Inflamm-aging of the stem cell niche: Breast cancer as a paradigmatic example

Breakdown of the multi-shell cytokine network fuels cancer in aged people

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Inflamm-aging is a relatively new terminology used to describe the age-related increase in the systemic pro-inflammatory status of humans. Here, we represent inflamm-aging as a breakdown in the multi-shell cytokine network, in which stem cells and stromal fibroblasts (referred to as the stem cell niche) become pro-inflammatory cytokine over-expressing cells due to the accumulation of DNA damage. Inflamm-aging self-propagates owing to the capability of pro-inflammatory cytokines to ignite the DNA-damage response in other cells surrounding DNA-damaged cells. Macrophages, the major cellular player in inflamm-aging, amplify the phenomenon, by broadcasting pro-inflammatory signals at both local and systemic levels. On the basis of this, we propose that inflamm-aging is a major contributor to the increase in cancer incidence and progression in aged people. Breast cancer will be presented as a paradigmatic example for this relationship.

Keywords:
ageing; cancer; DNA damage; inflammation; stem cell; stem cell niche

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Introduction

In this paper we hypothesize that inflamm-aging [1–3], the increase in the systemic pro-inflammatory status with age, is the major contributor to cancer progression and incidence in aged people [4–6]. On the basis of a literature review, we use breast cancer as a paradigm owing to the crucial role of pro-inflammatory cytokines and chemokines (e.g. interleukin-6, tumor necrosis factor alpha, interleukin-8) on the pathogenesis of this age-related malignancy [7, 8–13]. Interleukin-6 is taken as a reference molecule, based on its multi-functional role as an inflammatory mediator, but also as a breast cancer stem cell growth factor [8–10], stromal cell ageing inducer [11, 14–16], and systemic tumor marker [17]. In Fig. 1, we depict inflamm-aging as the consequence of a breakdown of the multi-shell pro-inflammatory cytokine network. Rather than referring to a strict description of the tissue architecture, the proposed multi-shell model represents a simplified view aimed at disentangling the contribution of different cell types to inflamm-aging.

In the inner shell, we represent stem cells that undergo an age-dependent shift toward a cytokine producing phenotype. We deliberately choose the over-simplified view that normal mammary gland stem cells are the target of malignant transformation, being aware that cancer-initiating cells potentially also arise from other normal cell compartments [18–20]. In the intermediate shell, stromal fibroblasts represent the stem cell niche, and we propose several mechanisms that drive such cells to acquire an age-dependent cytokine-producing phenotype. Macrophages, the major cellular actor of inflamm-aging [1–3, 21], which amplify local inflammatory stimuli and are part of the stem cell niche [22, 23] are represented in the outer shell. At the systemic level, macrophages broadcast pro-inflammatory signals that likely depend on age-related changes in other compartments, such as the intestinal microbiome [7, 24–26] and adipose tissue [27, 28]. Data on hematopoietic tissue are also highlighted, as this tissue represents the body compartment in which the physiologic and pathologic interactions between

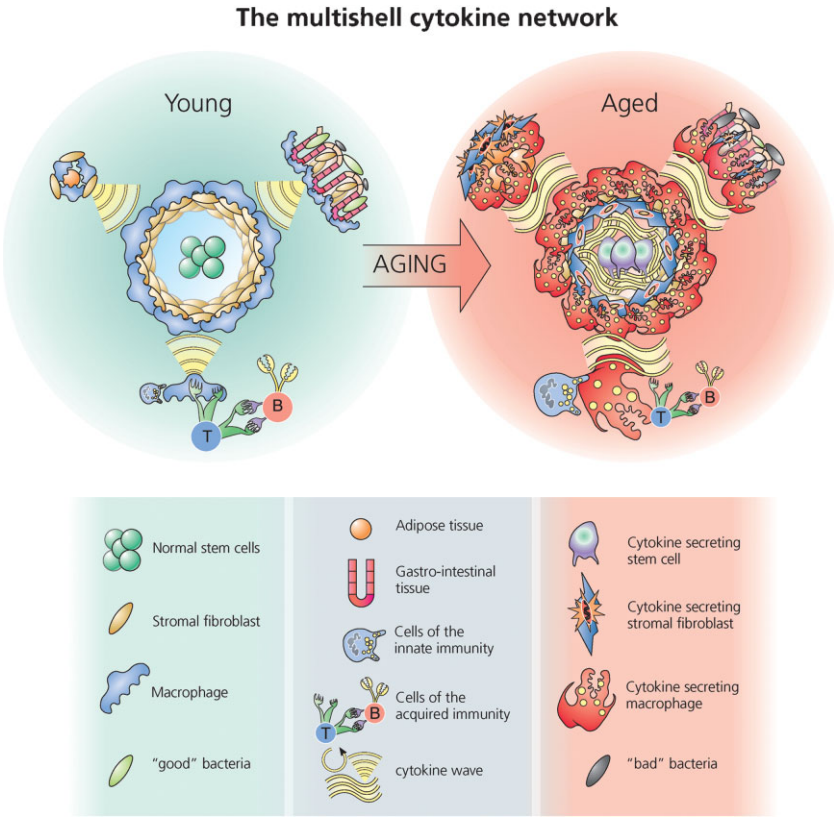

Figure 1. The multi-shell cytokine network in young and aged people. Inflamm-aging is represented as a multi-shell structure, which is filled by pro-inflammatory cytokine-producing cells during ageing. The different dimensions of the symbols intentionally highlight the quantitative modifications of cell compartments with age (Box 1). The proposed multi-shell model, rather than referring to a strict description of the tissue architecture, represents a simplified view aimed at disentangling the contribution of different cell types to inflamm-aging.

stroma and stem cells have been best characterized [29–31]. Finally, we illustrate the working hypothesis that, in the elderly, inflamm-aging promotes cancer development by exerting positive selection on tumor-initiating cells.

Acute inflammation, chronic inflammation, and inflamm-aging

Acute inflammation is a physiologic process that counteracts damage and promotes tissue repair [21]. A plethora of cells and molecules are involved in the process but, here, macrophage and interleukin-6 are taken as major representatives of this complex scenario [21]. The former is the key cellular regulator of innate immunity and coordinates the response toward any kind of agent that can lead to tissue damage [21]. The latter is a humoral mediator of the local and systemic inflammatory response, capable of targeting and activating immune and non-immune (e.g. epithelial) cells [21, 8–11]. An often neglected player in inflammation is the normal (epithelial) stem cell, whose role is to replace the non-stromal cellular compartment in damaged tissue [32]. It is reasonable to propose that pro-inflammatory cytokines target normal stem cells to promote survival and function [8, 33].

Despite the beneficial role of the acute inflammatory response [21], chronic inflammation is usually detrimental to tissue integrity [4, 5, 21]. In particular, an array of studies supports the central role of chronic inflammation in a variety of age-related diseases, including cancer [4, 5, 34–36]. Additionally, relevant epidemiologic data supports the notion

Box 1

Inflamm-aging: The pro-inflammatory status that develops in aged humans

Inflamm-aging is a major aspect of immune-senescence, i.e. the complex reshaping process, which the immune system undergoes during ageing [1–3]. As ageing proceeds, cells and humoral mediators of the innate immunity (e.g. macrophages and interleukin-6) are up-regulated [1–3, 38]. Such up-regulation accompanies the increased onset of a variety of inflammatory diseases [34, 38]. However, inflamm-aging occurs in aged individuals even in the absence of overt diseases [1, 3, 34, 38]. Nevertheless, markers of inflamm-aging, such as interleukin-6, are powerful predictors of morbidity and mortality among elderly people [38]. Additionally, other components of specific/acquired immunity (e.g. T and B lymphocytes) become less effective in combating infectious agents, as well as becoming more prone to contribute toward auto-immune and lympho-proliferative diseases [34, 39]. Inflamm-aging can be conceived as arising from the environmental attrition that becomes detrimental in the post-reproductive part of life [1–3, 39]. Interestingly, the aged mammary gland undergoes activation of an age-related inflammatory reprogramming, the mammary involution, that is likely to magnify the rate and the damaging effects of inflamm-aging [40].

that chronic inflammation increases individual susceptibility to developing various malignancies and that anti-inflammatory drugs exert anti-cancer activities [37].

One of the most persuasive observations regarding human ageing is the increase in pro-inflammatory mediators (e.g. interleukin-6) at both tissue and systemic levels, even in the absence of overt inflammatory diseases [1–3, 38]. Such a phenomenon has been named inflamm-aging (Box 1). Interestingly, irrespective of age, (breast) cancer patients also present a pro-inflammatory status, and the increase in inflammatory markers (e.g. interleukin-6) in such patients is associated with disease aggressiveness and recurrence [17]. Here, we try to illustrate the shared mechanisms at the basis of the pro-inflammatory status of aged people and cancer patients.

DNA damage and inflammation: A meaningful link

We propose that the accrual of DNA damage with age contributes significantly to inflamm-aging. We focus our attention on the observation that DNA damage, and the consequent response, elicits the secretion of pro-inflammatory cytokines [14, 15, 35, 41–44]. Such molecules, in turn, can induce DNA damage in neighboring cells, thereby inducing a propagating wave of cytokine responses, both in the surrounding local micro-environment and at a systemic level [14, 15, 35, 41–44]. The evolutionary role of this mechanism is to provide information to the surrounding tissue about the presence of DNA-damaged cells. However, considering that post-reproductive ageing is not under evolutionary selection [1–3, 21, 33], such a signaling system, endowed with the capability of self-propagation, becomes pervasive and detrimental during ageing. DNA damage in the first two layers of the cytokine network, i.e. stem cells and stromal cells, is therefore considered the major contributor to inflamm-aging (Fig. 2A). Due to their capability to respond to and to secrete inflammatory mediators [21, 36], macrophages, the third layer of the network, are regarded as local and systemic amplifiers of inflamm-aging (Fig. 2B).

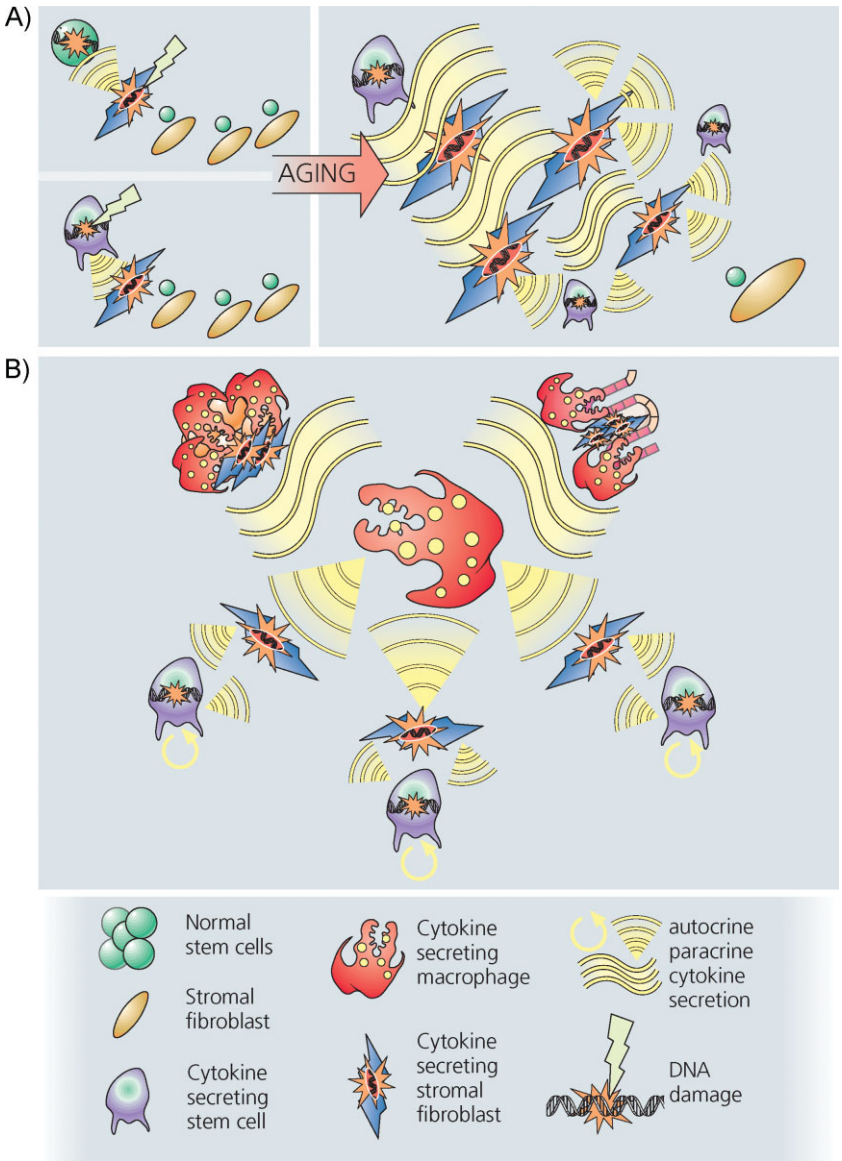

Figure 2. The inflammatory link between ageing and DNA damage. **A**: DNA damage in either stem cells or stromal fibroblasts elicits a pro-inflammatory cytokine wave that propagates the DNA damage to neighboring cells, **B**: macrophages play a crucial role in the local and systemic propagation of the pro-inflammatory wave.

Stem cells: The inner shell of the pro-inflammatory cytokine network

The dangerous affair between inflammation and mammary gland stem cells

In vitro and in vivo data suggest that inflammatory molecules and pathways promote *normal* mammary gland stem/progenitor cell function [8, 33, 40, 45, 46]. In particular, mammospheres, the standard in vitro cellular model for studying normal human mammary gland stem cells, respond to and produce inflammatory mediators (e.g. interleukin-6) to regulate their own survival and self-renewal [8]. Moreover, the epithelial to mesenchyme transition process, a complex molecular machinery that promotes the stem cell phenotype in mammary gland cells [47], is coordinated by inflammatory pathways [48]. In vivo, mammary gland development and morphogenesis, the major function of normal mammary gland stem cells, require the activation of pro-inflammatory pathways, whereas ablation leads to agenesis of the gland, reduced formation of lobules and impaired lactation [33]. Furthermore, mammary gland involution, a complex

physiologic, hormonally programmed tissue remodeling that creates a tumor-promoting environment, is indistinguishable from a pro-inflammatory process [40]. Such a tight physiological relationship between inflammatory pathways and mammary gland functioning, led to the hypothesis of an evolutionary origin of the mammary gland from innate immunity [49].

The intrinsic pro-inflammatory phenotype of breast cancer stem cells

Similar to the normal mammary gland, breast cancer tissue contains a minor subpopulation of cancer cells capable of sustaining tumor growth upon several transplants in xenografts, termed ''breast cancer stem cells'' [50]. These cells present a pro-inflammatory phenotype [8–10, 12, 46]. In particular, breast cancer stem cells produce high levels of interleukin-6 and other inflammatory cytokines that sustain autocrine pro-survival loops [8–10, 51]. Activation of inflammatory pathways is required for breast cancer malignant transformation and mammary gland carcinogenesis [8–10, 12, 33, 40]. A similar up-regulation of inflammatory pathways in cancer stem cells has also been observed in hematopoietic tissue, and inspired the targeting of such differences to pursue innovative cancer stem cell-targeting strategies [52]. We argue that such a pro-inflammatory phenotype can be attributed to the accumulation of DNA damage and to the consequent triggering of the DNA damage response (Fig. 3A).

We also suggest that two additional mechanisms in cancer stem cells, such as mutations in oncogenes and epigenetic reprogramming, likely contribute to inflamm-aging.

Oncogenic mutations: Another step toward the pro-inflammatory phenotype

Major oncogenic insults, i.e. the activation of oncogenes, the loss of tumor suppressors and the amplification/constitutive activation of membrane receptors, alter crucial cell autonomous mechanisms (e.g. cell cycle, cell death, and differentiation) that play a causative role in cancer phenotypes [53]. Such mutations contribute to the link between cancer and inflamm-aging by:

(i) the activation of oncogenes (e.g. the Human Rous Avian Sarcoma, RAS, or Schmidt-Ruppin A-2, SRC, oncogene), which leads to the overproduction of interleukin-6 that fuels tumor growth [54, 55];
(ii) the loss of tumor suppressors (e.g. tumor protein 53, TP53), accompanied by increased secretion of interleukin-6 [56];
(iii) the amplification of kinase receptors (such as epidermal growth factor receptor, EGFr or ERbB2), which promotes oncogenesis via the autocrine secretion of interleukin-6 and, in turn, promote cancer cell aggressiveness and sustain tumor growth [57, 58] (Fig. 3A).

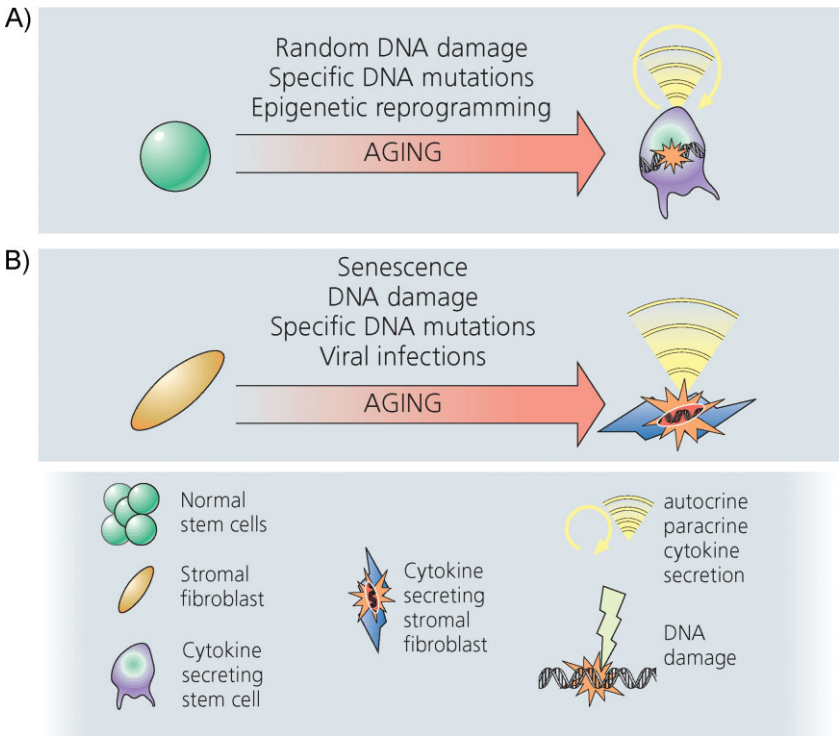

Figure 3. Accumulation of cytokine-secreting stem cells in the stem cell niche. Mechanisms leading to the accumulation of pro-inflammatory cytokine-producing cells in **A**: stem cells and in **B:** stromal fibroblasts.

On a wider perspective, increasing experimental evidence supports the notion that oncogene-driven tumorigenesis relies upon the induction of a pro-inflammatory tumor micro-environment [59, 60].

Epigenetic reprogramming as a further way to propagate inflamm-aging

Activation of the interleukin-6 signaling pathway activates chromatin-modifying enzymes, which are over-expressed in breast cancer stem cells, due to epigenetic reprogramming [56, 61, 62]. In breast cancer cells, interleukin-6 is at the center of an epigenetic reprogramming of chromatin that leads to the over-expression of the stem cell phenotype, which resembles that of TP53-deficient cells [56, 62]. Interleukin-6-mediated epigenetic regulation in stem cells also involves the control of mRNA stability through the regulation of specific microRNAs [55]. Thus, inflamm-aging may both cause and be the consequence of epigenetic reprogramming in normal and cancer stem cells. However, we surmise that, owing to the small dimensions of such cell compartments, its contribution to systemic inflamm-aging may be minor in respect to the role played by stromal cells.

Box 2

The stem cell niche; the micro-environment that regulates stem cell fate

Stem cell function is tightly linked with the surrounding environment; the so-called ''stem cell niche'' [30, 31], which contains stromal cells and macrophages [22, 23], and controls stem cell behavior by promoting quiescence [30]. To coordinate the response of stem cells to external cues and to maintain tissue homeostasis, the output of differentiating progeny must be balanced by the maintenance of the stem cell pool via asymmetric division, which depends strictly on the stem cell niche [30, 32]. Similar to their normal counterparts, cancer stem cells are also thought to be strongly affected by surrounding cells; collectively called ''the cancer stem cell niche'' [20]. So far, the relationship between the normal and cancer stem cell niche has not been established. However, because the stem cell niche restrains the growth of potential cancer-behaving cells [20], a fault in the stem cell niche may play a stimulatory role on cancer cells.

Stromal fibroblasts: The second shell of the pro-inflammatory network

As has been described in the previous paragraphs, DNA mutations alter the tumor micro-environment by promoting the secretion of inflammatory cytokines, thus contributing to inflamm-aging. We argue that such a mechanism is magnified several-fold by the second shell of the cytokine network, i.e. the stromal niche (Box 2). More generally, stromal cells play a major role in promoting breast cancer [61]. Indeed, although it is an established concept that specific DNA mutations are sufficient to trigger a cancer phenotype, a permissive environment is required to fully manifest the malignant potential of cancer cells [63–65]. In several models, the absence of human stromal cells leads to incapability to generate tumors in xeno-transplants, and the tumorigenicity of cancer cells is magnified through contact with stromal components that over-produce inflammatory cytokines [11, 14, 15]. Evidence indicates that stromal cells of neoplastic tissue have a pro-inflammatory phenotype compared to their normal counterparts [11, 65]. In the following paragraphs, we propose a variety of mechanisms that can induce stromal cells toward a pro-inflammatory phenotype during ageing, thereby leading to the generation of a pro-tumorigenic stem cell niche (Fig. 3B).

Cell senescence, the best characterized pro-inflammatory alteration of stromal cells

Senescent fibroblasts are potent promoters of cancer growth in xeno-transplants and magnify the malignant features of cancer cells [11, 14, 15]. The phenomenon of senescence, improperly referred to as in vitro cellular ageing, has been extensively studied in stromal fibroblasts, and it is provoked by exposure to a variety of damaging agents (e.g. ionizing radiations and oxygen free radicals, among others), as well as to pro-inflammatory cytokines [11, 14–16]. The senescent phenotype (cell cycle arrest, flattened appearance, expression of peculiar cytoplasmic enzymes such as beta-galactosidase, and nuclear morphologic features) is accompanied by up-regulation of the DNA damage-response system, and by the secretion of a pattern of pro-inflammatory cytokines, including interleukin-6, that maintain the phenotype [14, 16]. However, the in vivo role of senescent cells, and their contribution to the ageing phenotype at the tissue/organ level, remains unclear [14, 66]. Nevertheless, similar alterations occur in stromal fibroblasts adjacent to cancer cells that over-produce inflammatory cytokines [15, 67]. Moreover, it was recently reported that the senescent phenotype can be dissociated from the up-regulation of inflammatory cytokines [14, 15], suggesting that activation of the DNA damage-dependent up-regulation of pro-inflammatory cytokines can occur even in the absence of any overt senescent phenotype (Fig. 3B).

Specific genomic alterations contribute to the pro-inflammatory phenotype of stromal cells

Two specific genomic alterations, TP53 loss-of-function and RAS activation, induce strong pro-inflammatory cytokine production [54, 56], even in stromal fibroblasts, thereby up-regulating the pro-inflammatory phenotype of senescent cells [14, 15]. Although controversial [68], such mutations have been reported in cancer-associated stromal cells, and have been proposed as responsible for the shift toward a cancer-permissive stromal environment [69]. Stromal cells carrying TP53 loss-of-function enhance mammary tumor development in cancer-prone mice, and promote the growth of breast cancer xeno-transplants to a higher extent than in non-mutated counterparts [70, 71]. Interestingly, fibroblasts showing a down-regulation of a tumor suppressor (e.g. TP53) have been documented in close proximity to cancer cells [72]. Furthermore, stromal fibroblasts from cancer prone models with a genetic syndrome carrying the same tumorigenic TP53 mutation of their epithelial counterpart, secrete high amounts of inflammatory cytokines [73], thereby potentially synergizing with cancer cells to promote cancer growth [73]. A co-evolution model of tumor-stroma interactions has been proposed to explain the reciprocal advantages that arise due to specific DNA mutations at each tumor tissue component [74] (Fig. 3B).

Viral infection as a potential cause of DNA damage that enhances the pro-inflammatory phenotype of stromal cells

Highly prevalent viral species in the population, such as human papilloma virus (HPV) encode proteins that functionally inactivate tumor suppressors, e.g. TP53 [75]. Besides its acknowledged role in cervical carcinoma, the genome of HPV has been detected in breast cancer tissues [75, 76]. Interestingly, HPV-infected cells activate the DNA damage response pathway [75], suggesting that infected cells behave in a way indistinguishable from those accumulating random/specific DNA mutations. At least in principle, this phenomenon may be induced by a variety of viral species encoding factors that interfere with DNA repair (Fig. 3B).

The macrophage: The third shell of the pro-inflammatory cytokine network

Macrophages as local amplifiers of the pro-inflammatory wave

Macrophages represent the major cellular player in natural immunity [21] as well as crucial cellular factors in inflamm-aging [1–3], and are also components of the normal stem cell niche (mammary glands and hematopoietic tissue, among others) [22, 23]. Furthermore, macrophages are central players in the pathogenetic interplay between inflammation and cancer [4, 5, 36]. In particular, macrophages promote cancer progression and metastasis [4, 5, 36, 77, 78], and macrophage gene signatures associate with cancer aggressiveness in human breast cancer patients [79]. Cancer-associated macrophages are polarized toward a specific pro-inflammatory cytokine profile that differs from that of acute inflammation [36]. Intriguingly, oncogene mutations in cancer-initiating cells elicit the secretion of pro-inflammatory cytokines that activate and recruit macrophages to the tumor micro-environment [59, 60]. Due to their intrinsic capability to trigger the innate immune response [21], macrophages are the most likely culprit for local amplification of the pro-inflammatory wave originated in the ageing stem cell niche.

The macrophage as a systemic amplifier of the pro-inflammatory response through the bystander effect

Recent literature points to macrophages as being at the center of the systemic propagation of the local radiation-induced bystander effect [35, 42]. In particular, tumor associated-macrophages – either directly or via the secretion of pro-inflammatory cytokines – induce DNA damage at distant organs [35]. This phenomenon occurs even at the very early stage of neoplastic disease, thus suggesting that systemic inflamm-aging not only causes, but also follows, tumor growth [35]. It also explains the time lapse that occurs between the causative oncogenic insult and the onset of the neoplastic disease [42]. In this scenario, macrophages are central players that broadcast signals at a systemic level, via the secretion of pro-inflammatory cytokines. This is expected to constitute a physiologic evolutionary-based mechanism by which the localized DNA damage signal is systemically broadcasted, thus propagating inflamm-aging at a systemic level.

Macrophages in adipose tissue

The correlation between the gain in body weight (obesity) occurring with age and breast cancer risk has long been established [27]. High serum levels of interleukin-6 have been claimed to play a role in this association, as adipose tissue-derived interleukin-6 has been proposed to play a major role in breast cancer [80]. Macrophages are a major source of inflammatory cytokines in adipose tissue [27, 28]. Interestingly, mammary gland adipocytes have been proposed to form part of the mammary gland stem cell niche [81]. Furthermore, breast cancer-associated adipocytes secrete interleukin-6 and promote cancer growth and aggressiveness [82]. Moreover, it has been proposed that the increase with age of adipocytes may be a consequence of the age-related inflammatory derangement of mesenchymal stem cells [83]. On the whole, these data suggest that the inflammatory cross-communication between macrophages and adipocytes may contribute to the systemic breakdown of the cytokine network with age, and to the development of age-associated cancers.

Macrophages in the gastrointestinal system

The gut represents the largest part of the body that is exposed to a high bacterial load throughout life, due to the intestinal microbiota. Intestinal tissue stem cells require macrophages to support the local stem cell regenerative capability [84], supporting the notion that the function of the stem cell niche is intimately connected with the inflammatory response [84]. Intriguing data on cancer-prone mice reveal that cytokines from the gut may promote tumorigenesis in the breast [7]. In aged humans, evidence has been provided that the gut microbiota undergoes a profound rearrangement, with a decrease of ''good'' bacteria and enrichment of ''bad'' bacteria (facultative anaerobes, pathobionts), associated with an increased inflammatory status [24–26]. Such alteration of the gut microbial ecosystem in elderly people is correlated with high plasma levels of interleukin-6 and likely contributes to immunosenescence and local and systemic inflammation (inflamm-aging), as well as to the onset of a variety of age-related diseases, including cancer [25, 26]. Overall, macrophages appear to occupy the outer shell of the cytokine network, by transmitting local and systemic inflammatory cues to stem cells, thereby magnifying and accelerating the rate of inflamm-aging.

Inflamm-aging of the stem cell niche: Cues from the hematopoietic system

In humans and mice, ageing is associated with a reduction in the functional reserve of hematopoietic stem cell pool; although this stem cell pool still furnishes an adequate cell output, at least in the absence of tissue injuries and stress [85, 86]. An accumulation of DNA damage has been observed in aged hematopoietic stem cells [85, 87]. Interestingly, aged hematopoietic stem cells also show an up-regulation of inflammatory pathways [88]. These data suggest that the association between DNA damage and the up-regulation of inflammation also occurs in hematopoietic stem cells, and that aged hematopoietic stem cells are more similar to cancer stem cells than their younger counterparts [52, 88].

It has been suggested that the basal potential of hematopoietic stem/progenitor cells in humans is well preserved throughout life, including among centenarians, and that it is the hematopoietic cytokine network that undergoes complex remodeling with age [89]. In this regard, it has been observed that modifications of the functioning of the stem cell pool with age may depend upon the pro-inflammatory shift of the bone marrow micro-environment [86]. Studies on myelodysplasia, a hematopoietic malignancy of elderly people, indicate that genetic damage in stem cells is mirrored by substantial alterations in bone-marrow stromal cells [90]. Indeed, murine models demonstrate that genetic alterations in the stroma are enough to cause myelodysplasia; the phenomenon being dependent on the secretion of pro-inflammatory cytokines from stromal cells [29, 91]. In other hematopoietic disorders

that are highly prevalent in the elderly (e.g. B cell malignancies), the induction of pro-inflammatory cytokines by stromal cells is considered to be of major importance [92]. In particular, stromal-cell-derived interleukin-6, consequent to the DNA damage induced by anti-neoplastic therapy, has been shown to promote the survival of residual malignant B cells, thus creating a chemoresistant niche [93].

Intriguingly, it has been observed that modifications of the stem cell pool with age are responsible for an increased capability to generate myeloid progenitors [86], which in turn differentiate into macrophages, the major player in inflamm-aging [1–3]. Overall, these data suggest that the age-related shift of the hematopoietic micro-environment toward a pro-inflammatory phenotype can not only contribute to hematopoietic cancer, but can also exert a more general systemic pro-inflammatory effect.

Positive selection of DNA damaged tumor-initiating cells in the ageing niche

It is well documented that the biological role of inflammatory mediators, including pro-inflammatory cytokines, is quite complex, and that, depending on their concentrations, they can also exert toxic effects for cell survival and growth [94]. Indeed, cells defective for tumor suppressors are less prone to cytokine-induced cell death, and are more liable to acquire a stem cell phenotype upon exposure to cytokines [12, 95]. Therefore, it can be proposed that stem cells deficient in tumor suppressors may present a selective advantage for survival in an inflammatory environment. Thus, while the aged micro-environment may constitute a positive selective force for those stem cells carrying DNA mutations [96], the number of negatively selected stem cells is likely to increase with age, leading to an age-related decrease in tissue repair (Fig. 4A) [96]. Moreover, it can be hypothesized that both DNA damage repair defects and exposure to abnormal environmental insults increase cancer incidence and decrease tissue homeostasis [97, 98] by accelerating the rate of inflamm-aging of the stem cell niche (Fig. 4B).

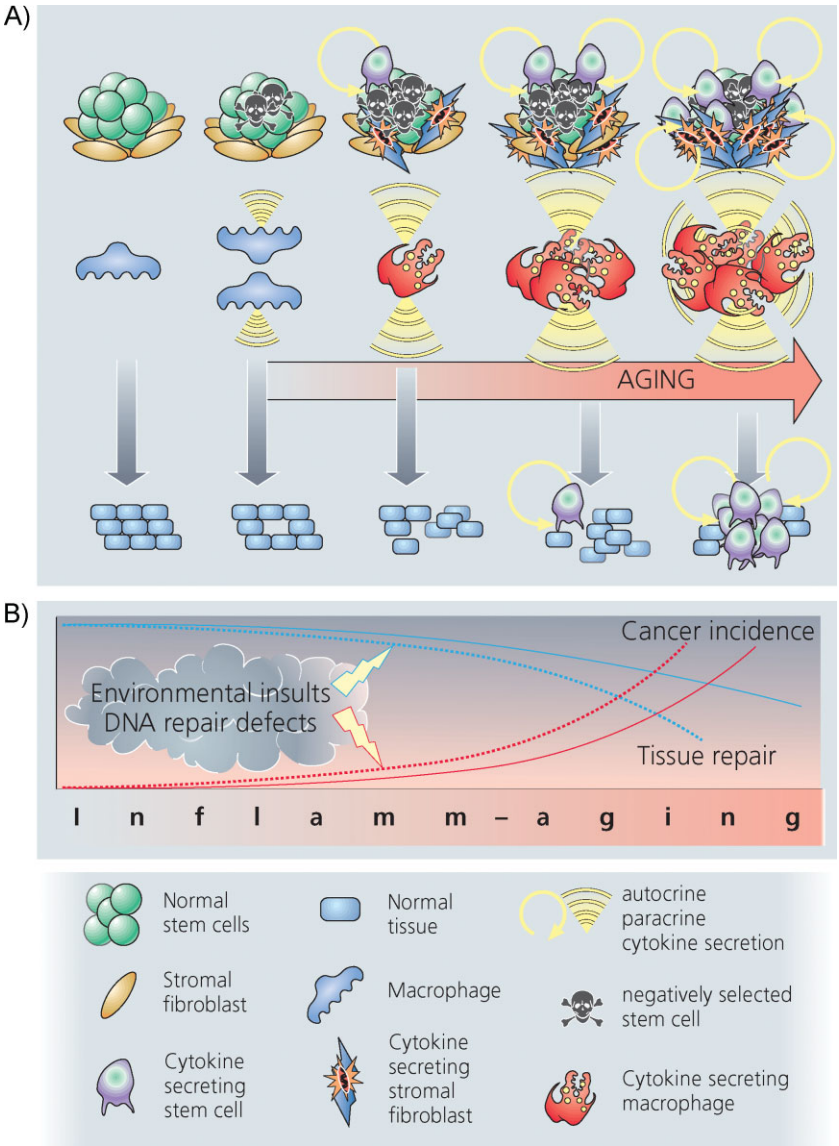

Figure 4. The role of inflamm-aging in the cancer stem cell niche. **A**: Inflamm-aging of the stem cell niche leads to a progressive loss of negatively selected stem cells and to a parallel increase in cytokine-secreting cancer stem cells. This scenario includes the activation of cytokine-secreting macrophages and a progressive deterioration of tissue integrity and homeostasis. **B**: Inflamm-aging of the stem cell niche leads to an increase in cancer incidence (solid red line), coupled with reduced tissue repair (solid blue line). Environmental insults and DNA damage repair defects accelerate the rate of inflamm-aging (dotted lines).

Conclusions

We surmise that inflamm-aging of the stem cell niche may help in understanding three major issues with regard to ageing and cancer, and subsequent therapeutic approaches:

(i) the increasing impact of the inflammatory niche on cancer with age suggests that cancer in the elderly is more dependent upon the (micro)environment, and that tumor cells in elderly people are endowed with a lower autonomous capability to grow and disseminate, in comparison with those in younger people. Such stromal dependence may be harnessed to improve cancer therapy, especially in the elderly who are particularly sensitive to the side effects of standard cancer therapy;

(ii) long-lived people, such as centenarians, who have escaped or consistently delayed cancer incidence may be genetically protected from the detrimental effects of inflamm-aging. The identification of such anti-inflammatory, protective genes [3] may lead to a better understanding of the non-autonomous cell mechanisms that promote cancer;
(iii) exposure to DNA damaging agents (accidental or due to therapeutic intervention) induces DNA damage in stromal cells that, in turn, sustain interleukin-6-dependent growth of residual cancer cells. Thus, interventions capable of reducing the rate of inflamm-aging are expected to directly impact cancer recurrence.

The scenario presented here suggests that cancer treatment in the elderly may be improved by the inhibition of pro-inflammatory cytokines by exploiting currently available antibodies used in chronic inflammatory diseases [13, 99]. We also anticipate that the identification of small molecular compounds capable of inhibiting pro-inflammatory cytokines, such as interleukin-6, will represent a new step in the cancer therapy of elderly patients. It is also conceivable that the mechanisms out-lined here also operate in young people that experience precocious inflamm-aging due to genetic alterations or through exposure to particularly intense inflammatory environmental stimuli for geographic or social-economic reasons.

The hypothesis presented here for elderly people may be extended beyond the field of cancer, involving other chronic degenerative age-related diseases that share with cancer inflamm-aging as an important pathogenetic component.

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