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REVIEWS: CURRENT TOPICS

Role of lipids in the metabolism and activation of immune cells

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Abstract

Immune cell plasticity has extensive implications in the pathogenesis and resolution of metabolic disorders, cancers, autoimmune diseases and chronic inflammatory disorders. Over the past decade, nutritional status has been discovered to influence the immune response. In metabolic disorders such as obesity, immune cells interact with various classes of lipids, which are capable of controlling the plasticity of macrophages and T lymphocytes. The purpose of this review is to discuss lipids and their impact on innate and adaptive immune responses, focusing on two areas: (1) the impact of altering lipid metabolism on immune cell activation, differentiation and function and (2) the mechanism by which lipids such as cholesterol and fatty acids regulate immune cell plasticity.

Keywords: Inflammation; Macrophages; T lymphocytes; Oxysterols; Fatty acids

1. Introduction

1.1. Immune cell polarization

The immune system protects the body from infection by destruction and removal of pathogens. The innate immune system acts as the first-line defense and involves the activation and recruitment of neutrophils and macrophages that phagocytose pathogens. The adaptive immune system acts as the second line of defense by providing long-term protection from specific pathogens through the production of antigen-specific antibodies. Pathogens are presented to B and T lymphocytes as antigens. This interaction leads the activation of T cells that release cytokines and stimulates B cells to produce antibodies that aid in the recognition and killing of invading pathogens.

Immune cells are classified based on the expression of cellular markers and secretion of cytokines. During bacterial infections, macrophages are defined as either classic (M1) or alternative activated (M2). M1 macrophages function to amplify the inflammatory response through release of cytokines that recruit other immune cells to the site of inflammation. They secrete inflammatory markers interferon gamma (IFN-γ), interleukins IL-1β and IL-6, C-X-C motif chemokines CXCL10 and CXCL9 and tumor necrosis factor TNF-α. M1 polarization is also identified by the presence of cellular makers CD319, CD274 and CD38 [1]. In contrast, M2 macrophages are involved in tissue repair and remodeling. M2 macrophages are defined by the expression of antiinflammatory markers IL-4, IL-13 and/or IL-10 and cell surface markers CD206, CD301 and CD163 [2].

Similar to macrophages, T lymphocytes secrete cytokines and soluble protein factors that suppress, activate and/or kill neighboring infected cells. T lymphocytes originate from naïve cells in the thymus that differentiate into two primary subsets of T lymphocytes and are distinguished by the presence of the cell surface markers CD8 and CD4. These cells further undergo proliferation and differentiate into effector or memory T lymphocytes. CD8 lymphocytes can differentiate into cytotoxic T lymphocytes (CTLs). CTLs induce apoptosis in targeted cells by secreting proteins, granzyme and perforin and also by inducing the Fas ligand/Fas signaling pathway [3]. CD4 effector T lymphocytes can differentiate into T helpers Th1, Th2 and Th17 or T regulatory (Tregs) lymphocytes. Similar to macrophages, Th1 lymphocytes are primarily classified as proinflammatory and defined by the secretion of IFN-γ and TNF-α [4]. Th2 lymphocytes are primarily antiinflammatory and defined by secretion of IL-13, IL-4, IL-10 and IL-5. Th17 T lymphocytes express a proinflammatory phenotype defined by the secretion of IL-17 and IL-22. Over the years, Tregs have received vast interest due to their ability to dampen inflammation [5–7]. These suppressive lymphocytes express the protein Foxp3 and CD25 and secrete cytokines such as TGF-β, IL-10 and IL-35 that directly suppress the inflammatory function of Th1, Th17, CTL and B cells [8].

1.2. Immune cell polarization in metabolic diseases

Altered lipid homeostasis underlies the etiology of some of the most common chronic diseases — obesity, cardiovascular disease (CVD) and liver disease. Not coincidentally, these conditions are also associated with chronic inflammation and inflammatory polarization of macrophages and T lymphocytes (Fig. 1). This correlation has led to much interest in understanding the impact lipids have on immune

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polarization and the impact immune polarization has on lipid handling in these metabolic diseases.

In 2007, Lumeng *et al.* first introduced the concept that adipose tissue macrophages (ATMs) could undergo a similar polarization as bacteriostatic macrophages [9]. In lean AT, ATMs primarily display an M2 phenotype while there are more M1 macrophages present under obese conditions. The M1 macrophages were classified as M1 because they secrete inflammatory cytokines, TNF-α and IL-1β, that further disrupt adipocyte homeostasis and perpetuate local and systemic insulin resistance [9]. This classification was considered the dogma for ATM classification. However, classifying tissue immune cell polarization based on phenotypes induced *in vitro* or during an infection does not fully portray their phenotype in other tissues [10].

In a recent study, proteomic analyses comparing ATMs from lean and obese adipose tissue (AT) introduced the concept of "metabolically activated (MMe) macrophages" in obese AT [1]. Inflammatory ATMs from obese AT were found to have a distinctly unique phenotype from M1 polarized macrophages present during bacterial infection. Macrophages acquired from bacterial infection and lipopolysaccharide (LPS)-treated macrophages express cellular markers CD319, CD274 and CD38 that are dependent on the type I interferon signaling response [1]. In contrast, ATMs from obese individuals express lipid transport proteins ATP-binding cassette member 1 (ABCA1) and fatty acid translocase (CD36) [1]. This MMe phenotype is reproducible *in vitro* by treating macrophages with palmitate, insulin and glucose [1]. The one consistent similarity between the M1 and MMe macrophages is the secretion of proinflammatory cytokines, TNF-α, IL-6 and IL-1β. In both types, IL-1β induction was dependent on the activation of the Toll-like receptors TLR2 and TLR4 [1]. These findings demonstrate that the classic nomenclature for M1 and M2 macrophages is upheld when macrophages are classified by cytokine production, but the mechanism of activation and other aspects of the functional phenotype depend on the tissue environment and disease state.

Macrophages are similarly important in liver disease and CVD. Much like the lean-to-obese adipose tissue transition, macrophages play an important role in the pathogenesis of chronic liver injury and nonalcoholic fatty liver disease (NAFLD). There are two main types of macrophages in the liver — embryonic-derived Kupffer cells and monocyte-derived $CD11b^{+}Ly6C^{+}$ macrophages [11]. Kupffer cells sense tissue injury and are responsible for initiating inflammatory stimuli. The $Ly6C^{hi}$ monocytes are recruited by CCR2-dependent mechanisms [12,13]. The conversion of $Ly6C^{hi}$ monocytes to macrophages promotes resolution of inflammation and regression of fibrosis [14–16].

Monocyte-derived macrophages are the primary immune cell to accumulate in atherosclerotic plaques [17]. The mere accumulation of macrophages in plaques increases the vulnerability of plaques to rupture. Both M1 and M2 polarized macrophages are present in plaques, although the importance of their relative ratios *in vivo* is still not well understood [18–20]. With regard to lipids, cholesterol efflux from macrophages is important for resolution of atherosclerosis. In early atherosclerotic plaques, monocytes that are differentiating into macrophages become cholesterol laden foam cells but undergo clearance via efferocytosis [21]. This resolves the inflammation in the plaque. In an advanced cell, efferocytosis declines and, under inflammatory stimuli, apoptotic macrophages become necrotic. Necrosis of macrophages induces degradation of the collagenous fibrous cap over the plaque and rupture [21,22].

Much like macrophages, Th1 lymphocytes are more prevalent in metabolic tissues (AT, liver) in disorders such as obesity, diabetes and

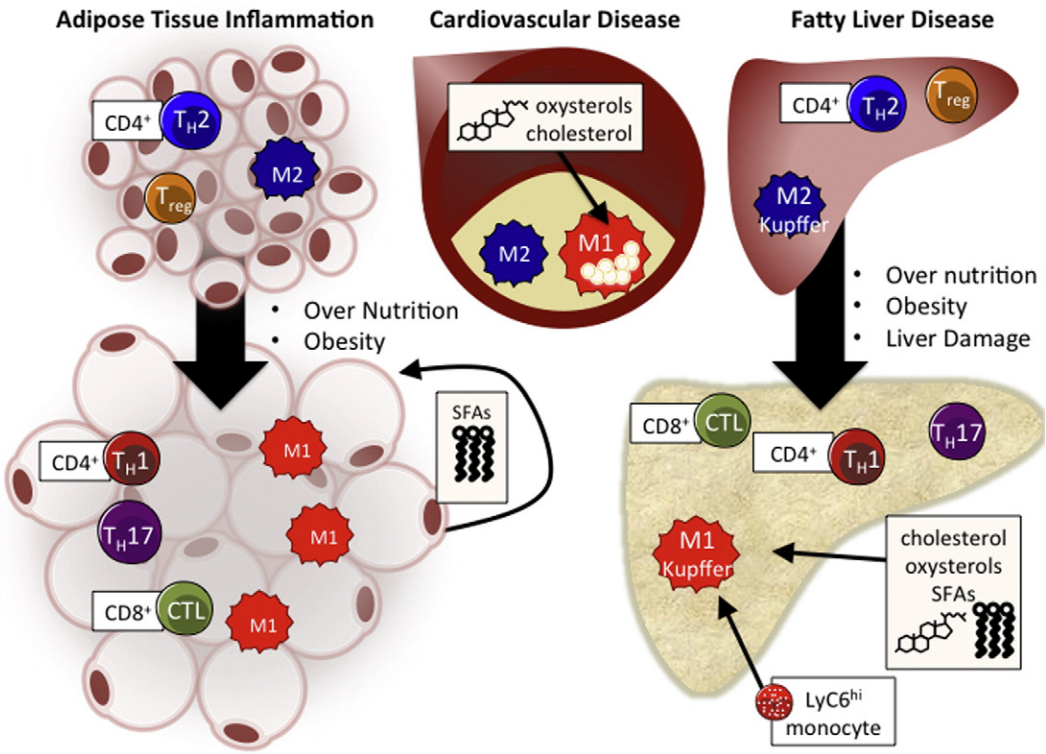

Fig. 1. **Immune cell phenotypes in adipose tissue, arteries and liver during metabolic disease.** In lean adipose tissue, $CD4^{+}$ lymphocytes and M2 macrophages express an antiinflammatory phenotype. During conditions of overnutrition or obesity, lipid mediators (SFA) are elevated and regulate the influx and activation of inflammatory macrophages (M1) and lymphocytes (Th1, CTL and Th17) in adipose tissue. In CVD, both M1 and M2 macrophages are present. In the arteries, macrophages infiltrate the arteries and engulf oxidized cholesterol, converting macrophages into foam cells. Similar to adipose tissue, the liver consists of antiinflammatory immune cells such as M2 associated Kupffer cells and $CD4^{+}$ lymphocytes (Th2 and Treg). In fatty liver disease, lipid levels are increased and lead to the recruitment of inflammatory monocytes ($Ly6C^{hi}$) that differentiate into M1 macrophages. Likewise, inflammatory Th1, CTL, and Th17 cells infiltrate the liver.