Harnessing dendritic cell metabolism for healthy aging: reducing the risk of cardiovascular disease?

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Main text

Dendritic cells orchestrate adaptive immune responses

Dendritic cells (DCs) are myeloid cells that develop in the bone marrow and subsequently colonize peripheral organs, including the heart[1,2]. Tissue-patrolling DCs collect antigen from their environment and sense potential danger signals (Figure 1). Such pathogen-associated or host cell-derived factors (e.g. from dead or dying cells), together with the milieu (e.g. inflammatory cytokines), induce the immunogenic activation of DCs. In the absence of danger and/or in the presence of anti-inflammatory mediators, DCs undergo a tolerogenic maturation. DCs then migrate from their respective peripheral tissue to draining lymph nodes (LNs, Figure 1). Resident DCs permanently inhabit lymphoid tissues and sample the lymph or blood for antigen and danger or tolerising signals. In LNs, mature immunogenic or tolerogenic DCs present antigen on MHC class I or II molecules, provide co-stimulation by specific surface molecules and secrete immune modulators such as cytokines to T cells (Figure 1). Thereby, antigen-specific naïve $CD4^+$ and $CD8^+$ T cells are primed and instructed to execute a precise function by DCs. Generally, DCs can polarize $CD4^+$ T cells into helper T cells (e.g. type 1 [Th1] for anti-cancer, bacterial and viral immunity or type 2 [Th2] for immunity against parasites) or regulatory T cells (Treg, for suppressing inflammation and promoting immune tolerance). DCs stimulate $CD8^+$ T cells to become cytotoxic T cells to combat intracellular danger (e.g. cancer or virus-infected cells). Activated antigen-experienced T cells migrate from lymphoid organs to sites of danger for containment, mediate immunity or maintain tolerance. Tissue-patrolling DCs at distant sites further shape immune responses by re-stimulating arriving T cells[1,3] (Figure 1).

Importantly, DCs comprise several subsets that differ in their ontogeny and functions. Conventional type 1 and 2 DCs (cDC1s and cDC2s), DC3s, plasmacytoid DCs and monocyte-derived DCs. cDCs are the most potent antigen-presenting cells to control the activities of naïve $CD4^+$ and $CD8^+$ T cells. cDC1s excel at Th1 and $CD8^+$ T cell activation, while cDC2s generally specialize on Th2 and Treg induction[1,3].

Dendritic cells become dysfunctional in aging, which may affect cardiovascular diseases

The ability of DCs to control immunity and tolerance by instructing T cell responses is hampered in the elderly, causing immunosenescence (unresponsiveness of the immune system against pathogens) and loss of immune tolerance. With advancing age, DCs spontaneously secrete low-levels of immunogenic cytokines that contribute to autoimmunity and exaggerated inflammatory responses upon activation[4]. Also, the

capability of cDCs to take up antigens and activate protective $CD8^+$ T cells declines in aged mice[5], which enhances the susceptibility to infection and other diseases[4].

Notably, DCs can drive pathological T cell responses in cardiovascular diseases (CVD), such as myocarditis or myocardial infarction (MI)[6]. cDC1s and cDC2s aggravate the severity of MI-induced heart damage and hamper recovery by induction of autoreactive Th1 and $CD8^+$ T cells in mouse models[6,7]. Nevertheless, priming of protective virus-controlling $CD8^+$ T cells by cDC1s can prevent heart failure due to viral myocarditis[2]. The immune tolerising activities of DCs to limit uncontrolled T cell activation also protect against CVD. For example, DCs halt the progression of several pre-clinical models of CVD and the transfer of tolerogenic DCs to stimulate anti-inflammatory T cells in myocarditis or MI are actively explored[6].

Overall, those pioneering studies demonstrate the plasticity of DC functions as detrimental or favourable for preventing CVD and DC-based interventions emerge as promising treatment options. Hence, the aberrant capacity of DCs to regulate immunity in the elderly may contribute to CVD and advanced age is indeed a risk factor[4]. Enhancing our understanding on how to modulate the activities of DC subsets towards immunogenicity or tolerance induction may open novel therapeutic avenues to facilitate healthy aging and thereby lower the risk for CVD.

Tissue-specific immunometabolism of dendritic cells: a potential therapeutic target for healthy aging?

Divergent metabolic adaptions underlie the pro- and anti-inflammatory in vitro activation of macrophages, another type of myeloid cell[8]. Likewise, a distinct metabolic remodelling was reported for immunogenic vs tolerogenic DCs in culture[3]. Hence, regulating DC metabolism may represent a novel strategy to control immune responses in aging[3,5,6].

Cell metabolism is a network of chemical reactions or pathways that utilise biochemical nutrients to produce energy (catabolism) and the synthesis of cellular building blocks (anabolism). Those reactions take place in different cellular compartments; such as endocytic vesicles, cytosol or mitochondria; and are mostly mediated by specific enzymes that convert metabolites derived from sugars (e.g. glucose), proteins (e.g. amino acids) and lipids (e.g. fatty acids)[3]. Generally, cultured tolerogenic DCs appear to engage several metabolic pathways to fuel their functions to limit inflammation and immunity; with a central relevance of fatty acid oxidation and mitochondrial metabolism, but also the use of glucose and amino acids[3,9]. In contrast, DCs in vitro and ex vivo preferably upregulate glycolysis to obtain energy upon sensing of bacterial or viral danger signals, which is crucial for the induction of T cell immunity[3]. However, in the cancer setting in vivo, the ability of cDC1s to stimulate cytotoxic $CD8^+$ T cell responses

is regulated by intratumoral availability of the amino acid glutamine, and its supplementation promotes the cancer-protective functions of cDC1s[10]. Notably, the activities of cDC2s within the same cancer microenvironment are less influenced by glutamine or a related metabolic adaption[10]. Overall, those data reveal that the metabolic plasticity of DCs is intertwined with their functionality. Importantly, both appear highly dependent on the DC subset, disease-context and local milieu.

Different tissue environments have a distinct biological and chemical composition with varying pH, oxygen and nutrient availability. In fact, the survival and functions of macrophages are orchestrated by the biochemical makeup of their surroundings. Tissue-resident macrophages differentially engage their mitochondrial metabolism in an organ-specific manner and, in turn, exhibit distinct metabolic vulnerabilities that depend on their tissue of residence[8]. DCs, foremost cDC1s and cDC2s, are also present in virtually all organs of the body for immune surveillance and the maintenance of immune tolerance[1] (Figure 1). Yet, in contrast to permanently tissue-resident macrophages[8], cDCs differentiate in the adult bone marrow[1]. Hence, DCs have to constantly adapt to their new environments when colonizing peripheral tissues and, especially, upon subsequent migration to draining LNs. Those adaptions of DCs are likely influenced by the age-related deterioration of their homing tissues. For example, DCs in the spleen of aged mice are unaltered in number, but exhibit signs of dysfunctional mitochondria that contribute to their impaired T cell stimulation capacity via aberrant production of reactive oxygen spiecies[5]. However, how distinct biochemical environments in different body tissues can affect the cellular metabolism of DCs in health, disease and advanced age is largely elusive.

The investigation of the tissue-, context- and subset-dependent immunometabolism of DCs in vivo may reveal location-specific metabolic requirements or vulnerabilities of those cells that are suitable for therapeutic exploitation to prevent aging-related diseases and immunosenescence.

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Declarations

Disclosure of interest

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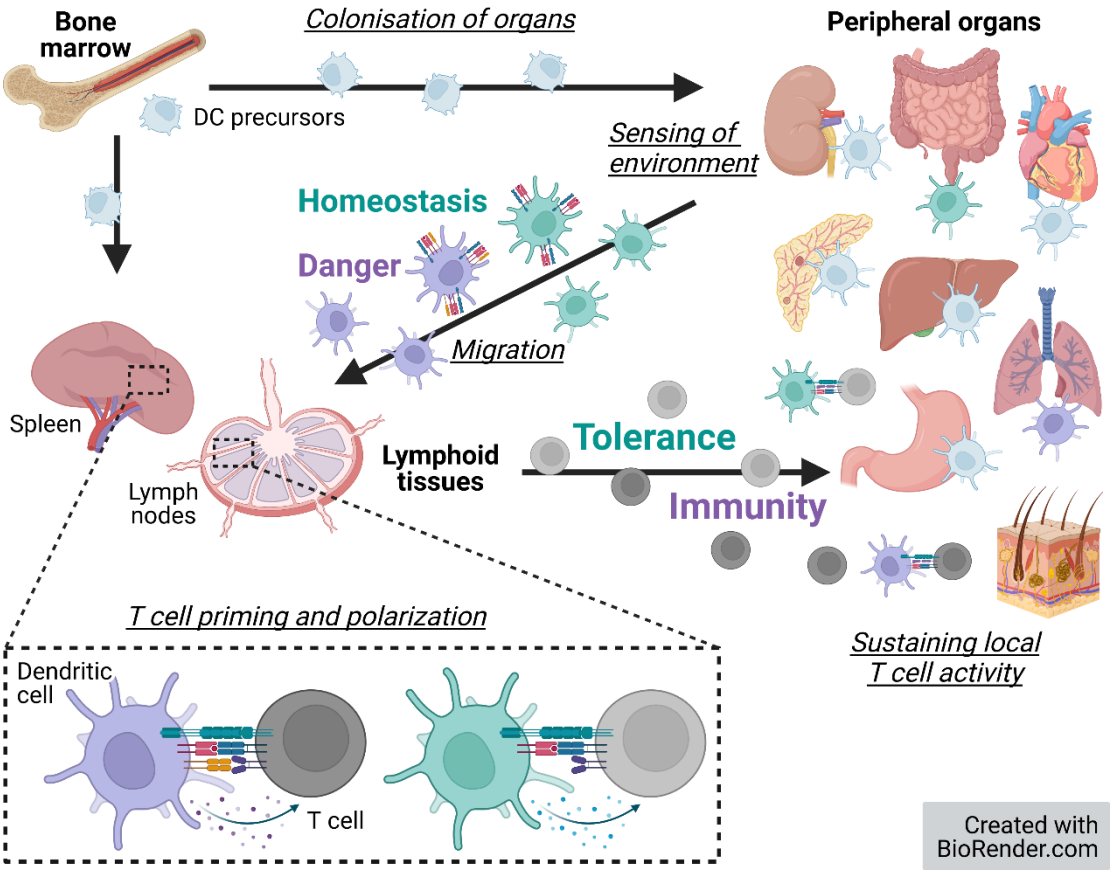

Figure 1: Overview on dendritic cell-mediated control of T cell responses

Dendritic cell (DC) precursors migrate to distant organs and differentiate into DCs. In tissues, DCs collect and integrate environmental danger- as well as homeostasis-associated signals and undergo a respective functional maturation. Activated and mature DCs migrate to draining LNs to prime and polarize T cells to mediate immunity or immune tolerance in (peripheral) tissues.