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Hematopoietic stem/progenitor involvement in retinal microvascular repair during diabetes: Implications for bone marrow rejuvenation

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ABSTRACT

The widespread nature of diabetes affects all organ systems of an individual including the bone marrow. Long-term damage to the cellular and extracellular components of the bone marrow leads to a rapid decline in the bone marrow-hematopoietic stem/progenitor cells (HS/PCs) compartment. This review will highlight the importance of bone marrow microenvironment in maintaining bone marrow HS/PC populations and the contribution of these key populations in microvascular repair during the natural history of diabetes. The autonomic nervous system can initiate and propagate bone marrow dysfunction in diabetes. Systemic pharmacological strategies designed to protect the bone marrow-HS/PC population from diabetes induced-oxidative stress and advanced glycation end product accumulation represent a new approach to target diabetic retinopathy progression. Protecting HS/PCs ensures their participation in vascular repair and reduces the risk of vasogdegeneration occurring in the retina.

1. Introduction

Based on an epidemiology study published in 2014, diabetes affects 382 million people worldwide (Forouhi & Wareham, 2014)). Moreover, the prevalence of diabetes continues to increase globally: about 592 million people are estimated to be diagnosed with diabetes by 2035 (Forouhi & Wareham, 2014). Diabetic retinopathy (DR) is the most prevalent complication of diabetes and affects about 93 million individuals worldwide. DR accounts for 4.8% of the number of cases of blindness (37 million) worldwide (Antonetti et al., 2006; Cheung, Mitchell, & Wong, 2010; Klein, 2007). The number of individuals with vision-threatening DR, such as severe non-proliferative DR (NPDR) and PDR, is estimated to rise to 191 million by 2030. The number of individuals with diabetic macular edema (DME) is expected to increase to 56.3 million by that same year (International Diabetes Federation, 2015; Yau et al., 2012). Importantly, the presence of DR indicates microcirculatory dysfunction in other organ systems (Tooke, 1989). Despite better control of the modifiable risk factors (glucose, blood pressure and lipids) and better screening programs, DR remains a global health issue. A weakness of current therapies for DR (laser photocoagulation, injection of corticosteroids or anti-VEGF antibodies, or vitreoretinal surgery) is that these approaches do not correct the underlying pathology and carry significant side effects.

The pathogenesis of DR suggests that it is a progressive vasodegenerative condition associated first with the loss of contractile pericytes followed by a widespread death of endothelial cells. Loss of this cellular support system culminates in under perfused areas of ischemia, depriving retina of a vital nutrient supply which triggers the remaining endothelium to release “vessel building” cytokines and growth factors such as vascular endothelial growth factor (VEGF). In addition, the retina faces a unique challenge in diabetes due to the combination of high metabolic demand and minimal vascular supply. This limits the retina’s ability to adapt to the metabolic stress of diabetes. The retina can lose as much as 38% of resident endothelial cells within 20 months of experimental diabetes (Joussen et al., 2009).

DR typically progresses because hyperglycemia and dyslipidemia are not adequately controlled (Kilpatrick, Rigby, & Atkin, 2006; Orlandi et al., 2010). While all microvascular beds are affected by diabetes, the ones resulting in the most profound impact on the diabetic individual are the kidney, retina, and nerves. The resultant nephropathy, retinopathy, and neuropathy share common etiologies and pathogenic mechanisms including altered metabolic and functional/hemodynamic

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factors and disturbed interactions between environmental, hormonal and genetic factors (Marcovecchio, Tossavainen, & Dunger, 2010).

In this review, we are focusing on understanding the contribution of the bone marrow in the pathogenesis of DR and we provide an argument that the bone marrow should be considered a new target tissue for treatment of DR.

2. Bone marrow and hematopoietic stem/progenitor cells (HS/PCs)

The bone marrow provides the primary conducive environment to harbor HS/PCs in adults and children. The bone marrow can selectively give rise to a variety of cell types, including lymphoid and myeloid cells, platelets, and red blood cells (Calvi & Link, 2014; Morrison & Scadden, 2014). About a million mature blood cells are produced per second in the normal adult human bone marrow. While the majority of HSCs are in G0 phase, it is interesting to note that under physiologic conditions, there exists a perfect balance between responding to the enormous demand for hematopoietic cells and the preservation of an adequate pool of HSCs. This balance between regulated self-renewal, expansion, and differentiation is of critical importance as too little self-renewal can jeopardize the ability of the bone marrow to sustain hematopoiesis throughout the lifetime of the individual while excessive differentiation can result in aberrant phenotypes such as leukemogenesis (Attar & Scadden, 2004). Normally, HSCs give rise to 10% myeloid and 90% lymphoid donor type cells; however, this balance may shift towards more myeloid and less lymphoid cell types with a disease state such as diabetes or in aging, creating myeoloidosis (Muller-Sieburg & Sieburg, 2008).

Diabetes leads to changes in cellular metabolism that result in overproduction of reactive oxygen species, genetic instability, and disruption of homeostatic pathways. These metabolic changes, not unexpectedly, adversely affect the bone marrow and lead to the myeoloidosis (Hazra et al., 2013). The bone marrow provides specialized niches for specific stem cell types (Morrison & Scadden, 2014). The spindle-shaped N-cadherin expressing osteoblast cells (SNO) lining the endosteal bone surface act as the endosteal niche for the HSCs while the bone marrow sinusoids together with HSCs constitute the vascular niche in the bone marrow (Fig. 1). The HSCs near the endosteum are the longest-lived cells possessing unlimited self-renewal potential and are called long-term repopulating HSCs (LTR-HSCs). The well-orchestrated dynamics of the processes of self-renewal and release governs the supply of HSCs present in the circulation (Muller-Sieburg & Sieburg, 2008). LTR-HSCs respond to stimuli or injury and travel to the sinusoid; at this point, they lose their unlimited self-renewal capability and become committed short-term repopulating HSCs (STR-HSCs). Typically, 60% of STR-HSCs are found near sinusoidal niche, while only 20% of HSCs (i.e. LTR-HSCs) are at the endosteal surface. These two bone marrow stem cell niches have different oxygen levels further distinguishing their specialization.

2.1. Key molecular targets affecting bone marrow function

We reported that ataxia telangiectasia mutated (ATM) is critical for maintaining long-term populating HSCs in the bone marrow (Bhatwadekar et al., 2016). ATM helps correct DNA damage by recruiting DNA repair proteins to sites of DNA damage. The ATM is necessary for the survival of LTR-HSCs and the loss of ATM results in an increase in more committed STR-HSCs. This imbalance may eventually contribute to the development of/the DR. Forkhead box-O (FoxO) also plays a critical role in maintaining HSC population. Conditional deletion of FoxO isoforms FoxO1, FoxO3, and FoxO4 from bone marrow induces HSC imbalance (less LTR-HSC and more STR-HSC) results in an increase in oxidative stress (Coffer & Burgering, 2007; Furukawa-Hibi, Yoshida-Araki, Ohta, Ikeda, & Motoyama, 2002; Tothova et al., 2007), whereas overexpression of FoxO decreases oxidative stress and apoptosis (Kops et al., 2002). The functional interaction between FoxO3 and ATM halts DNA damage due to activation of DNA damage-inducible gene 45 (Gadd45).

In addition to hyperglycemia-induced bone marrow damage, we also reported that dyslipidemia critically affects bone marrow function. Our published studies demonstrate that diabetes-induced derailment of cholesterol and sphingolipid metabolism leads to shift in LTR/STR-HSCs, as well as myeloid/lymphoid cell balance. As we previously demonstrated, the central enzyme of sphingolipid metabolism, acid sphingomyelinase (ASM) is highly upregulated in bone marrow niche in diabetes. As shown in Fig. 2, when injected into the vitreous, control HSC migrate into the areas of retinal vascular damage, home to the vasculature and aid in the repair process. Diabetic HSCs with a high level of ASM expression level lose the ability to migrate and thus remain

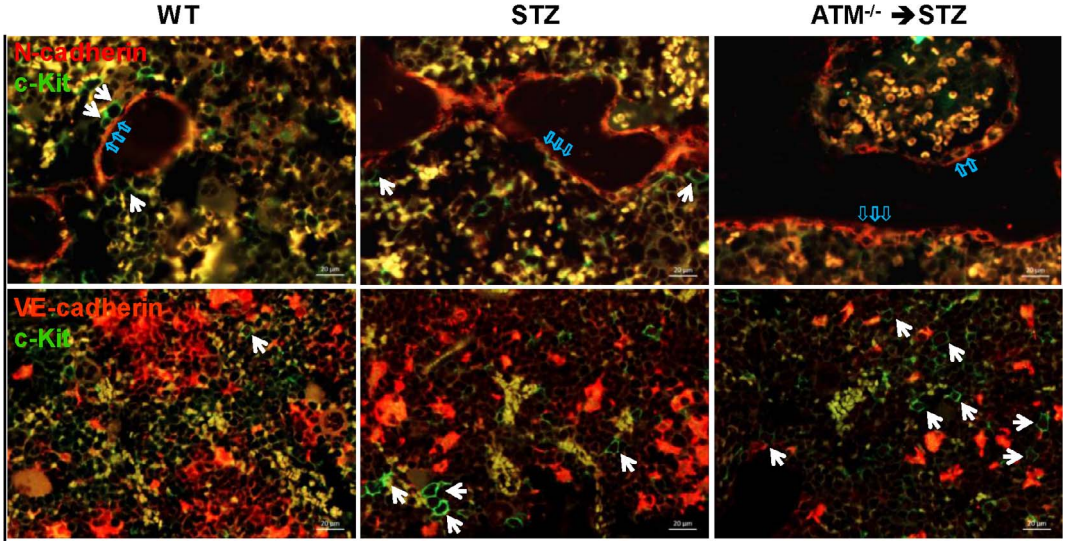

Fig. 1. Localization of c-Kit$^+$ cells in mouse bone marrow. Upper panel: immunofluorescence staining of N-cadherin (red) and c-Kit (green) in demineralized mouse femurs. Some c-Kit$^+$ cells (white arrow) localized to endosteal niche (blue arrow) are defined as long-term repopulating (LTR)-hematopoietic stem cells (HSCs); Lower panel: mouse femurs stained for VE-cadherin (red) and c-Kit (green). c-Kit$^+$ cells (white arrow) located at vascular niche are defined as short-term repopulating (STR)-HSCs. Representative images showing a reduced number of LTR-HSCs and increased STR-HSCs/LTR-HSCs in the STZ-induced diabetic bone marrow. ATM$^{-/-}$ intensified diabetes-mediated defects of LTR- and STR-HSCs imbalance in the bone marrow. *Abbreviations:* WT, wild type; STZ, streptozotocin; ATM, ataxia telangiectasia mutated.