studies in order to characterize the link between the cellular stress response, inflammatory signaling and process of oncogenesis so as to understand the mechanism of cancer development and devise better chemotherapeutic strategies.

INFLAMMATION, OXIDATIVE STRESS AND CARCINOGENESIS: THE BATTLE OF FORCES

Extensive studies have shown that chronic inflammation and cancer are related where oxidative stress serves as the critical mediator (43). In response to any damaging insult or stimuli such as pathogenic invasion, mechanical injury, toxicity or exposure to tumor promoters, the recruitment of an arsenal of inflammatory cells increase the release and accumulation of ROS at the site of damage (Hussain et al., 2003). These free radicals are major chemical effectors that act as a link between inflammation and cancer via activation of intracellular signaling pathways leading to transformation of normal cell to tumor cell (Reuter et al., 2010). The two most critical pathways that are modulated by ROS and lead to the pathogenesis involve: modulation of numerous key molecular players such as prostaglandins and cytokines, various transcription factors, and kinase pathways such as NF- κ B, MAP kinase pathways besides others. Furthermore, the ROS induced oxidative stress promotes the tumorigenesis by amplifying the damages to bio-molecules and causing a change in the tumor microenvironment to facilitate pathways that promote various stages of cancer development. For example, the free radical induced peroxidation of lipids can initiate a cascade of oxidative damage. This event plays an important role in causing DNA damage as seen in the pathogenesis of numerous chronic premalignant human diseases such as cancers (Rosin et al., 1994). The RONS contribute to mutagenesis of DNA by inducing strand breaks, oxidation of purine bases, formation of DNA-

protein cross-links culmination in changes in chromatin structure and altered gene expression (Rahman, 2003). This damage to bio-molecules not only can result in ROS generation, but makes the cells more susceptible to tumorigenesis via continuous ROS production and sustained inflammation.

Additionally, chronic inflammation resulting from oxidative damage can promote the outgrowth of neoplastic lesions via aberrant expression of inflammatory prostaglandins and cytokines. The activation of specific cytokine such as TNF α , IL-1 β , IL-6 and COX-2 derived prostaglandins results in activation of specific protein-kinase signaling leading to specific ROS production in a positive feedback manner. For example, TNF- α enhances the formation of ROS by neutrophils and other cells, while interleukin-1 β (IL-1 β), TNF- α and interferon (IFN)- γ stimulate the expression of inducible nitric oxide synthase in inflammatory and epithelial cells. Moreover, the oxidative metabolism of arachidonic acid by upregulation of COX-2 in inflammatory cells also causes increased oxidative insult by formation of various prostaglandins that contribute to the development of various types of cancer (Baron and Sandler, 2000, Prescott and Fitzpatrick, 2000). Existence of a significant interaction and synergy among these mediators of inflammation until cancer development is evident from the studies indicating stimulated production of IL-6 by PGE₂ derived from COX-2 (Hinson et al., 1996, Shacter et al., 1992).

Although it is evident that both ROS and inflammation are indispensable for carcinogenesis, it is not clear which leads to the other (**Figure 1**). The lack of understanding in this direction poses a challenge to target either of these towards finding a cure for cancer exploiting ROS or inflammation.

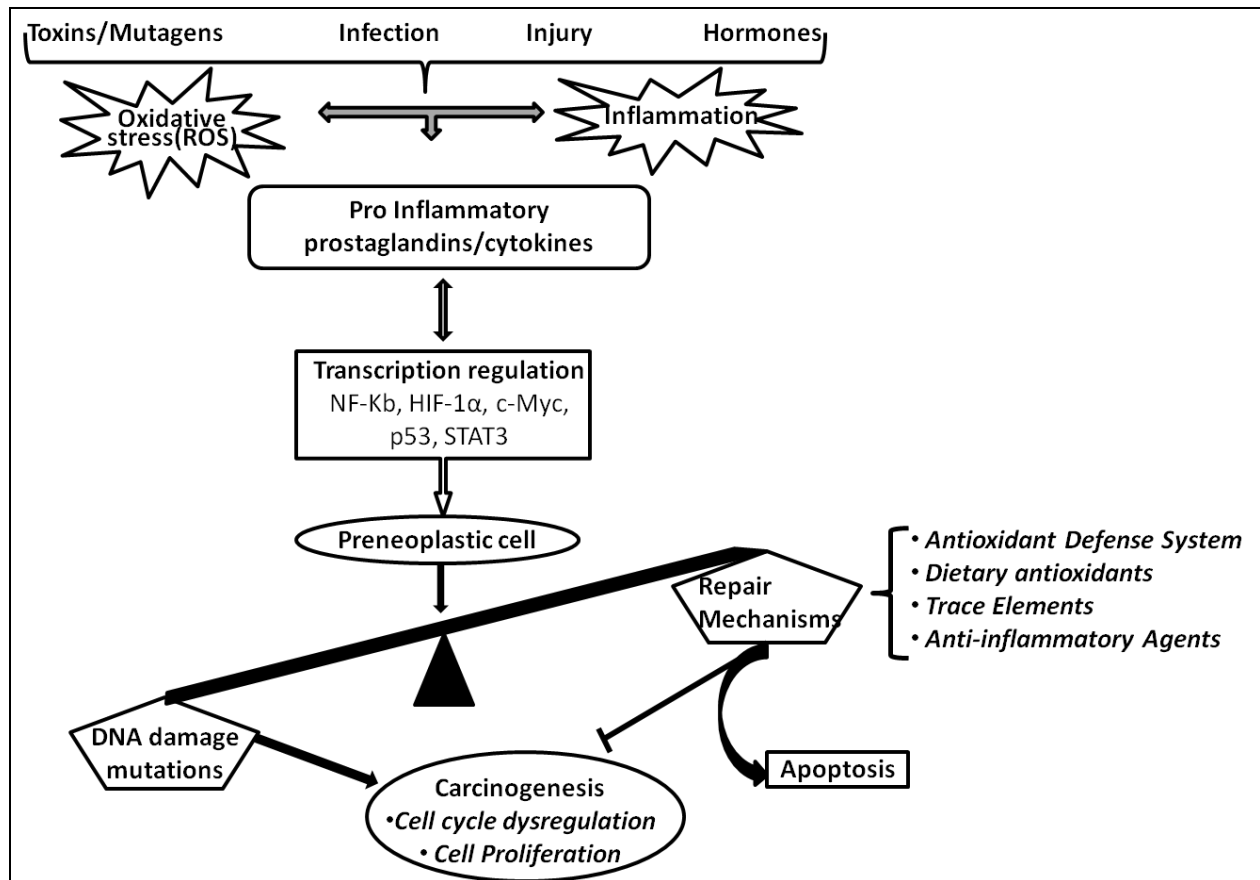


Figure 1. Schematic representation indicating the role of reactive oxygen species and inflammation in carcinogenesis. A shift in the balance towards pro-oxidants (sources of ROS and inflammatory agents) cause oxidation of cellular biomolecules, thus inducing cancer.

FINDING WAYS TOWARDS A CURE: TARGETING ROS AND INFLAMMATION

Research over the decades has tried to find the answer to carcinogenesis by developing numerous antioxidant or anti-inflammatory therapies specific either for ROS mediated oxidative stress, inflammation or both. These strategies of targeting cancer through managing ROS and inflammation has been broadly classified and described below.

PHYSIOLOGICAL ANTIOXIDANT DEFENSE SYSTEM:

In response to oxidative environment and inflammatory insults, cells have evolved an elaborate system called "antioxidant defense

system (ADS)" to protect themselves from these pathological states. This system mainly constitutes cytochrome p450 and enzymes such as catalase, superoxide dismutase (SOD), glutathione peroxidases.

Catalase is a heme-containing protein is found in the peroxisome and is an efficient antioxidant enzyme that mitigates inflammation (Goyal and Basak, Valko et al., 2006). It scavenges H_2O_2 , and reduces it to water and molecular oxygen via a two-step reaction (Valko et al., 2006). Also, catalase protects the body against high levels of exogenous H_2O_2 , which could lead to the induction of inflammatory genes from specific immune cells (Goyal and Basak). SOD exists as three major isoforms: Cu/Zn-SOD, Mn/Fe-SOD, and Ni-SOD with each isoform having different

functions and features. However, they all serve to reduce pro-oxidants by defending the cells by dismutation of superoxide ions to H_2O_2 . Thus, SOD-catalase enzymatic couple efficiently reduces pro-oxidant superoxide to water and molecular oxygen. Literature suggests that SODs plays an important role in chemoprevention suggesting the importance of ADS in normal physiology (Goyal and Basak, Valko et al., 2006). Glutathione peroxidase targets lipid and hydrogen peroxides reducing them to water and reduced form of glutathione (Valko et al., 2006). Inability to tackle the uncontrolled production of these peroxides can cause dysregulated inflammation and, subsequently cancer (Winrow et al., 1993).

NUTRITION-BASED ANTIOXIDANTS:

Numerous dietary constituents act as molecular antioxidants and anti-inflammatory agents that are potential anti-carcinogens. Since COX-2 is up-regulated in cancer, anti-inflammatory COX-2 inhibitors are already being used clinically for cancer prevention. The fact that carcinogenesis is a multi-step (accumulated genetic and epigenetic alterations), multi-path (multiple functional pathways) and multi-focal process, a combination of drugs with different targets is likely to enhance the efficiency of cancer treatment and chemoprevention. Many of these compounds are derived from natural products or food supplements. For example, resveratrol, a plant based polyphenol and an anti-oxidant has been shown to be a potent anti-pancreatic cancer agent and also a COX inhibitor (Bhat and Pezzuto, 2002). Similarly other active anti-carcinogenic compounds derived from natural products such from garlic, green tea and certain herbal medicines that interface with the COX-2 enzyme, have been reported to possess anti-cancer activities (Dirsch and Vollmar, 2001, Pinto et al., 2001, Yang et al., 2002, Wargovich et al., 2001).

Additionally, certain small molecules present in foods, complement the ADS to mitigate oxidative stress and inflammation based

carcinogenesis. This group constitutes certain vitamins, minerals, and trace elements, which are maintain a homeostatic environment, and any inadequacies in their levels can have pathological implications. Folate, vitamin E, vitamin B6, vitamin C, vitamin D, and vitamin A, are such important molecules that mitigate oxidative stress-dependent inflammation. Fat-soluble vitamins (vitamin E, vitamin D, and vitamin A) are also known to act as antioxidants. Vitamin E, in particular, has been extensively studied due to its great potential as free radical quencher and anti-carcinogenic role. Numerous epidemiological studies have indicated that Vit-E by itself or in combination with other molecules such as micronutrient selenium is as an effective and regenerating antioxidant system that aids in cancer prevention.

ESSENTIAL TRACE ELEMENTS:

In addition to the above mentioned antioxidants described certain trace elements as part of biomolecules such as proteins or cofactors of certain enzymes facilitate the protection from oxidative stress. Selenium, zinc, copper, and iron, are some of the major trace metals that represent this group of antioxidants.

The essential micronutrient selenium (Se) is co-translationally incorporated into a class of cellular proteins, selenoproteins, in the form of the 21st amino acid, selenocysteine (Sec). Glutathione peroxidase (GPx) and thioredoxin reductase (TR) are two of the most important selenoproteins that are involved in regeneration of antioxidant systems, maintenance of intracellular redox state and membrane integrity, as well as gene regulation by redox control of binding of transcription factors to DNA (Rayman, 2000). In particular, supra-nutritional doses of Se have been reported to have anti-carcinogenic properties through mechanisms such as perturbation of tumor cell metabolism, induction of apoptosis, and inhibition of angiogenesis, which suggest a

certain degree of overlap between the anti-inflammatory and anti-proliferative effects of Se (Jackson and Combs, 2008).

Recently, an inverse co-relationship between the level of Se and that of cellular COX-2 and inducible nitric oxide (iNOS) was demonstrated using a murine macrophage model. These studies revealed that cellular Se status negatively regulates the NF- κ B family of transcription factors, which are pivotal for carcinogenesis. Furthermore, studies in our laboratory demonstrated that bioavailable forms of Se modulate the COX-2 dependent AA-pathway metabolic pathways from pro-inflammatory mediators like PGE₂ and TXA₂ towards the production of protective anti-inflammatory downstream PGD₂ products, Δ^{12} -PGJ₂ and 15d-PGJ₂ (Gandhi et al., 2011). These studies lend credence to the fact that Se works at different hierarchical levels to perform their chemo-preventive abilities.

Apart from selenoproteins, many organic seleno-compounds such as seleno-methionine and ebselen (a Se-containing small molecule that functions as a GPx mimetic) have been discovered, which have ROS scavenging activity. (Klotz and Sies, 2003). Selenocarbamate and selenourea compounds have superoxide scavenging activity, which can be significant in the treatment of oxidative stress and superoxide radical-associated disorders (Takahashi et al., 2005).

Similarly zinc (Zn) and Copper (Cu) exerts their antioxidant properties via low-molecular-weight metal binding proteins called metallothioneins (MT) and as cofactors of enzymes such as Cu/Zn SOD. MTs, which are Cys-rich proteins, act as thiol donors to protect against DNA damage (Abel and de Ruiter, 1989) commonly seen in various cancers. Zinc also protects against lipid oxidation on membranes by acting synergistically with lipid and water-soluble antioxidants like α -tocopherol and epicatechin (Zago and Oteiza, 2001). Cu²⁺ as part of Cu/Zn SOD, (Antonyuk et al., 2009) catalyze the

dismutation of the superoxide radical (O₂^{•-}) into molecular oxygen (O₂) and H₂O₂. Apart from these enzymes, Cu is also important in the production of ceruloplasmin (Cp). Cp is a multi-copper oxidase (MCO) that displays antioxidant properties where it oxidizes free Fe²⁺ and Cu⁺ to favor a "subdued" oxidizing environment in tissues (Texel et al., 2008).

ANTI-INFLAMMATORY DRUGS:

In the recent past, myriad pro-tumor effects of inflammation and oxidative stress have introduced the cancer prevention strategies and therapies using them as potential targets. Since, dysregulated inflammation is important for cancers numerous anti-inflammatory agents have been used for these indications (Pari et al., 2008). Along with their anti-inflammatory roles, many of these agents exhibit other properties such as anti-angiogenic (Monnier et al., 2005), anti-proliferative, and pro-apoptotic activities (Gridelli et al., 2007), making them potential candidates for cancer therapy or prevention.

In this direction COX-2 has evolved as one of the most frequently evaluated anti-cancer anti-inflammatory target along with others such as NF- κ B, cytokines/cytokine receptors, chemokines/chemokine receptors, FGF/FGFR (fibroblast growth factor/receptor), and VEGF (Van Waes, 2007, Rose-John et al., 2007, Galliera et al., 2008, Knowles, 2008). NSAIDs (non-steroidal anti-inflammatory drugs), which are known cyclooxygenase inhibitors have been found to possess anti cancer properties and decrease the incidences of various cancers (Waddell and Loughry, 1983, Kune et al., 1988, Wang and Dubois, 2006). Some of the commonly used NSAIDs in this field are aspirin, sulindac and celecoxib. However, the toxic effects associated with these broad-spectrum NSAIDs limits their benefits. These toxicities are due to lack of their specificity to inhibit COX-1 and COX-2, which are constitutive and inducible respectively. Nonetheless, the toxicity of these drugs still remains modest compared to conventional chemotherapeutic agents and

thus is still being investigated for cancer therapy and prevention. One of the distinct potential of these anti-inflammatory agents, including the NSAIDs is alteration of the tumors themselves or the tumor microenvironment leading to decreased migration (Zlotnik, 2006), increased apoptosis (Jana, 2008), and increased sensitivity to other therapies (de Groot et al., 2007). Thus, NSAIDs and other anti-inflammatory agents that can modulate critical molecular pathways of carcinogenesis such as COX-2 inhibition and inhibition of NF- κ B signaling; have immense promise against cancer.

SUMMARY AND CONCLUSION

ROS mediated oxidative stress and inflammation are two of the most common and general denominators in carcinogenesis. ROS as small effectors activate molecular signaling pathways of inflammation leading to dysregulated cell cycle and hence development

of cancers. The conundrum where ROS and inflammation potentiate each other to ultimately cause cancer reflects their complex relationship. Epidemiological and intervention studies suggest a direct correlation between cancer incidences and the levels of ROS and inflammation. Plethora of mechanisms has been suggested by which inflammatory molecules and oxidative insult can cause tumorigenesis. Such an understanding of the basis for the development of novel therapies using antioxidants and anti-inflammatory agents with a possibility to find a cure for cancer is likely to make a huge bearing on the current cancer therapy landscape. Despite these advancements, still most of these treatments does not cater to individual variations and thus are not practiced in clinic. Therefore, there is a need to study the unique and specific therapeutic agents targeting these cancer mediators with an aim to reach clinically relevant endpoints.

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