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Review article

Role of inflammation in the aging bones

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ABSTRACT

Chronic inflammation in aging is characterized by increased inflammatory cytokines, bone loss, decreased adaptation, and defective tissue repair in response to injury. Aging leads to inherent changes in mesenchymal stem cell (MSC) differentiation, resulting in impaired osteoblastogenesis. Also, the pro-inflammatory cytokines increase with aging, leading to enhanced myelopoiesis and osteoclastogenesis. Bone marrow macrophages (BMMs) play pivotal roles in osteoblast differentiation, the maintenance of hematopoietic stem cells (HSCs), and subsequent bone repair. However, during aging, little is known about the role of macrophages in the differentiation and function of MSC and HSC. Aged mammals have higher circulating pro-inflammatory cytokines than young adults, supporting the hypothesis of increased inflammation with aging. This review will aid in the understanding of the potential role(s) of pro-inflammatory (M1) and anti-inflammatory (M2) macrophages in differentiation and function of osteoblasts and osteoclasts in relation to aging.

Contents

Introduction

The population of Americans aged 65 and older is expected to double in the next 25 years due to increased life expectancy. The anticipated growth in the aging population will result in an expected 25% increase in health care costs by 2030 [53]. Aging is associated with chronic inflammation and with the consequent higher risk for diseases, morbidity and perhaps mortality. Chronic systemic inflammation is a common problem associated with aging and is responsible for 7 out of 10 deaths in the elderly, resulting in more than 1.7 million deaths every year and accounting for more than 75% of two trillion dollars spent on health care per year in the U.S. [63,184]. Serum levels of circulating pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF-α) are typically elevated two-to four-fold in the elderly when compared to the young population, even in the absence of chronic disease [40]. These multifunctional cytokines have been associated with

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morbidity and mortality in the elderly. There is supportive evidence for a direct role of TNF-α in the pathogeneses of atherosclerosis, diabetes mellitus type-2, and Alzheimer's disease in aged individuals [72,109,133]. High levels of circulating IL-6 may also be a risk factor for thromboembolic complications [141]. Furthermore, even in healthy, elderly populations, high circulating levels of inflammatory cytokines are predictive of mortality [40]. The objective of this review is to characterize the potential role(s) of macrophages in age-related bone loss.

Aging results from the accumulation of detrimental changes at the cellular and molecular levels in all organs and tissues, changes that ultimately lead to increased risk for several diseases [181]. Young adult mammals are able to survive their reproductive years because of strong immune and inflammation responses. However, the same immune mechanisms can lead to deleterious effects in humans that survive to older ages [147]. Aging is a complex process in which body organs and tissues lose their structural integrity leading to increased prevalence for age-related diseases, such as osteoporosis, osteoarthritis, dementia and cancer. Although the etiology of the aging process is not fully understood [181], altered inflammatory processes play a major role in aging [55].

Inflammation occurs subsequent to trauma or infection at the cellular level [23,27,28]. As a result, inflammatory cells, e.g. macrophages and monocytes, are activated and release several inflammatory cytokines into the systemic circulation, including IL-1β, IL-6 and TNF-α. These cytokines in return are responsible for the humoral immune responses [27,28,50]. The aim of inflammation is to initiate the repair processes that restore the tissue to its physiological condition [76] (Fig. 1). Inflammatory cascades can also induce tissue catabolism if not regulated properly. Several epidemiological studies have characterized the immune response in aged individuals. Levels of inflammatory cytokines and mediators increase with aging even in the absence of acute infections or other physiologic stressors [181]. Chronic increases of inflammatory mediators underlie many aging-related conditions, such as autoimmune diseases and malignancies [55,189]. For example, rheumatoid arthritis is characterized by high levels of pro-inflammatory cytokines not only in the patient serum, but also in their affected joints [84]. Similarly, in multiple myeloma, a neoplasm of B-cell origin [15], the cancer cells secrete numerous pro-inflammatory cytokine-induced chemotaxis of osteoclasts, resulting in profound bone resorption and enhanced tumor growth [138,201].

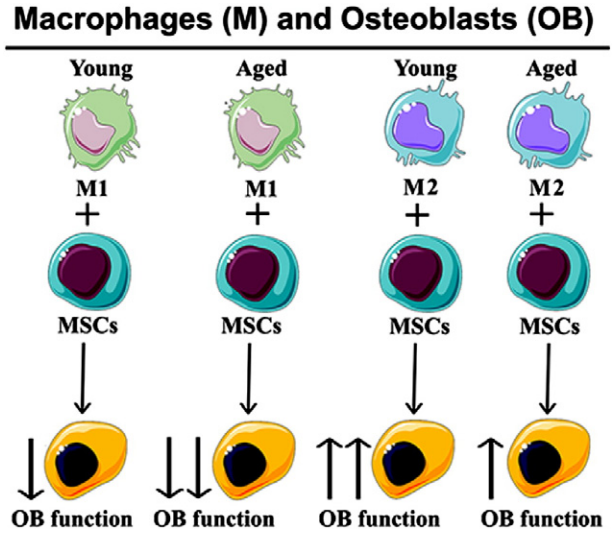

Fig. 1. Proposed model for the effects of M1/M2 polarization on osteoblast differentiation. M1 macrophages (macs) decrease the differentiation of MSC into osteoblasts (OB) in young adults. However, with aging, M1 macs are inherently increased, leading to further reduction in MSC differentiation into OB. M2 macs are increased with inflammation in young adults, a change that will result in increased MSC differentiation and OB function. The latter will decrease with aging, due to reduced M2 cells.

Studies conducted by other groups have shown that anti-inflammatory macrophages (M2) regulate MSC differentiation needed for tissue repair [130]. Based on our previously published reports and preliminary data, we suggest that macrophage polarization is shifted towards the pro-inflammatory macrophages (M1) as a consequence of aging. This phenotypic change is exacerbated by chronic inflammation or injury, due to the steady release of inflammatory cytokines from injured cells and tissues, compared with the acute increases of the same cytokines [200]. Combined, this results in reduced bone quality in aged populations (Fig. 2). However, the role of macrophage polarization in bone homeostasis has not been previously studied.

Macrophage polarization and differentiation

Macrophages are tissue resident phagocytes that differentiate from circulating peripheral blood monocytes and perform important regulatory functions in innate as well as adaptive immunity [140]. Macrophages and antigen presenting (dendritic)-cells differentiate from the monocytic lineage, however, they are distinct from each other. Macrophages are derived from CD16+ monocytes [113], whereas dendritic cells differentiate from CD34+ bone marrow- or CD14+ circulating monocytes [73].

Although it is well studied that the adaptive immune system including both B and T lymphocytes deteriorates with advancing age [45,129], the effects of the innate immune response mediated by macrophages have been under-investigated. One aspect that has not been explored is the effect of aging on macrophage polarization.

Macrophages isolated from aged humans and mice display reduced functions, ranging from a defective response in the early immune defense to decreased efficiency in the development of specific immune reaction [124,127,163,186]. Macrophages can be classified into classically activated M1 cells, or, alternatively, as activated M2 macrophages, based on their polarization status. M1 macrophages can be elicited by lipopolysaccharide (LPS) derived from bacteria or a combination of T helper cells (Th1) cytokines, such as IFN-γ and TNF-α. Inflammatory M1 macrophages also up-regulate pro-inflammatory mediators, including IL-1β, TNF-α, IL-6, IL-12, and their receptors. Moreover, M1 macrophages increase the production of reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS) and other nitrogen intermediates [86,185]. In contrast, M2 macrophages can be induced by Th2 cytokines and differentiated into 3 subtypes, M2a, M2b, M2c, and M2d TAM which is a distinctive subtype. M2a macrophages are stimulated by IL-4 and IL-13 [85,202]. M2b is induced by immune complex, IL-1β and LPS [182], while M2c macrophages are activated by IL-10, TGFβ, and glucocorticoids [126]. M2d TAMs are tumor associated macrophages that are distinct from M2a–c, and are induced by IL-6, leukocyte inhibitory factor (LIF) and MCSF [68]. The discrete differentiation of the M2a, M2b, and M2c macrophage subsets determine their relative efficacy in treating chronic diseases. Anti-inflammatory M2 macrophages up-regulate the expression of arginase-1 (Arg-1), scavenger and mannose receptors, as well as several intracellular proteins, such as Found in Inflammatory Zone 1 (FIZZ-1), T-lymphocyte-derived eosinophil chemotactic factor (ECF-L) and chitinase-like protein (Ym-1). Arginine is metabolized by Arg-1 to ornithine and polyamines in M2 macrophages, thus, decreasing substrate availability for M1 macrophages to produce nitric oxide (NO). FIZZ-1 and Ym1 are produced in large amounts during allergic inflammation and other pathological states in which a highly polarized Th2 response is prevalent [140] [140,142,143]) (Fig. 3). Recent study demonstrated that macrophages are capable of complete repolarization from M2 to M1 *in vitro*, and vice versa, in response to changes in the cytokine environment [64]. It has been well reported that Th1 cells are increased with age, unlike Th2 cells, and that the ratio of Th1/Th2 increases with aging [176,191] (Fig. 4). The altered percentage of Th1 to Th2 cells