METABOLISM CLINICAL AND EXPERIMENTAL 67 (2016) 106–114

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Mechanisms of marrow adiposity and its implications for skeletal health

Annegreet G. Veldhuis-Vlug[a], *Clifford J. Rosen*[b,*]

[a] *Department of Endocrinology and Metabolism, Academic Medical Center Amsterdam, The Netherlands*
[b] *Maine Medical Center Research Institute, Scarborough, ME, USA*

ARTICLE INFO

Article history:
Received 13 July 2016
Accepted 22 November 2016

Keywords:
Mesenchymal stem cell
Osteoblast
Adipocyte
Bone marrow adiposity
Energy utilization

ABSTRACT

The bone marrow niche is composed of cells from hematopoietic and mesenchymal origin. Both require energy to power differentiation and these processes are intimately connected to systemic metabolic homeostasis. Glycolysis is the preferred substrate for mesenchymal stromal cells in the niche, although fatty acid oxidation and glutaminolysis are important during stage specific differentiation. Autophagy and lipophagy, in part triggered by adenosine monophosphate-activated protein kinase (AMPK), may also play an important but temporal specific role in osteoblast differentiation. Enhanced marrow adiposity is caused by clinical factors that are genetically, environmentally, and hormonally mediated. These determinants mediate a switch from the osteogenic to the adipogenic lineage. Preliminary evidence supports an important role for fuel utilization in those cell fate decisions. Although both the origin and function of the marrow adipocyte remain to be determined, and in some genetic mouse models high marrow adiposity may co-exist with greater bone mass, in humans changes in marrow adiposity are closely linked to adverse changes in skeletal metabolism. This supports an intimate relationship between bone and fat in the marrow. Future studies will likely shed more light on the relationship of cellular as well as whole body metabolism on the ultimate fate of bone marrow stromal cells.

1. Introduction

The bone marrow is composed of distinct cell types that exist at several developmental levels. Hematopoietic elements are the most prevalent and include erythrocytes, neutrophils, lymphocytes, and platelets. Hematopoietic stem cells (HSCs) are also found in even more abundance, primarily in or near niches adjacent to the endosteal bone surface or capillaries [1]. These HSCs are multi-potent with short and long term regenerative capacity to differentiate into the myeloid, lymphoid and erythroid lineages. Recently, attention has turned to cells within the marrow that originate from a mesenchymal source; these include a wide array of developmentally distinct cells including adipocytes, osteoblasts, and stromal fibroblasts. Mesenchymal stromal cells (MSCs) are also multi-potent and within the marrow can become mature adipocytes or osteoblasts [2]. These cells differ from HSCs in several important ways, including their origin, their ability to adhere to plastic in vitro and potentially their use of substrates for differentiation [3]. (See Fig. 1.)

The bone marrow niche is an anatomical and functional unit that integrates endocrine, autocrine and paracrine signals for whole body homeostasis and provides a unique home for the stem cell [4]. Therefore it is not surprising that substrate availability plays an important role in cell fate decisions. Cells in the niche also influence their neighbors; for example adult mesenchymal cells, and in particular the osteoblast, have a vital role in maintaining the bone marrow niche for hematopoiesis

* *Corresponding author at:* 81 Research Drive, Scarborough, ME, 04074.
E-mail addresses: a.g.veldhuis-vlug@amc.uva.nl (A.G. Veldhuis-Vlug), rosenc@mmc.org (C.J. Rosen).

http://dx.doi.org/10.1016/j.metabol.2016.11.013
0026-0495/

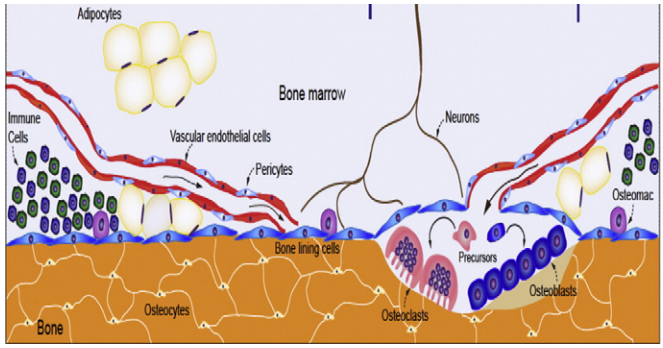

Fig. 1 – The bone marrow niche is a multicellular compartment of mesenchymal and hematopoietic progenitors that is highly vascularized. Blood supplies basic nutrients that are needed for each of the cell types shown. The marrow adipocytes are located on the endosteal surface of bone as well as throughout the marrow, and are increased in conditions such as calorie restriction and diabetes. It is conceivable that marrow adipocytes could arise from vascular endothelial cells, pericytes, bone lining cells or mesenchymal precursors. Notwithstanding their unclear origin, both osteoblast and adipocyte precursors require nutrients to fuel the needs of differentiation. This need links the marrow compartment with the peripheral sources of energy, particularly fat depots and the liver. Hence, both transcriptional programming and metabolic programming determine the fate of mesenchymal progenitors, which in turn, define the marrow adiposity phenotype.

[5]. The role of the adipocyte in hematopoiesis is more controversial but it is thought that these cells prevent active hematopoiesis at least during times of repopulation of the marrow after HSC transplantation [6].

The bone marrow niche has tremendous energy requirements. Over 2 million erythrocytes leave the marrow every second just to sustain the hemoglobin carrying capacity for oxygen, and this is only one of many hematopoietic cell types that are differentiating and then exiting the niche. During an inflammatory response anywhere in the body or activation of the sympathetic nervous system, neutrophils and some hematopoietic progenitors enter the circulation in large amounts [7]. These processes require adenosine triphosphate (ATP) and those molecules are principally derived from either glycolysis or oxidative phosphorylation in each cell. Moreover, the niche has to nourish progenitors and this requires not only nutrients but also support for their metabolism to generate ATP for subsequent use by the cell. During acute infectious episodes, hematopoietic cells may require an additional energy burst, probably through oxidation of fatty acids, to function properly. The bone marrow niche is uniquely suited anatomically to provide that support because of its rich vasculature, and, in the endosteal niche, abundant neural innervation [8]. There are also areas of hypoxia, which are attractive regions for HSC homing, particularly for quiescent cells [9]. Hypoxia is a potent stimulus for hypoxia-inducible factor 1-alpha (HIF1a), which can then induce a differentiation program for both pre-osteoblasts and HSCs [10]. HIF1a also serves to stimulate vascular endothelial growth factor (VEGF) that can in turn enhance vascular development and promote glycolysis through up-regulation of several key genes including glucose transporter 1 (GLUT1) [11].

In this review, we will discuss the energy needs of bone marrow MSCs particularly as it relates to lineage allocation between osteoblasts and adipocytes. We will then support the premise that those cell fate decisions have major clinical implications.

2. Bioenergetics of Mesenchymal Stem Cells, Osteoblast and Adipocyte

Each of the cells in the bone marrow niche has its own specific nutrient requirement in order to survive, particularly in a hypoxic environment and these, in turn, are linked to ATP demands. In general, the more differentiated the cell, the greater the energy needs. However, within that context, there are major differences between mature osteoblasts and adipocytes. First, when considering survival and maintenance of MSC 'stemness' in the relative hypoxia of the marrow, there is a need for metabolic adaptation. Stemness allows a stable pool of progenitors that can be called on in numerous circumstances, particularly injury and inflammatory states [12]. Hypoxia induces the stabilization of HIF1a, a major transcription factor for stem cells and progenitors as well as multiple downstream target genes, particularly VEGFa [13]. Metabolic reprogramming of quiescent cells is necessary to prevent differentiation and this occurs through a shift from oxidative phosphorylation to glycolysis. Importantly, glycolysis, although less efficient in generating ATP than mitochondrial oxidation, reduces oxidative stress and reactive oxygen species (ROS) generation, key elements that drive stem cell differentiation.

Although glycolysis is the major driver of ATP generation in MSCs, entrance into a specific differentiation program, either adipogenic or osteogenic, requires distinct metabolic requirements that are very context specific [14]. For adipocytic differentiation, several studies have suggested that mitochondrial oxidation of fatty acids and the generation of ROS are essential to achieve full maturation. The process of glucose entry and fatty acid oxidation through the Krebs Cycle generates more molecules of ATP per mol of glucose (36:1) than glycolysis (2:1), but it comes at a cost as mitochondrial respiration leads to the generation of ROS from the electron transport chain (ETC). ROS (e.g. H_2O_2, superoxides) can further suppress mitochondrial respiration and promote an adipogenic program that is associated with more