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Review Article

Does metabolic reprogramming underpin age-associated changes in T cell phenotype and function?

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ABSTRACT

T cells are required for an effective adaptive immune response. The principal function of T cells is to promote efficient removal of foreign material by identifying and mounting a specific response to nonself. A decline in T cell function in aging is thought to contribute to reduced response to infection and vaccination and an increase in autoimmunity. This may in part be due to the age-related decrease in naïve $CD4^+$ T cells and increase in antigen-experienced $CD4^+$ T cells, loss of redox homeostasis, and impaired metabolic switching. Switching between subsets is triggered by the integration of extracellular signals sensed through surface receptors and the activation of discrete intracellular metabolic pathways. This article explores how metabolic programming and loss of redox homeostasis during aging may contribute to age-associated changes in T cell phenotype and function.

Contents

Introduction

The circulating T cell pool is highly diverse and derives from bone marrow stem cells, which undergo maturation in the thymus (Fig. 1; discussed in Section 2 of this review). T cell subsets can seem confusing; they are simply defined by the cytokines they secrete and the presence of specific cell differentiation (CD)[1] antigens, e.g., CD3 is expressed on all T cells in humans and so T cells are referred to as $CD3^+$. T cells rely on reactive oxygen species (ROS) as regulatory molecules (discussed in Section 3 of this review) and there are several examples in which failure to produce superoxide anion radicals effectively has been implicated

Abbreviations: APC, antigen-presenting cell; BSO, buthionine sulfoximine; CD, cell differentiation; GLUT, glucose transporter; GSH, glutathione; GSSG, oxidized glutathione; IFN, interferon; IGF-1 R, insulin growth factor receptor 1; IL, interleukin; mROS, mitochondrial ROS; MHC, major histocompatibility complex; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor κB; NOX, NADPH oxidase; RA, rheumatoid arthritis; ROS, reactive oxygen species; S1P, sphingosine 1 phosphate; TCR, T cell receptor; Th, T helper cell; Treg, regulatory T cell; Trx, thioredoxin; TNF, tumor necrosis factor

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in autoimmune conditions [1]. This review focuses on members of the CD4$^+$ T cell family whose frequency and distribution change with aging and that have been implicated in age-associated immune decline (Section 4).

Naïve CD4$^+$ T cells can differentiate into the highly proliferative effector T cell arm (including T helper (h) 1, Th2, and Th17), which provides acquired immunity to pathogens and undergoes metabolic activation and clonal expansion. On the other hand, those that react to self-antigens would normally become nonresponsive (anergic) during development, and a subset of specialized regulatory T cells (Tregs), which modulate the immune system, is metabolically quiescent [2]. The frequency of Tregs is increased in aged mice and humans thereby restraining immune responses to pathogens (Section 4).

An increasingly recognized pathway for modulation of signaling in a number of cells is mediated by ROS, through local oxidation, e.g., of protein tyrosine phosphatases, thereby ensuring phosphorylating signals remain active for longer. The sources and nature of ROS that are important in modulating signaling are likely to be hydroperoxides derived from superoxide anion radicals produced by NADPH oxidase enzymes (NOX) and mitochondria [3]; mitochondrial ROS production is further enhanced when cytochrome oxidase efficiency is lower, e.g., during aging (Section 5). This change is further compounded by metabolic changes in older adults, which have been attributed to a redistribution of body fat to visceral deposition and insulin insensitivity, providing an increase in fatty acid metabolic substrate concentrations for oxidative phosphorylation (Fig. 2). In turn, an

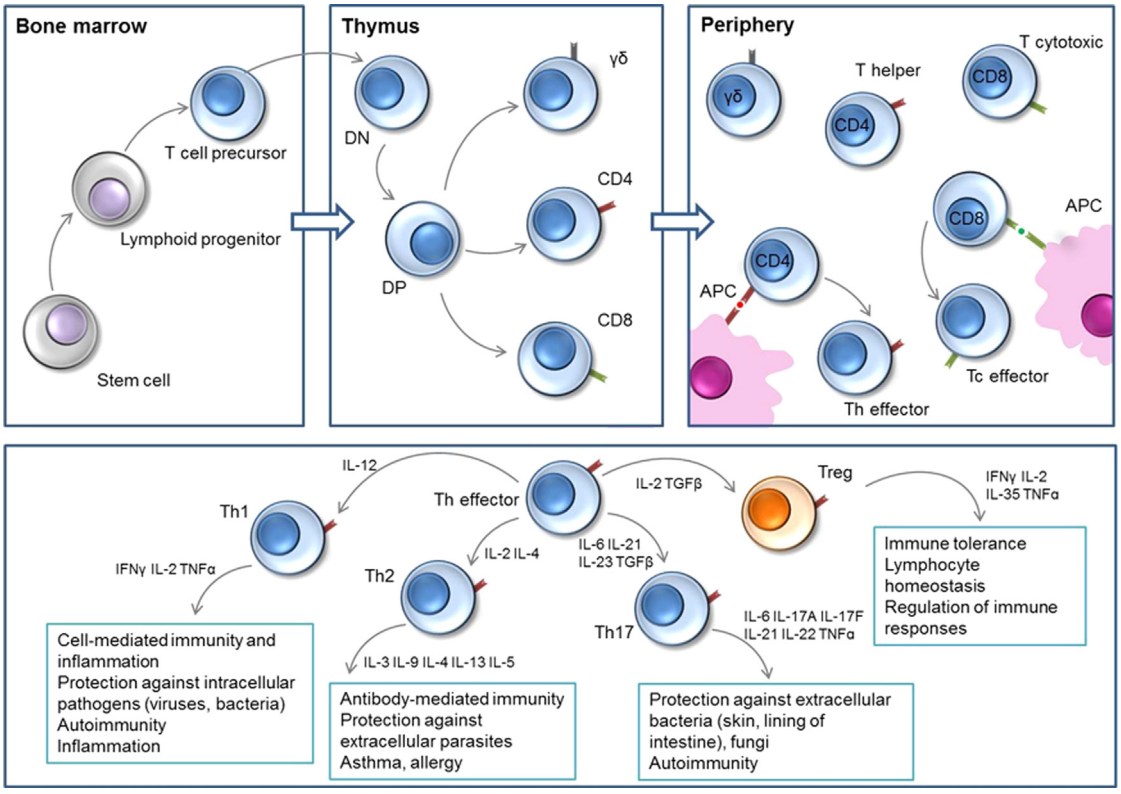

Fig. 1. Pathways of T cell maturation and regulatory cytokine involvement in terminal differentiation.

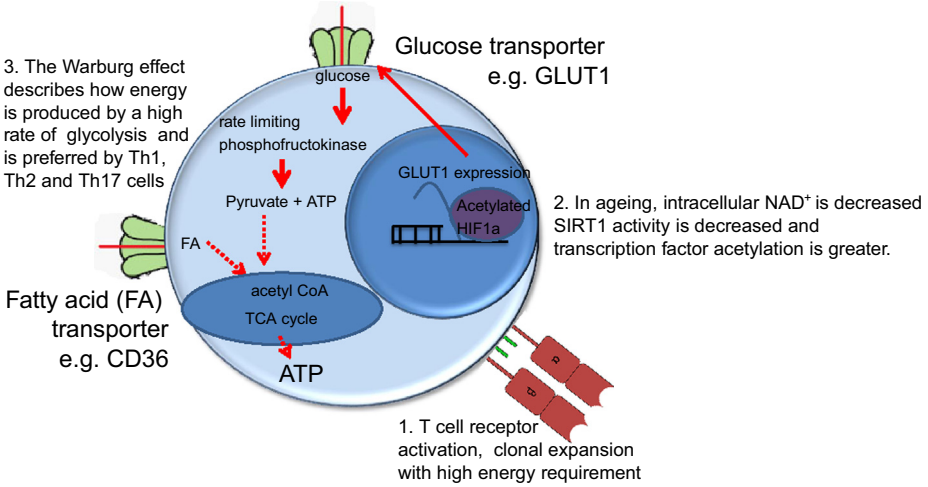

Fig. 2. Metabolic control nodes of glycolysis and oxidative phosphorylation and the Warburg effect.