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Review

Stem cells and bone diseases: New tools, new perspective

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ABSTRACT

Postnatal skeletal stem cells are a unique class of progenitors with biological properties that extend well beyond the limits of stemness as commonly defined. Skeletal stem cells sustain skeletal tissue homeostasis, organize and maintain the complex architectural structure of the bone marrow microenvironment and provide a niche for hematopoietic progenitor cells. The identification of stem cells in the human post-natal skeleton has profoundly changed our approach to the physiology and pathology of this system. Skeletal diseases have been long interpreted essentially in terms of defective function of differentiated cells and/or abnormal turnover of the matrix that they produce. The notion of a skeletal stem cell has brought forth multiple, novel concepts in skeletal biology that provide potential alternative concepts. At the same time, the recognition of the complex functions played by skeletal progenitors, such as the structural and functional organization of the bone marrow, has provided an innovative, unifying perspective for understanding bone and bone marrow changes simultaneously occurring in many disorders. Finally, the possibility to isolate and highly enrich for skeletal progenitors, enables us to reproduce perfectly normal or pathological organ miniatures. These, in turn, provide suitable models to investigate and manipulate the pathogenetic mechanisms of many genetic and non-genetic skeletal diseases. **This article is part of a Special Issue entitled Stem cells and Bone.**

Contents

Introduction

Post-natal stem cells self-renew and differentiate to replenish the mature cell compartments of the tissues in which they reside. The very fact that stem cells for bone reside in bone marrow may suffice to highlight the fact that bone and bone marrow are functionally and anatomically continuous with one another. The continuity of bone and bone marrow is best reflected in the use of the term bone/bone marrow organ, which Maureen Owen introduced as the existence of a common progenitor for all skeletal tissues in the bone marrow emerged [1]. Bone and bone marrow share their vascularity, which includes vessels traversing the boundaries between bone and marrow space in both directions and often originating from and returning to the bone marrow after looping through bone. In situ, stem cells for bone are perivascular cells [2,3], and at least some of the defining phenotypic features of perivascular progenitors in the bone marrow are shared by perivascular

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cells found within bone proper [4]. Bone formation and adipogenesis, which represent the canonical differentiation pathways of bone marrow stromal progenitors, are both perivascular events, as both osteoblasts and adipocytes are themselves perivascular cells. These simple facts would suggest that any attempt to understand the pathophysiology of bone in terms of cell dynamics should not exclude consideration of the bone marrow. However, the dominant paradigm adopted in pursuing an understanding of bone pathophysiology at the cellular level has been centered for years on the dynamics of osteoblasts and osteoclasts. On the other hand, and understandably enough, the dominant view of stem cells in bone has been centered, as in other fields, on the potential use of stem cells as therapeutic tools: replacement bricks for bone tissue engineering, or perhaps vehicles for gene therapy (as successfully pursued in other fields) in what is commonly referred to as "innovative therapies" as part of "regenerative medicine." However, in all systems, the notion of stem cells is per se coupled to an appreciation that differentiated tissues are part of a lineage, and that diseases of a given system, in turn, can be seen as diseases of differentiated cells, or of the lineage as a whole; and may reflect inherent dysfunction of differentiated cells or of lineages, as well as secondary effects of exogenous signals, regulators or cues. Pathogenic effects of a gene defect can be manifested in mature cells only, as is the case, for example, in sickle cell anemia; or conversely, they can affect the entire lineage, as for example in thalassemia. The following pages are devoted to a brief discussion of how the notion of stem cells in bone can be bent to profit not only for treating, but also for understanding diseases, based on the assumption that proper understanding is key to effective therapy. In doing so, we will adhere to the dual nature and function of skeletal stem cells, which act as progenitors, and act as non-progenitors [5]. Skeletal stem cells (also known as bone marrow-derived "mesenchymal" stem cells) generate all different lineages that together comprise the skeleton, and those lineages only. At the same time, they organize the vasculature of bone and bone marrow [2], establish the microenvironment for growth and differentiation of hematopoietic cells and establish the "niche" for hematopoietic stem cells (HSCs) [2,3,6]. This notion comes originally from studies using human cells and refined in vivo transplantation approaches [2], which were then confirmed in their key conceptual advances by a wealth of subsequent studies in the mouse, either using similar approaches, or genetic tools, or combinations of both [3,7–11]. At this time, efforts are being made to elucidate the potential diversity of local bone marrow territories with respect to hematopoietic functions, and the specific functions of putative (and as yet, not conclusively identified) stromal subsets, or non-stromal cell types such as endothelial cells [10,12,13] or neural cells [14,15]. However, recent data in the mouse directly support the general key concept that perivascular stromal skeletal stem cells (otherwise known as bone marrow-derived "mesenchymal" stem cells [16]) act both as progenitors for skeletal tissues and as key players of the perivascular HME/niche also in the mouse [11,13]. The manner in which the function of skeletal stem cells is probed in the human system [i.e., heterotopic transplantation, also of clonal, single cell-derived populations [reviewed in [16]], to the effect of recapitulating the organogenesis of bone, illustrates these functions and their unique nature most effectively, in sharp contrast with other types of stem cells. Transplantation is the mainstay of stem cell biology. Transplantation of HSCs results in reconstitution of hematopoiesis; transplantation of epithelial stem cells in the reconstitution of epithelial tissues; transplantation of pluripotent embryonic stem cells results in teratomas (i.e., in the chaotic admixture of all differentiated lineages); transplantation of skeletal stem cells results in the generation of different skeletal tissues, yes, but also in a highly coordinated, mutual organization of donor tissues with host tissues in a chimeric organoid [2,5,6].

Skeletal stem cells are found in the bone marrow stroma. In situ, the bone marrow stroma is a highly elusive tissue, due to the simple fact that the key cell type, the adventitial reticular cell, escapes detection in conventional histological sections, and can only be visualized using a cytochemical stain (alkaline phosphatase) [17–19] or immunocytochemical markers (e.g., CD146, CD105, CD90) [2]. Changes in number, density, phenotype and function of stromal cells result in gross changes in the organization of the bone marrow stroma, which accompany changes in bone. Osteoporosis, the most common bone disease, is not only a reduction in bone mass, it is also an increase in marrow adiposity and a reduction in alkaline phosphatase expressing stromal cells [20]. Endosteal fibrosis of secondary hyperparathyroidism is the local accumulation of bone marrow stromal cells at the endosteum [21,22]. The fibrosis of fibrous dysplasia of bone (FD) is the local accumulation of stromal cells in an abnormal marrow space [23], is coupled to the loss of adipocytes and of the hematopoietic microenvironment, and also to profound subversion of bone architecture, matrix composition, mineralization, internal texture and mechanical competence. Vascularity of the bone marrow is profoundly altered in osteoporosis, Paget's disease, FD, and many more bone diseases. Many more examples could be given illustrating the point that calling an individual disease a "bone disease" rather than a "bone marrow disease" can be seen as the result of a conventional choice, or simply of a bias.

Skeletal stem cells and genetic diseases

The introduction of the induced pluripotent stem (iPS) cell technology [24] was saluted with enthusiasm as it conveyed both a reliable technological tool for generating pluripotent cells and theoretically any differentiated lineage, and relief from a heated "ethical" controversy, while illustrating the extraordinary notion that less than a handful of genes could reprogram an adult cell into pluripotency. Shortly thereafter, the value of iPS cells as tools for modeling disease became widely appreciated [25], and currently predominates over the still immature use of iPS cells for direct replacement of diseased tissues. The use of iPS cells for disease modeling encompasses investigative as well as directly applicative avenues: the generation of patient-specific diseased and differentiated cell types, in which to seek disease mechanisms, but also a tool for high-throughput drug screening. iPS cells have been used to model rare diseases such as Fibrodysplasia Ossificans Progressiva [26] and metatropic dysplasia [27], revealing altered patterns of cartilaginous differentiation through the use, notably, of assays in fact developed for the study of postnatal stem cells. However, the notion that skeletal diseases could be modeled through stem cells precedes the development of the iPS cell technology. Based on the recognition that obvious changes in the bone marrow stroma occur in FD, Bianco et al. [28] hypothesized that heterotopic transplantation of stromal cells from the abnormal marrow of FD patients could recapitulate in vivo the abnormal architecture of FD bone and bone marrow. This provided evidence that a human non-neoplastic disease could be transferred to immunocompromised mice, and also the first use of stem cells for transferring disease into the mouse. A few years before, John Dick and coworkers had shown that human leukemia could be transferred to SCID/bg mice, through the transplantation of leukemic cells [29,30]; from these studies, the concept that cancer could be transferred to immunocompromised mice by putative cancer stem cells, and the very idea of cancer stem cells, was to arise later [31]. The same approach as used for FD contributed decisively to identify and name Gnathodiaphyseal Dysplasia as a separate disease, distinct from both FD and Osteogenesis Imperfecta, and to predict from the cell-autonomous properties of stromal progenitors [32], its genetic nature, which was to be identified shortly thereafter [33]. Specific dysfunction in skeletal and dental progenitors was recognized in Cleidocranial Dysplasia [34], while heterotopic transplants of stromal progenitors from patients with Hurler's disease, conversely, dispel an inherent disruption of stromal cell differentiation [35]. However, the use of novel types of heterotopic transplantation assays [6] reveals specific changes in cartilage metabolism in Hurler's disease (Serafini et al., manuscript in preparation). Heterotopic transplantation of stromal progenitor cells serves also to demonstrate in vivo the functional impact of gene knockout or of transgenes [36,37].

The adoption of stem cells as a model of disease has been remarkably productive in the specific area in which it was most intensively pursued, Fibrous Dysplasia. Use of cultures of FD-derived bone marrow stromal