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Aging and the dendritic cell system: Implications for cancer

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Contents

Abstract

The immune system shows a decline in responsiveness to antigens both with aging, as well as in the presence of tumors. The malfunction of the immune system with age can be attributed to developmental and functional alterations in several cell populations. Previous studies have shown defects in humoral responses and abnormalities in T cell function in aged individuals, but have not distinguished between abnormalities in antigen presentation and intrinsic T cell or B cell defects in aged individuals. Dendritic cells (DC) play a pivotal role in regulating immune responses by presenting antigens to naïve T lymphocytes, modulating Th1/Th2/Th3/Treg balance, producing numerous regulatory cytokines and chemokines, and modifying survival of immune effectors. DC are receiving increased attention due to their involvement in the immunobiology of tolerance and autoimmunity, as well as their potential role as biological adjuvants in tumor vaccines. Recent advances in the molecular and cell biology of different DC populations allow for addressing the issue of DC and aging both in rodents and humans. Since DC play a crucial role in initiating and regulating immune responses, it is reasonable to hypothesize that they are directly involved in altered antitumor immunity in aging. However, the results of studies focusing on DC in the elderly are conflicting. The present review summarizes the available human and experimental animal data on quantitative and qualitative alterations of DC in aging and discusses the potential role of the DC system in the increased incidence of cancer in the elderly.

Keywords: Dendritic cells; Aging; Cancer; Immunosuppression; Immunosenescence

1. Introduction

Immunosenescence refers to the decline in immune function associated with aging in humans and animals [1]. Many diseases observed in the elderly have an immunological basis

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and are associated with the decline of immune response to exogenous antigens and an increased propensity to autoimmune reactivity. Clinically, the consequences of impaired immune functions in the elderly include an increased susceptibility to infections, malignancies and autoimmunity, as well as diminished responses to vaccination [2,3]. Both T and B cell immune responses are dramatically affected by aging [4,5], although age-associated immunological alterations also occur in innate immune cells, affecting both the phenotype and function. Macrophages, neutrophils, natural killer (NK) cells and NKT cells are all affected by aging [6]. However, the gerontologic literature on potential alterations in dendritic cells (DC) associated with aging is scant. Definitive studies on age-related changes in antigen processing remain to be done.

DC have received increasing attention due to their potential use as biological adjuvants in tumor vaccines and their involvement in the immunobiology of tolerance and autoimmunity. DC are known to be the most potent antigen-presenting cells (APC) capable of activating naïve T cells and modulating key immune responses. DC are present in non-lymphoid peripheral tissues where they sample antigens from the environment. Thus, any foreign or tumor antigen(s) that is encountered can become rapidly endocytosed, processed, and presented to T cells resulting in the initiation of antigen-specific immune responses or immune tolerance. In recent years, it has become apparent that there are different subclasses of DC whose interactions with T cells have different outcomes [7]. Formerly called 'myeloid' and 'lymphoid' DC, DC1 and DC2, or conventional (mDC) and plasmacytoid DC (pDC) subpopulations, respectively, these subsets differentially regulate immunity, tolerance, and Th1/Th2/Treg balance [8,9]. Follicular DC are not discussed in this review and their alterations in aging have been recently summarized elsewhere [10].

Few groups have addressed the topic of DC and aging [11,12]. The multifactorial control of aging has been analyzed to some extent to identify the parameters that influence life span and confirm that immune responsiveness is centrally involved in aging. Results from these studies support the hypothesis that age-related immune dysfunction might have an impact on life span. In fact, results from studies on centenarians demonstrate that healthy individuals who have reached the extreme limit of human life in a good clinical condition are equipped with well-preserved and efficient immune defense mechanisms [13]. Since both pDC and mDC play a crucial role in immune responses, it is conceivable that they also regulate antitumor immunity in aging. However, there is little information in this area of research, and we are only now beginning to understand the role of DC dysfunction in cancer [14] and its importance in the regulation of antitumor immune responses [15–17]. However, much remains to be learned about these cells and their functions in tumor immunosurveillance during aging.

2. Animal studies

2.1. Dendritic cell numbers in aged experimental animals

Analysis of the numbers of DC in the dermis (Langerhans cells, LC) was among the first and commonly used methods to compare DC in young and old experimental animals (Table 1). In 1983, Schwartz et al. reported that the number of LC was statistically decreased in the hamster cheek pouch in old animals [18]. Sprecher et al. have demonstrated decreased density and impaired function of epidermal DC populations in aged mice [19]. Similarly, decreased numbers of DC were described in the epidermis and mucosa from aged animals by other groups. For instance, the number of major histocompatibility complex (MHC) class II+ LC in skin from aged (16–18-month old) BALB/c mice was approximately 40% lower than that in the skin from young (2–3-month old) mice [20]. Choi and Sauder have reported that aged (18 months old) mice have approximately two-thirds the number of LC that young (10–12 weeks old) animals of the same strain did [21]. These data were recently confirmed by Cumberbatch et al. who showed that the frequency of MHC class II + LC in the epidermis of older (6-month-old) mice was found to be reduced significantly compared with that observed for young (6–8-week-old) mice [22].

In the study of Hazlett et al., the morphology, distribution and quantitation of DC were determined in epithelial flat mounts from naturally resistant (Swiss-Webster and CD2F1) 6–8 week young and 24-month-old mice before and after experimental infection with *Pseudomonas aeruginosa* topically applied to the scarified cornea [23]. The young mice recovered from their infection and restored corneal clarity while the aged mice had extensive ocular destruction and corneal scarring. Conjunctival limbal DC numbers in young mice were found to be significantly increased at day 7 post infection and then returned to the baseline levels. In contrast, conjunctival limbal DC numbers in aged mice were found to increase slowly and to peak at 14 days after infection. Other differences between the two ages included an initial increase in DC 5 h post infection in the young groups and an initial decrease at 5 h in the aged groups of mice [23]. Using epithelial sheets from the cheek and palate mucosa, and from ear and footpad skin of 3-month-old and 24-month-old mice stained for MHC class II surface antigen to demonstrate LC, Rittman et al. reported that the general distribution of such cells was unchanged with age, but those in epithelia from the old mice were more varied in shape, with irregular cell bodies and more elongated dendritic processes [24]. The numerical density of LC in old mice was reduced by up to 60% compared with that in young mice. The densities of feline epidermal DC expressing CD18, MHC class II and CD1a antigens were determined for four anatomical locations in 19 cats. The densities of CD1a+ LC in the skin were significantly different, with young and old animals displaying less stained cells than adults [25].