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Mini-review

Immuno-metabolism and adipose tissue: The key role of hematopoietic stem cells

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ABSTRACT

The field of immunometabolism has come a long way in the past decade, leading to the emergence of a new role for white adipose tissue (WAT) that is now recognized to stand at the junction of immune and metabolic regulations. Interestingly, a crucial role of the abundant and heterogeneous immune population present in WAT has been proposed in the induction and development of metabolic diseases. Although a large body of data focused on mature immune cells, only few scattered studies are dedicated to leukocyte production, and the activity of hematopoietic stem cells (HSC) in these pathological states. Considering that blood cell production and the differentiation of HSCs and their progeny is orchestrated, in part, by complex interacting signals emanating from their microenvironment, it thus seems worth to better understand the relationships between metabolism and HSC. This review discusses the alterations of hematopoietic process described in metabolic diseases and focused on the emerging data concerning HSC present in WAT.

1. Introduction

The last decades have challenged the traditional concept of white adipose tissue (WAT), transforming it from an inert storage depot into a highly metabolic active tissue and an important endocrine organ playing a pivotal role in controlling whole-body energy homeostasis [1,2]. Moreover, largely described immunological mechanisms underlie WAT metabolic control and have instigated a new field of research termed immunometabolism [3]. In this Review we outline the advances in our understanding of these new metabolic players, focusing on the emerging data concerning hematopoietic stem cells.

2. Crucial role of immune components in metabolic homeostasis

Several lines of evidence underscore the close relationship between metabolism and immunology in WAT. Indeed, an abundant and heterogeneous immune cell population is co-localized with adipocytes in WAT [4]. In mice, as in humans, these immune cells account for 30–40% of the stroma-vascular fraction, and therefore for almost 20% of the total cells in WAT, in both subcutaneous and visceral fat pads. Considering the large amount of WAT in the body, immune cells present in this tissue may play a crucial role in immunity and physiopathology. In physiological conditions, innate and adaptive immune cells fulfil important housekeeping functions [5], among which the clearance of apoptotic adipocytes, extracellular matrix modeling, angiogenesis, adipogenesis and the preservation of insulin sensitivity in lean subjects [6].

The immune composition of WAT is regulated both by acute and chronic stimuli including diet, body weight status, cold exposure, and feeding and fasting [4]. Seminal works in 2003 have

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demonstrated that obesity is associated with a low-grade inflammation and an increase in macrophage population [7,8]. Numerous reports have since demonstrated that in obesity the number and phenotype of WAT resident immune cells is altered, contributing to metabolic dysfunctions [9]. Obesity and insulin-resistance have the capacity to skew immune cells from anti-inflammatory subtypes toward more pro-inflammatory subtypes. This includes a switching of macrophage polarization from M2-like cells to more pro-inflammatory M1-like cells and the loss of regulatory T cells in WAT [10,11]. The local effects of these compositional changes during obesity drive WAT inflammation and influence the capacity of adipocytes to store lipid, their insulin sensitivity, the systemic glucose metabolism, and metabolic homeostasis [4]. In contrast, studies on animal models show that whatever the method used, the resolution of inflammation prevents or almost invariably delay the onset of obesity and/or insulin resistance [12]. Moreover, in humans, weight loss in obese patients resulted in marked reductions of inflammatory cells in WAT, and an improvement in insulin sensitivity [13]. Metabolism and inflammation are thus tightly connected in WAT, and an ever-increasing body of work demonstrates that reciprocal interactions between metabolic systems and subsets of cells of the immune system have pivotal roles in the pathogenesis of obesity-associated diseases. For example, the severity of metabolic disorder observed in obese people directly correlates with the amount of WAT myeloid and lymphoid cells [7,14–16].

Metabolic disorders do not only induce low grade inflammation in WAT, they are also associated with disorders in circulating leukocytes. Indeed, in humans, obesity and insulin resistance are associated with an increase in peripheral blood white blood cell and of inflammation parameters such as the C-reactive protein [17–21] parameters that decrease after gastric bypass surgery [22]. In mice, leptin-deficient ob/ob mice as well as db/db mice, which have an inactive leptin receptor, have a reduced lymphocyte number in peripheral blood [23,24]. An association between blood leukocyte count and diabetes risk has also been recently suggested [25,26]. Moreover, published data suggest that obesity and insulin resistance also impair adaptive immune response, leading to altered response to pathogens [4,27]. Given the crucial role of leucocytes in the development of metabolic diseases, it is logical to assume that leukocyte production is altered by disease states.

3. Metabolic disorders and bone marrow hematopoiesis

Circulating blood cells as well as tissue resident immune cells are produced via the tightly regulated process of hematopoiesis that produces billions of new leukocytes and erythrocytes each day. Indeed, the lifespan of individual cell types varies tremendously, ranging from a few hours for certain granulocytes, to many years for classes of lymphocytes, including memory T-cells. The classical hematopoietic ontogeny has long been described as hierarchical system originating in the hematopoietic stem cell (HSC) that differentiates into myeloid and lymphoid lineages through a series of proliferative, lineage-restricted progenitor cells, culminating in terminal, mature myeloid and lymphoid elements [28] (Fig. 1). HSCs, as other stem cells, are defined by their ability to self-renew, and to differentiate into multiple lineages.

In adult mammals, the bone marrow (BM) is described as a complex architecture wherein a rare population of HSC and progenitor cells occupy a specific micro-environment (niche) composed of multiple cell types, including osteoblastic, perivascular, endothelial and mesenchymal cells as well as adipocytes. In addition, the BM functions as a primary and secondary lymphoid organ and hosts various mature immune cell types, including T and B cells, dendritic cells and macrophages that contribute to the HSC

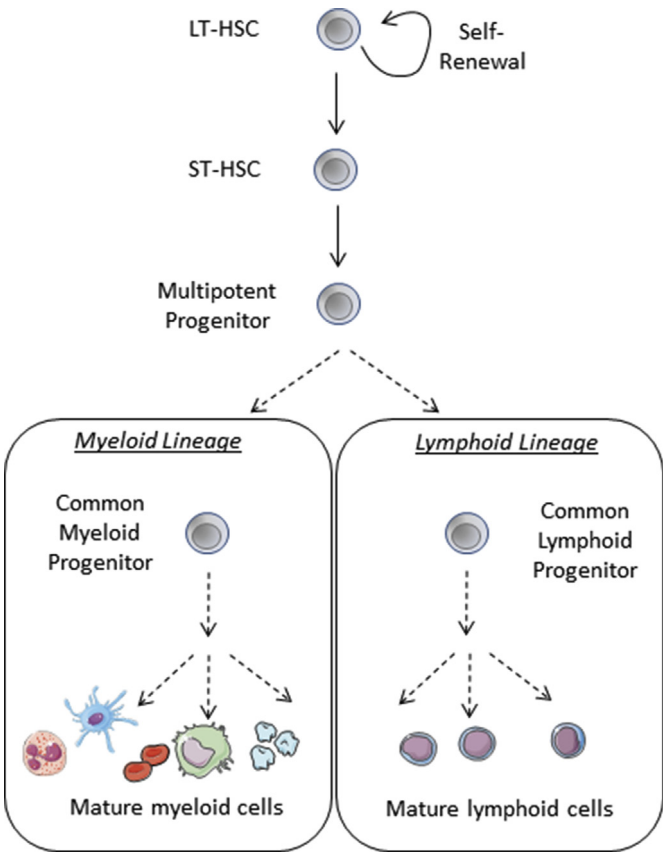

Fig. 1. Schematic representation of hematopoietic process. LT-HSC: Long-Term Hematopoietic Stem Cells; ST-HSC: Short-Term Hematopoietic Stem Cells.

niche [29,30]. Last, HSCs are not randomly located in the BM, but have differentiation stage-specific or age-specific positions, and their positioning exposes them to differing conditions. One hypothesis holds that the positioning corresponds to the heterogeneity of the HSC pool in term of cell cycling or responsiveness to mobilization signals [31].

The precise integrated mechanisms that underlie HSC fate decisions are the purpose of many studies, and it is generally accepted that these decisions are regulated by both intrinsic factors and extrinsic cues provided by their niches [32]. Indeed, a large and still not fully characterized repertoire of molecules ranging from cell surface receptors through signal transduction molecules and a myriad of transcription factors are now recognized for their regulatory roles in HSCs. Among these so-called “intrinsic regulators”, transcription factors have attracted much attention given their essential roles in the initial development, expansion and maintenance of HSC, but also in the development of pathologies such as leukemia [33–35]. In parallel, signals derived from the HSC niche are necessary to regulate demand-adapted responses of HSCs and progenitor cells throughout life. Indeed, the HSC niche comprises a number of important signaling pathways, an array of adhesive molecules and many soluble cytokines. The interplay between these components predominantly keeps HSCs in a quiescent state, but can also accelerate mature blood cell replenishment in cases of urgent need, such as during infection or excessive blood loss. A great number of molecules described in the adult BM niche display functions as HSC regulators, overlapping in function or interacting with each other to modulate HSC behavior [36]. The discovery that perturbations of the HSC niche can lead to hematopoietic disorders,