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Aging and Inflammation: Etiological Culprits of Cancer

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Abstract

The biochemical phenomenon of aging, as universal as it is, still remains poorly understood. A number of diseases are associated with aging either as a cause or consequence of the aging process. The incidence of human cancers increases exponentially with age and therefore cancer stands out as a disease that is intricately connected to the process of aging. Emerging evidence clearly suggests that there is a symbiotic relationship between aging, inflammation and chronic diseases such as cancer; however, it is not clear whether aging leads to the induction of inflammatory processes thereby resulting in the development and maintenance of chronic diseases or whether inflammation is the causative factor for inducing both aging and chronic diseases such as cancer. Moreover, the development of chronic diseases especially cancer could also lead to the induction of inflammatory processes and may cause premature aging, suggesting that longitudinal research strategies must be employed for dissecting the interrelationships between aging, inflammation and cancer. Here, we have described our current understanding on the importance of inflammation, activation of NF- κ B and various cytokines and chemokines in the processes of aging and in the development of chronic diseases especially cancer. We have also reviewed the prevailing theories of aging and provided succinct evidence in support of novel theories such as those involving cancer stem cells, the molecular understanding of which would likely hold a great promise towards unraveling the complex relationships between aging, inflammation and cancer.

Keywords

Aging; cancer; inflammation; immunity; NF- κ B

THE UNIVERSAL FACT OF LIFE: AGING PROCESS

Aging is an inevitable universal truth for every living organism. Onset of aging can broadly be visualized as a time-driven worn out process of otherwise an extraordinarily robust and efficient machinery. The process of aging leads to marked malfunction of multiple cellular and molecular events that ultimately get translated into various chronic ailments and diseases, which severely compromises the quality of life and demise of living beings. Among many

chronic conditions such as neurological disorders and diabetes, cancer remains one of the leading causes of deaths worldwide and, as such, aging is believed to be positively correlated with poor prognosis of cancer patients. In view of the central role or the involvement of the processes of aging in several diseases, including cancer, there has been a considerable interest among many researchers from diverse fields of expertise to fully understand the processes of aging and chronic diseases. Many theories have been put forward to test the molecular regulation of aging and chronic diseases, yet our understanding of the subject remains in its infancy. The efforts towards elucidating the exact role of aging in individual diseases are as diverse as the spectrum of diseases itself that are routinely faced by humans and, therefore, it would be beyond the scope of this article to discuss the entire spectrum of aging and its associated diseases. Thus, we will focus our discussion on the current “state-of-knowledge” on the biological relationships between aging, inflammation and cancer.

Because aging is a diverse and complex process of cellular malfunction across the human population, it shares the complexity with the complexities of cancer. What is known with certainty is that aging populations are more prone to cancer development and progression. The reasons for this could be multiple such as: the worn-out cellular machinery tends to accumulate enough errors with time leading to genomic instability; or the spontaneous mutations (although mutations could be accumulated from the very early stages of life but in the latter stages of life they are just too overwhelming for the ailing subject to orchestrate corrective mechanisms); or there is an accumulation of damaged nucleic acids and proteins along with the generation of toxic substances causing unresolved chronic inflammation as the life progresses. Whatever the real cause(s), a noticeable end-result is the susceptibility to oncogene activation and suppression of suppressor gene function, which ultimately leads to the development and progression of cancer.

It has been well established that the incidences of cancer rise sharply with age and the majority of cancer cases are detected in patients over the age of 65 years. Such a direct correlation between cancer incidences with advanced age in most cancers clearly suggests that the phenomenon of aging and cancer are intricately connected. Another key factor that plays an important role in the aging-cancer nexus is inflammation. In addition, many non-cancer chronic diseases such as diabetes, Alzheimer's disease, Parkinson's disease, atherosclerosis, sarcopenia, and osteoporosis are also intimately connected with aging. An interesting point with all these diseases is that they are initiated or worsened by systemic inflammation which suggests the biochemical relevance of inflammation in cancer and other chronic diseases that are mechanistically associated with aging [1].

Of particular interest to researchers studying the complex relationship between aging and cancer is the nexus involving inflammation and immune system. A major school of thought relates aging to free radical-induced/mediated generation/activation of signaling molecules and transcription factors associated with the generation of pro-inflammatory molecules and induction of a chronic inflammatory state [2–5]. These evidences suggest an increase in tumor incidence with advancing age preceded in part by chronic disorders including inflammation. The etiological causes of inflammation are many folds and include viruses, bacteria, environmental pollutants, and stress as well as food factors. Chronic inflammation as risk factor for most cancers is well recognized. A close survey at the relationship between inflammation, aging and cancer provides evidence of several common links shared among these pathophysiological states as discussed in the following sections.

INFLAMMATION

Inflammation results from host response to trauma or as defense mechanism against invasive organisms or non-biological xenobiotic agents; it is a well coordinated and sequential series

of protective events that eventually lead to redness, pain, swelling and temperature, which subsides with passage of time once the desired task of wound healing and tissue repair or defense is accomplished. It evokes inflammatory cells (macrophages, neutrophils, monocytes, dendritic and mast cells) to invade at the site of infection or wound establishing an 'inflammatory microenvironment' that leads to the death and degradation of the organism, agent or affected cells, and eventual restoration of cellular or organ repair processes [6]. During chronic inflammation, this sequence is driven by a few important key molecular players such as prostaglandins, cytokines, nuclear factor- κ B (NF- κ B), cytokines, chemokines and angiogenic factors, which could also predispose the inflamed tissues to malignant transformation apart from healing [7]. NF- κ B activity has been shown to increase with aging in the gastric mucosa of rats [8].

Approximately 20% of all human cancers in adults result either from chronic inflammatory state or have inflammatory etiology [9–11]. There is ample epidemiological data showing higher incidence of colon cancer in patients harboring infection to *H. pylori*, and also increased susceptibility to colon cancer in patients diagnosed with Crohn's disease or ulcerative colitis [12–14]. It is currently hypothesized that within inflammatory milieu, the above mentioned key molecular players promote mutagenesis followed by classic stages of carcinogenesis which include initiation (selection of mutated cell), promotion (selective expansion of mutated/initiated cell) and progression (cancer cell division), leading to selective growth advantage and proliferation of molecularly damaged cells together with suppression of apoptotic cell death processes [15]. Indeed, increased mucosal proliferation and decreased apoptosis during aging have been observed in the gastric and colonic mucosa of rats [16–18]. Morphologic studies of the colonic mucosa of human volunteers have further revealed that, whereas cell proliferation in young is confined to the lower two-thirds of the crypt, with aging there is a major shift from the base to the middle and upper-third of the gland [19], a pattern commonly observed in colorectal cancer. It is important to note that the failure in the complex regulation of inflammatory processes to resolve cellular damage could lead to sustained malfunctioning of immune processes in aging subject, which eventually causes chronic diseases such as cancer.

INFLAMMATION, IMMUNE SYSTEM AND AGING

It is widely accepted that progression of age is associated with compromise of immune system. Aging is associated with profound alterations in the innate immune system as exemplified by alterations in the T and B cell compartments, involution of the thymus gland, functional decline in the monocytes and macrophages, low expression of Toll-like receptors from activated splenic and peritoneal macrophages and an altered secretion of several chemokines and cytokines [20]. In humans as well as in experimental animals, aging leads to decrease in humoral and cellular immune responses ([21], reviewed in [22]). Such an undesirable modulation of immune system invariably leads to increase in the incidence and intensity of various diseases and ailments. Further, residential macrophages with aging phenomenon also impair the proliferative response of activated peripheral T-lymphocytes. Also, aged residential phagocytes such as macrophages and neutrophils within host sometimes exhibit inappropriate respiratory burst with concomitant release of reactive nitrogen and oxygen intermediates which may decrease the ability to destroy pathogens [23]. Additionally, aged dendritic cells (DCs) have been reportedly found to be less efficient in activating T and B cell populations, and aged natural killer (NK) cells exhibit reduced ability and efficiency in killing tumor cells. In sharp contrast, mitogen activated peripheral blood mononuclear cells isolated from elderly population show higher production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF- α *ex-vivo*, compared to young people. This phenomenon has also been emulated *in vivo* in old subjects during inflammatory response. Up-regulated COX-2 expression, and the resulting increase in the production of prostaglandin E2 (PGE2), has been reported as critical factor associated with age related inflammatory changes [24]. Therefore the complex

regulation of immune system due to inflammation must be corrected efficiently which, if failed, will lead to pathological manifestation of chronic diseases, including cancer, in the aging subject.

Key manifestations of changes in immune system that progress with age are: reduced efficacy of vaccine-induced protection against infections/diseases and poor response to new pathogens [25,26]. However, the immune responses established at early ages are affected to a lesser extent [27]. This study [27] showed that the memory generated by naive T cells from young mice is functional even 1 year after priming but the memory generated by old T cells is defective, suggesting that naive CD4 cells from aged mice are defective in generating efficient memory. Additionally, CD4 cells from old mice produce less IL-2, exhibit poor proliferation and differentiation upon antigen stimulation [28]. Though the effects of aging on innate as well as adaptive immunity have been demonstrated, defects in T-cell-mediated immunity stand out as the best characterized and understood process [26,29]. Restoration of T-cell population balance and numbers has been shown to lead to a marked improvement in immunogenic response [30].

Alterations in B cells have also been recognized in age-related changes in immune system. The available antibody repertoires to specific antigens and pathogens are markedly different in old vs. young splenic or peripheral blood B cells [22,31]. Also, peripheral B lymphocytes in aged mice have lower turnover rates possibly associated with the decline seen in B lymphopoiesis in bone marrow [22,32]. In humans, peripheral B cell percentages and numbers significantly decrease with age [22]. Further, antibodies generated in old mice (20 months or older) and in humans (65 years or older) are less protective compared with the antibodies generated in the young individuals [33,34]. Specific antibody responses in humans immunized with vaccines against tetanus toxin, encephalitis viruses, *Salmonella* or pneumococcus decrease with age [21]. The total IgG response to influenza vaccine is also decreased in individuals over the age of 65 years [35] and these studies along with many other studies clearly suggest that the normal functioning of the immune system is severely compromised in aged individuals which together with many other complex cellular malfunctions eventually leads to the development and progression of cancer because the initiated cancer cells could easily evade the immune surveillance.

In response to disturbed tissue homeostasis, a diverse assortment of innate immune cells belonging to leukocyte pedigree at site of tissue injury or infection coordinate the inflammatory process. Macrophages, granulocytes, mast cells, DCs, and NK cells, represent the first line of defense against pathogens and foreign agents. In response to disturbed homeostasis at site of injury, tissue-resident macrophages and mast cells locally secrete soluble factors such as cytokines, chemokines, bioactive mediators, and matrix-remodeling proteins that enables the recruitment of additional migratory inflammatory cells into the inflamed damaged tissue from local circulation [36,37]. These locally recruited innate immune cells mount a challenge and directly eliminate pathogenic agents *in situ*, while DCs take-up foreign antigens (including tumor antigens) and migrate to lymphoid organs, where they present their antigens to adaptive immune cells. These foreign antigens presented by DCs or other antigen-presenting cells stimulate adaptive immune cells, such as T lymphocytes or B lymphocytes, to undergo clonal expansion and mount an 'adaptive' response targeted against the foreign agent [38–40]. Thus, acute activation of innate immunity triggers activation of more refined, antigenically committed, adaptive immune responses. Once foreign agents have been eliminated, inflammation resolves and tissue homeostasis is restored. In contrast, chronic activation of immune response without resolution of damage, often results in accumulation of regulatory T cells, Th2 cells and activated B cells, which in turn secrete growth promoting factors such as IL-4, IL-6, IL-10, IL-13, transforming growth factor- (TGF- β), and immunoglobulins that complement pro-tumorigenic responses in innate immune cells, and inactivate CTL

cytotoxicity, thus favoring tumor promotion [38]. Additionally, it has been shown that during chronic inflammation, generation and accumulation of cytokines, growth factors, free radicals, matrix metalloproteinase and prostaglandins, initiate a vicious cascade of events that mounts a pro-tumorigenic response including DNA damage, protein modification, changes in gene expression profiles and the expression of specific microRNAs (miRNAs), which eventually leads to the dysregulation of homeostasis driving the processes of carcinogenesis [41]. In the tissue microenvironment, collective stromal-epithelial interactions and immune suppressive effect of adaptive immune response bolster tumor development and invasion [42], which is typically favored in aged subject compared to young individual.

It has been widely conceptualized that chronic antigenic stress throughout life causes the accumulation of molecular and cellular scars which acts as potential trigger in mounting the inflammatory response associated with the pathogenesis of all age related diseases [43]. This synergizes with a wide range of other etiological factors such as prevalence of low grade inflammatory activity in elderly populations coupled with decreased sex steroids, life style patterns including smoking history and obesity, and a low grade of cytokine production caused by sub-clinical disorder due to asymptomatic infection with bacterium. In elderly population a low grade increase in the levels of circulating TNF- α , IL-6, soluble IL-2 receptors, CRP (C-reactive protein) and cholesterol, which act as inflammatory mediators, has been reported [43–46]. Also, there appears to be a direct correlation between an individual's exposure to past infection leading to a rise in the levels of chronic inflammatory markers and subsequent development of an increased susceptibility to risk of heart attack, stroke, and cancer [47]. Interestingly, the causative role of inflammatory milieu in geriatric medicine is becoming an interesting area for further in-depth research.

INFLAMMATION AND CANCER

Based on current presumption, it is estimated that inflammation is a contributory factor for at least 15%, if not more, of all solid tumors and is being driven by NF- κ B as a key player. While sporadic or inherited genetic mutations in critical genes regulating cell cycle, programmed cell death, differentiation and adhesion may represent initiating events in tumorigenesis ('initiation'), chronic inflammation favors selection of additional features in initiated cells that may promote their full malignant transition ('promotion'). Within tumor tissue, inflammatory microenvironment has been characterized by the presence of host leucocytes both in the supporting stroma and tumor mass. In this "niche", inflammatory cells produce numerous substances that contribute to tumor growth and survival [48]. It is speculated that a vicious cycle ensues wherein macrophages produce among several substances, growth factors, enzymes- that help the tumor cells to disseminate, further resulting in the production of pro-angiogenic factors, and TNF- α which, in turn, can up-regulate NF- κ B in both- macrophages themselves and could also target tumor cells, resulting in enhanced tumor growth. Tumor cells also produce substances such as colony-stimulating Factor-1(CSF-1) and COX-2 that give further boost to inflammatory process, as well as proteins such as Bcl-2 that inhibit apoptosis [48]. COX-2 is needed for the synthesis of a pro-inflammatory bioactive substance such as PGE2 which can bring in more immune cells to maintain the inflammation and augment tumor growth. COX-2 also promotes blood vessel growth by feeding more nutrients to the tumor cells for aggressive growth [48]. It has been observed that people regularly taking non-steroidal anti-inflammatory drugs (NSAIDs) have lower risk of developing cancer than people who don't take the drugs [48]. CSF-1 is a cytokine that attracts macrophages, and elevated levels of CSF-1 in human ovarian, breast and uterine cancers has been correlated with poor prognosis [48]. Moreover, macrophages within tumor mass also release reactive oxygen species (ROS) that endanger rapidly dividing cells to carcinogenic mutations [48].

With emerging evidence, it is becoming increasingly clear that oncogenes, besides driving the processes of carcinogenesis in terms of their ability to promote tumor growth and survival, also orchestrate the induction of a pro-inflammatory and pro-tumor microenvironment. The well known oncogenes such as *ras* and *myc* have been causally linked to tumor-inflammation axis [49]. The *ras* oncogene plays a critical role in tumor angiogenesis through CXCL8 induction, whereas *myc* oncogene is linked to remodeling of the tumor stroma and angiogenesis [49]. These “hallmarks” are in common with the situation prevailing in the inflammatory state. Sparman and Bar-Sagi provided evidence on the role of *ras* oncogene-dependent induction of the chemokine CXCL8 and tumor angiogenesis [50]. In support of their hypothesis, inhibition of CXCL8 in a xenograft model reduced the recruitment of host inflammatory cells to tumor and led to a substantial decrease in tumor vasculature and extensive tumor necrosis. Recently, it has been reported that *ras*-induced secretion of IL-6 is required for tumorigenesis [51]. Additional evidence for this link is derived from thyroid tumors where many genetic tumor-initiating events have been identified; it has been observed that same oncogene can drive tumorigenesis and induce an inflammatory program [52–54]. The *Arf*, a tumor suppressor gene, has been reported to be working in tandem with p53 pathway to protect mammalian organisms from cancer and aging. Its expression levels are normally low, but transcription of *Arf* is highly induced when oncogenes are introduced into normal cells, thus a unified picture of the *Arf*/p53 pathway in cancer and aging has been put forward by Matheu *et al.* [55]. Accordingly, constitutive activation of *Arf*/p53 could be beneficial or detrimental for aging depending on their intensity and regulation. Constitutive activation of *Arf*/p53 may produce unscheduled and excessive cell death or cell senescence, which may eventually exhaust the regenerative potential of tissues thereby accelerating aging. In contrast, a modest increase but otherwise normally regulated *Arf*/p53 pathway may decrease the damage associated with the aging process [55]. These tantalizing findings clearly suggest molecular links between aging, inflammation and cancer.

ROLE OF CYTOKINES AND CHEMOKINES IN INFLAMMATION AND CARCINOGENESIS

Several locally produced humoral chemotactic factors such as, extracellular proteases, pro-angiogenic factors and cytokines play a vital role in initiating and maintaining the inflammatory response by attracting other immunological competent monocytes and macrophages within inflammatory focus and further activating these cells. Moreover, each cytokine can evoke within inflammatory cells the synthesis and release of other cytokines, which play primary role in counteracting and neutralizing toxicity of the invading organism, and in addition cause fibroblast proliferation, vasodilatation, increases vascular permeability, and promote vascularization [56]. Additionally, these factors are also capable of facilitating tumorigenesis by stimulating cell growth, and inhibiting apoptosis of damaged cells [57]. Among these, the cytokines are small molecules induced via the classical NF- κ B pathway that profoundly affect inflammation by their role in either to activate or deactivate genes that exacerbate inflammation, such as iNOS and COX-2 as well as, directly influencing tumor-suppressor function and oncogene induction. Their importance in the inflammatory neoplastic environment is best revealed in animal knockout models showing increased predisposition of knockout animals to cancer development [9]. Also a growing body of evidence shows that numerous cytokine polymorphisms are associated with increased risk of inflammatory diseases and cancer [58].

Key pro-inflammatory cytokines include IL-1, IL-6, IL-8, IL-12, IL-18, TNF- α and macrophage MIF (migration inhibitory factor) [59,60]; these pro-inflammatory cytokines activate NF- κ B, AP-1, STAT1 and STAT3 transcription factors and have been implicated in inflammation linked tumors depending on cell types [61]. Anti-inflammatory cytokines include IL-4, IL-10, IFN (interferon)- α and - β . In pancreatic cancer, autocrine production of IL-1 β

promotes growth and confers chemo-resistance [62]. MIF and IL-6 are both known to ameliorate p53 function which favors cell survival [63,64]. In renal carcinoma cell lines, mutation in p53 causes greater autocrine secretion of IL-6 than cells harboring wild type p53 [65]. In contrast, in other cancer cell types such as multiple myeloma, non Hodgekin lymphoma, bladder and colon cancer, IL-6 acts as a paracrine growth factor and causes tumorigenesis and induces other anti-apoptotic genes including Bcl-2 and Bcl-xL [66]. Over-expression of IL-8 cytokine by human melanoma up-regulates MMP-2 activity and increases growth and metastasis; neutralizing antibodies to IL-8 inhibit angiogenesis, tumor growth and metastasis of human melanoma [67]. Cytokines also affect cell death and cell cycle pathways, for example IL-2 and TNF- α are able to induce apoptosis in colon cancer cells [68,69]. IL-10 is secreted by tumor cells as well as macrophages and, among other effects, it inhibits cytotoxic T-cells and thus aids in suppressing the immune response against the tumor [10]. Quite often, it is the profile of cytokines existing at an inflammatory site that plays pivotal role in defining the outcome in tissue or organ homeostasis. For example, TNF- α , which is produced mainly by macrophages but also by tumor cells, is associated with tissue destruction and plays a role in destroying tumor blood supply [60]. However, when chronically produced, it can act as a tumor promoter by contributing to tissue remodeling and stromal development [9,70]. In addition, pro-inflammatory cytokine gene polymorphism also closely correlates with the likelihood of an individual developing cancer [60]. These results clearly delineate the role of inflammation, inflammatory cytokines and immune function during the development of tumors.

Chemokines are a large family of proteins that play pivotal roles in cancer progression by stimulating angiogenesis and tumor growth either directly or indirectly by trafficking migration and activation of leucocytes to sites of inflammation, driving a pro-tumorigenic effect. Chemokines also stimulate cells to release proteolytic enzymes, which helps in the digestion of the ECM and promotes further inflammatory cell migration, tumor growth and metastasis [71]. Chemokines are grouped into four classes based on the positions of key cysteine residues [72]: C, CC, CXC, and CX3C. The CC chemokine, MCP (macrophage chemotactic protein)-1, has been shown to be a major determinant of monocyte/macrophage infiltration in tumors [60]. Our laboratory has documented therapeutic potential of modulating the expression of chemokine receptor-CXCR4 in human breast cancer cells [73]. Correspondingly, their ligands are expressed in the organs where the predisposition and affinity for its metastases are high. It has recently been shown that CXCL12/CXCR4 could influence the metastasis of breast cancer to the brain [74]. In some cancer cell types, it has been found that chemokine activation also induces epidermal growth factor receptor (EGFR) trans-activation and establishes an environment suboptimal for cell proliferation and tumor growth [75]. Tumor epithelial areas have also been found to express MCP-1, whereas additional chemokines such as MIP (macrophage inflammatory protein)-1 β and RANTES (regulated upon activation, normal T-cell expressed and secreted) may be detected in the stroma, and regulate the infiltration of other inflammatory cells including T-cells [60]. These complex regulations of chemokines and cytokines in relation to inflammation and carcinogenesis are an active area of research focusing on finding specific targets for the treatment of cancer.

THE CENTRAL ROLE OF NUCLEAR FACTOR-B

NF- κ B is a transcription factor critically important for the regulation of innate immune response, inflammation, cell proliferation and apoptosis and has been extensively reviewed by many authors [7,11,15,60,76–80]. NF- κ B exists in a latent state in the cytoplasm bound to specific inhibitory proteins, I κ Bs. Many pro-inflammatory stimuli can activate NF- κ B, and lead to IKK-dependent phosphorylation and subsequent proteasome-mediated degradation of I κ B proteins. Activated NF- κ B migrates into the nucleus to regulate the transcription of multiple target genes, including cytokines, chemokines, and anti-apoptotic factors. The

expression of TNF- α mainly by macrophages and lymphocytes during inflammation is regulated by NF- κ B, and, in turn, TNF α is a strong regulator of NF- κ B activation. In addition to the inhibition of apoptosis, the expression of several angiogenic factors is also regulated by NF- κ B. Macrophages and tumor cells have been reported to produce vascular endothelial growth factor (VEGF) under the control of NF- κ B activation, and VEGF promotes the proliferation and migration of endothelial cells. The expression of chemokine IL-8 by leukocytes during inflammation is regulated by NF- κ B and it functions as a blood vessel growth factor in tumor tissue. Additionally the matrix metalloproteinases (MMPs) produced by inflammatory cells and tumor cells are key players in the degradation of extracellular matrix and basement membranes, and thus are important in tumor invasion; their expression is also regulated by NF- κ B activation. In view of critical role and functional involvement of NF- κ B activation in inflammation and various disease states, including cancer, potentially efficient inhibitors of NF- κ B activation are currently being actively pursued for the treatment of many diseases including cancer [81]. Chemical inhibitors that block NF- κ B activation acting directly on IKK or on the proteasome machinery have shown anti-tumor and pro-apoptotic activity both in preclinical and clinical studies [82]; however further research is in progress for optimizing these drugs.

A few studies were carried out to examine the relationship correlation between NF- κ B and aging. It was reported that although aging had no effect on the expression of NF- κ B mRNAs (p50, p52, p65, and c-rel) or on the protein levels of the main I kappa B inhibitors (I kappa B alpha and I kappa B beta) or I kappa B kinase (IKK)-complex subunits (IKK alpha, -beta, and -gamma) involved in NF-kappa B activation in the rat liver, there was a marked increase in the DNA-binding activity of NF- κ B complexes [83]. Levels of p52 and p65 were found to be significantly elevated in nuclear as opposed to cytoplasmic fractions in the tissues of old rodents [83]. Aging has also shown to increase the DNA binding activity of NF- κ B in the gastric mucosa of rats [8]. These observations led investigators to imply that retention of NF- κ B proteins in the nuclei is increased during aging [78]. Recent advances in the field have provided irrefutable evidence connecting NF- κ B, inflammation, immune system and cancer and thus, provide justification for further studies aimed at the master switch, NF- κ B as a potential therapeutic target [84,85]. The interrelationship between aging, inflammation and cancer with respect to the role of NF- κ B is diagrammatically represented in Fig. (1).

AGING: CURRENT THEORIES IN PERSPECTIVE

The process of aging is an interplay of multi-faceted events that are associated with chronic diseases and also linked with many cellular processes including carcinogenesis which is further summarized in the following sections.

Calorie Restriction

Calorie restriction, a process of marked reduction of food intake, has been shown to be associated with prolonged healthy life span [86–88]. In *S. cerevisiae*, such restriction-induced longevity is mediated by silent information regulator protein 2 (sir2) [89]. The sir2 protein identified in *S. cerevisiae* belongs to a larger family of proteins called 'sirtuins', mammalian counterparts of which are 7 in total, named SIRT1 through SIRT7. Expression of SIRT1, a well characterized member of the family is known to be elevated in response to calorie restriction [88,90–92]. As an evidence, SIRT1-deficient mice have recently been shown to be unable to adapt to conditions of calorie restriction [93]. The role of sirtuins in the process of aging has led to an interest in identifying agents that can modify sirtuins and/or the cellular pathways involving sirtuins as a potential target for intervention. One of the earliest naturally occurring agent identified in this regard was resveratrol which was shown to increase lifespan by mimicking calorie restriction [94]. A few other agents with SIRT1 modulating activity have since been identified [95]. Many beneficial biological activities, such as enhanced longevity

and anti-inflammatory, mediated by SIRT1 have been attributed to its ability to modulate NF- κ B activity [96,97]. Interestingly, resveratrol, an anti-cancer agent [98–100] and a SIRT1 modulating agent, is itself known to inhibit NF- κ B activity [101]. It is therefore not surprising that resveratrol is increasingly being implicated as an agent beneficial against aging associated diseases including cancer [102,103].

DNA Damage

The relationship between DNA damage and aging has also been a subject of active investigation and stems from the notion that nuclear DNA, a blueprint of all cellular RNA and proteins, is irreplaceable and, therefore, any acquired error may have irreversible consequences [104]. To that end, ROS remains an important factor causing the majority of endogenous DNA damage [105]. Genetic crosses in mice have revealed a correlation between severity and type of DNA repair defect and the severity and age of onset of premature aging features [106]. The actual molecular events leading from DNA damage to the activation of aging pathways, however, remain to be elucidated [104]. The current understanding on the subject is that DNA damage is, more appropriately, a double-edged sword. Damage to DNA invariably leads to cellular malfunctioning and such a damage can either cause cancer and senescence or it can cause cell death and loss of homeostasis leading to aging [104,107].

Autophagy

As reviewed recently by Yen and Klionsky [108], and with the recent advancements in our understanding of the phenomenon of autophagy, it is increasingly being realized that autophagy plays a role in the processes of aging. With time, cells tend to accumulate macromolecules and organelles [109] as well as oxidatively damaged proteins and DNA [110,111]. This results in declining cellular function and pathways [112]. Lack of efficient autophagy has been identified as a major reason for the accumulation of such damaged intracellular machinery in aging cells [113]. In support of the validation of this theory, it has been reported that the loss-of-function in autophagy genes leads to the accumulation of damaged proteins and organelles in mice [114] and accelerates aging thereby shortening the lifespan in *C. elegans* [115] and *Drosophila* [116]. On the other hand, increased autophagy leads to increased life span in *Drosophila* by preventing the accumulation of dysfunctional mitochondria [117]. Another identified feature of aging cells is the decline in mitochondrial function [108,118], which leads to manifestations such as the decline in ATP production [119]. The above observations clearly suggest that the process of aging is a multi-faceted complex process of dysfunctional homeostasis and thus understanding of age-related chronic diseases including cancer requires further in-depth research.

Reactive Oxygen Species

Since mitochondrial integrity and function is associated with the processes of aging, the role of reactive oxygen species (ROS) in aging has also been followed with interest [108] primarily because mitochondria serves as a source as well as the target of ROS. The involvement of ROS in the processes of aging is still controversial and there are evidences in the literature that support as well as contradict the role of ROS and mitochondrial theory of aging [108,110]. It has recently been suggested [110] that oxidative stress, generated by mitochondria, is important but not the sole cause of aging. Using estrogen receptor (ER)-positive breast cancer cells as a model, Benz and Yau [110] reviewed available data to conclude that it is still unclear whether aging causes or simply permits cancer development. Current evidence strongly supports an association between free radicals derived from oxygen (ROI) and nitrogen (RNI) as an important chemical effector that links inflammation to carcinogenesis by inflicting oxidative stress [42,120–122]. Within the inflammatory milieu, reactive oxygen and nitrogen species sets off a cascade of deleterious effect inflicting either damage to tumor suppressor machinery

or *via* post-translational modification of proteins inhibiting apoptosis, DNA repair process and abrogating cell cycle checkpoints thereby abetting proliferating signals [122]. Furthermore, the reactive nitrogen products are known to activate signal transduction of cell survival pathways including MAPK signaling leading to the activation of protooncogenes including *c-fos*, *c-jun*, and *AP-1*. The major sites of their generation in a cell include the mitochondria, peroxisomes and the cytochrome P450 enzyme system [123]. It is conceivable that free radicals play important roles in genetic alterations, as well as damaging cellular structural and chemical components, leading to cancer initiation, promotion and progression. The ROI derivatives of molecular oxygen include superoxide, hydrogen peroxide, hypochlorous acid, singlet oxygen and the hydroxyl radicals, whereas RNI derivatives include nitric oxide, peroxynitrite, and S-nitrosothiols. Hussain et al. reported that nitric oxide modifies p53 and *Rb* tumor suppressor genes post-translationally at residues that are supposedly critical for their functioning [42]. In addition their presence also leads to the production of other reactive species, for example, MDA and 4 HNE through excessive lipid peroxidation within tumors [124,125]. These products of lipid peroxidation can cause point mutations in tumor suppressor genes augmenting the risk of carcinogenesis, suggesting the complexities of the molecular connection between the processes of aging, inflammation and cancer.

Under normal conditions a state of 'redox homeostasis' is maintained by well coordinated balance between the ubiquitous generation and efficient removal of ROS by the cellular antioxidant defense machinery which includes enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione S-transferase and proteins that efficiently sequester and neutralize them such as reduced glutathione. When an imbalance in redox status due to saturation and/or exhaustion of the antioxidant defense machinery occurs, oxidative stress develops that triggers cells to enhance its antioxidant potential or activate the system of caspases leading to apoptosis [126–128]. Other alternatives that may override oxidative stress include release of cytochrome-c and depletion of mitochondrial ATP triggering necrosis. Peroxynitrite (ONOO⁻), a highly reactive species generated from reaction of NO with superoxide anion (O₂⁻) also causes cells to undergo apoptosis by altering the functioning of several signaling molecules [129–132]. Failure to counteract perturbation in 'redox homeostasis' by any mechanism leads to the generation of oxidative stress and increases the frequency of mutation in cells by damaging DNA, which, if locked at key sites in the genetic material may cause activation of proto oncogene or inactivation of tumor suppressor gene, leading to the loss of control of cell proliferation and the development of carcinogenesis. Mitochondrial DNA, unlike the nuclear DNA lacks histone proteins and efficient repair mechanism and is therefore more susceptible to deleterious effect of free radicals generated in its close proximity such as hydroxyl radical in absence of an efficient scavenging system [133]. Additionally, mitochondrial DNA encodes some important proteins that are involved in intracellular communications and its damage is likely to have wide ramification in reactions leading to amplification of oxidative stress and carcinogenesis in aged subjects.

Stem Cells

In multi-cellular organisms, there are many checks and balances that are important in the maintenance of homeostasis. Sustained damage to the cellular components could trigger cell death for the elimination of damaged cells; the stem cells are capable of replacing lost cells thereby maintaining homeostasis. In contrast, damaged cells without their elimination appear to be in part responsible for the development of cancer. Stem cells are multi-potent cells that possess enormous capability to self-renew as well as to give rise to differentiated cells in various tissues and organs. Stem cells play important role in the development of organisms as well as in the tissue maintenance and homeostasis. As such, investigations are underway to ascertain the role of stem cells in the processes of aging, which itself is a manifestation of diminished homeostasis. Emerging evidence suggests that diverse tissue-specific stem cell reserves decline

with advancing age giving rise to patho-physiological consequences that are identifiable with aging [134]. Such observations have been made in hematopoietic as well as non-hematopoietic tissues (reviewed in [134]). As a proof, a meta-analysis conducted using the National Marrow Donor Program (NMDP) registry revealed that advanced donor age was positively correlated with overall reduced disease-free survival [135]. The study assessed multiple donor traits, including the age of donors, in relation to bone marrow transplant successes in 6978 transplant recipients. In the context of cancer, like normal tissues, various cancerous tissues also harbor a minor population of cells with enormous self-renewal and tumor-initiating capacity. Such cells are referred to as tumor-initiating cells or cancer stem cells, which offer an attractive target for cancer therapy [136] provided that normal stem cells are spared from the side effects of therapy. A number of molecular events that mark stem cell aging also occur in tumors in the elderly [134] and, as such, play important roles in the processes of cancer and aging, suggesting that these two processes are intertwined.

The role of specialized support cells that regulate stem cell self-renewal is also under active investigation. Stem cells and their activity is influenced and controlled within restrictive local microenvironments known as 'niches' [137]. Aging is associated with reduced regenerative capacity and there is evidence to suggest that this can, at least, partially be attributed to changes in the niche with aging. In the testis [138,139] and ovary [140] of *Drosophila* it has been reported that the number of germline stem cells, their mitotic activity and the number of progeny they produce all decline with age, suggesting stem cell loss with advancing age. Reduced expression of E-cadherin and Unpaired in hub cells in the niche contributes to this phenomenon in males [139] and over-expression of Unpaired in the hub cells of older males rescues such age-related phenomenon. In females, E-cadherin and BMP levels within the niche decline with age and their restoration enhances the function and lifetime of aging stem cells [140]. These results provide hopes to the scientific community for continuation of this line of research, which is likely to be able to pave the way for discovery of novel approaches by which losses in stem cells due to aging could be reversed and by doing so, the risk of cancer may also be reduced with advancing age.

INFLAMMATION, HYPOXIA AND CANCER STEM CELLS

As described above, the processes of inflammation and aging are closely related. It is increasingly being realized that the micro-environmental conditions found in inflamed and injured tissues are characterized by high concentrations of inflammatory mediators as well as low levels of oxygen and glucose [141,142]. Low oxygen levels or hypoxia are associated with a number of pathologies including cancers [143]. Solid tumors contain poorly vascularized regions characterized by severe hypoxia (oxygen deprivation), low pH, and nutrient starvation [144–146]. Such regions within the tumors are hypoxic due in part to the chaotic architecture of tumor blood vessels, defective tumor vessel auto-regulation, and altered blood rheology leading to transient interruptions in tumor blood flow [147]. Tumor hypoxia is typically associated with poor patient prognosis, partly because low oxygen levels reduce the effectiveness of radiation therapy, which kills tumor cells by generating reactive oxygen species [144].

Many of the cellular responses to hypoxia are mediated through changes in gene expression, and hypoxic microenvironments contribute to cancer progression by transcriptional regulation of processes that promote cell survival, motility and angiogenesis. The transcription factors primarily responsible for these cellular effects are the hypoxia-inducible factors (HIFs) [146]. HIFs consist of an α (HIF- α) and a β (HIF- β , or ARNT) subunit and influence the expression of about 150 genes that regulate cellular metabolism, survival, motility, basement membrane integrity, angiogenesis, hematopoiesis, and other functions. As oxygen levels decrease below 8%–10%, HIF- α proteins become increasingly stabilized. Increased HIF- α levels have been

documented in many solid tumors [148], thus establishing a link between hypoxia and cancer. Also, activation of HIF-1 α -dependent genes has been shown to be associated with increased patient mortality in several cancer types [149]. In pre-clinical studies, inhibition of HIF-1 activity has marked effects on tumor growth, and thus efforts are underway to identify inhibitors of HIF-1 and to test their efficacy as anticancer therapeutics [149,150]. It is believed that the inflammatory cytokines appears to be under transcriptional regulation by HIF-1 α or NF- κ B in mast cells under hypoxic conditions [151]. In addition to its effects on HIF- α gene expression and protein synthesis, NF- κ B also exerts modulating effects on HIF-1 activity (reviewed in [141]).

The concept that cancers can grow from a discrete subpopulation of malignant cells with stem cell properties (cancer stem cells) is widely gaining ground [144,152,153]. Cancer stem cells are similar to normal stem cells in that they self renew and produce more committed progenitor cells whose progeny differentiate to produce the bulk of the tumor. Stem cells, as well as multipotent progenitor cells and germ cells reside in a complex microenvironment or “niche” [154,155]. Stem cell niches are defined as particular locations or micro-environments that maintain the combined properties of stem cell self renewal and multi-potency [144]. Several studies have revealed that oxygen levels might profoundly influence stem cell niches and can promote the differentiation of certain types of stem or progenitor cells, while inhibiting the differentiation of other cells. These differing results have been demonstrated in experiments in which stem cell populations have been cultured under hypoxic conditions *in vitro* (reviewed in [155]). For example, murine placental trophoblast stem cells adopt a spongiotrophoblast cell fate as opposed to a trophoblast giant cell fate when cultured at lower oxygen levels of 3% [156]. Local oxygen concentrations can directly influence stem cell self renewal and differentiation. One attractive hypothesis is that stem cells, particularly in long-lived animals, might benefit from residing in hypoxic niches where oxidative DNA damage may be reduced [144].

Haematopoietic stem cells (HSC) and their proliferating progenitors are naturally distributed along oxygen gradient in human bone marrow, with the HSCs occupying the most hypoxic niches [157,158]. Further, Danet et al. demonstrated that culturing bone marrow HSCs at 1.5% O₂ promoted their ability to engraft and repopulate the haematopoietic organ of immunocompromised recipient mice [159]. Wherever HSCs reside, their proliferation and function is clearly affected by oxygen (reviewed in [144]). Similar observations have been made for hematopoietic progenitors isolated from embryonic yolk sacs [160] and such oxygen-dependent effects are not limited to HSCs. Culturing neuronal stem cells under hypoxic conditions (5% O₂) has been shown to promote proliferation with disturbance of cellular differentiation toward specific fates [161,162]. Hypoxia has been shown to influence the differentiation of human placental cytotrophoblast cells [163] and confer a more immature phenotype on human neuroblastoma and breast cancer cell lines [164]. Embryonic stem (ES) cells also grow more efficiently under low O₂ conditions (reviewed in [155]). Although human ES cells proliferate at a similar rate when cultured at either 3–5% O₂ or 21% O₂ [165], however, the appearance of differentiated regions in these ES cultures, as assessed by morphology and the loss of stem cell markers is substantially reduced under hypoxic conditions ([165] and reviewed in [155]). The conclusion from these studies is that the hypoxic conditions are required to maintain full pluri-potency of mammalian ES cells.

Another factor that is being implicated in aggressiveness of solid tumors and survival of cancer stem cells is the Notch receptor [166]. Evidence is emerging connecting hypoxia, Notch and cancer stem cells, and, accordingly, it has been proposed that HIF regulation of Notch activity may also contribute to cancer stem cell function (reviewed in [144]). Notch pathway is known to interact with other pathways that control stem cell function. For example, Wnt and Shh signaling are repressed in murine epidermal cells in a Notch-dependent manner [167].

Interestingly, Notch has recently been shown to activate the expression of *c-Myc*, suggesting an indirect mechanism whereby HIF-1 α may regulate Notch signaling [168]. It has therefore been proposed [144] that HIF stabilization in hypoxic tumor cells may promote the adoption of stem cell properties, including self renewal and multi-potency, by stimulating the expression or activity of Oct4, Notch, and other critical signaling pathways. This suggests that hypoxic tumor tissues could be a breeding ground for cancer stem cells. Thus, inhibiting HIF activity could reduce Notch or OCT4 levels below the threshold that is required to maintain stem cell identity, and thereby promote tumor dormancy [144,155].

CONCLUSION

The incidence of cancer in humans increases exponentially with advancing age, which suggests that the biochemical process of aging is intricately connected with the development of cancer. A number of biochemical factors appear to strengthen this relationship (Fig. 1) although further molecular evidence in support of cause or consequence of aging and cancer must be investigated. As discussed in this article, inflammation plays an important role in aging as well as in the development of cancer, and the role of NF- κ B appears to be crucial in these inflammation-driven events. Compromising the function of immune system is also invariably associated with advancing aging and the development of cancer, which is clearly mediated by aberrant expression and function of chemokines and cytokines. All these abnormalities eventually disturb the physiological homeostasis with advancing age leading to the development of cancer and the maintenance of its chronic conditions.

The pre-existing and recent emerging data clearly suggest a complex and vicious relationship between the processes of aging, inflammation, hypoxia and cancer. Inflammation triggers the process of aging and also leads to hypoxic conditions. Such hypoxic conditions are conducive to the survival and spread of cancers because, in one hand, hypoxic conditions leads to the induction of factors such as HIF-1 that facilitate migration, angiogenesis and general aggressiveness of cancers and, on the other hand, hypoxic conditions provide a niche or micro-environment that favor the survival and proliferation of pluri-potent cancer stem cells. As the researchers unveil this complex sequence of events, it is evident that the relationship between individual players in this complex equation of carcinogenesis is highly complex, suggesting that by targeting a single pathway in the hope of disrupting the sequence of events might not be very beneficial for the treatment of cancer, especially because it has been demonstrated by several failed pre-clinical and clinical studies. A multi-targeted approach might be the better approach for the treatment of cancer especially by targeting both cancer cells (cancer stem cells) and its microenvironment. However, our understanding on the role of stem cells or cancer stem cells is still in its infancy, and more data would be needed for designing multi-targeted therapeutic strategy for the treatment of cancer. Therefore, we believe that a comprehensive molecular understanding of the complexities and interrelationships between the process of inflammation, aging and cancer would be able to arm the scientific community with real arsenal for the prevention and/or treatment of individuals at high-risk of developing cancer and/or patients diagnosed with cancers in the future.

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Fig. (1). Schematic representation of various biochemical events that connect the processes of aging and cancer

Inflammation is an important factor involved in the induction of aging as well as chronic diseases, including cancer. Interestingly, inflammation is also observed as a consequence of these processes. NF-κB is well-known to be involved in the process of cancer development; emerging data suggests its involvement in the aging process as well.