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Review

Stem cells and bone: A historical perspective

Paolo Bianco

Department of Molecular Medicine, Sapienza University of Rome, Viale Regina Elena 324, 00161 Rome, Italy

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ABSTRACT

Bone physiology and stem cells were tightly intertwined with one another, both conceptually and experimentally, long before the current explosion of interest in stem cells and so-called regenerative medicine. Bone is home to the two best known and best characterized systems of postnatal stem cells, and it is the only organ in which two stem cells and their dependent lineages coordinate the overall adaptive responses of two major physiological systems. All along, the nature and the evolutionary significance of the interplay of bone and hematopoiesis have remained a major scientific challenge, but also allowed for some of the most spectacular developments in cell biology-based medicine, such as hematopoietic stem cell transplantation. This question recurs in novel forms at multiple turning points over time: today, it finds in the biology of the "niche" its popular phrasing. Entirely new avenues of investigation emerge as a new view of bone in physiology and medicine is progressively established. Looking at bone and stem cells in a historical perspective provides a unique case study to highlight the general evolution of science in biomedicine since the end of World War II to the present day. A paradigm shift in science and in its relation to society and policies occurred in the second half of the XXth century, with major implications thereof for health, industry, drug development, market and society. Current interest in stem cells in bone as in other fields is intertwined with that shift. New opportunities andalso new challenges arise. **This article is part of a Special Issue entitled "Stem cells and bone".**

Contents

Introduction

Bone morphogenetic proteins, hematopoietic "niche," and "mesenchymal" stem cells represent three totemic achievements in bone biology during the last century, three of the most research-intensive areas of the last three decades, and three of the most "translation"-intensive research areas of the present day. The three fields emerged from an unusual concentration in space and time of a handful of seminal experimental observations. In just a few years, we learned that heterotopic transplantation of transitional epithelium into skeletal muscle induces heterotopic bone formation [1]; that heterotopic transplants of bone marrow also do so [2,3], but that the two phenomena are radically distinct from one another: the former is dependent on the release of a soluble factor, while the latter is not. Identification of BMPs [4–6,7] and perisinusoidal reticular cells as the specific factor and cell type

E-mail address: paolo.bianco@uniroma1.it.

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generating bone in heterotopic transplants of transitional epithelium and bone marrow, respectively, represents the ending point of two long and diverging journeys that originated from those seminal experiments. Likewise, the definition of the bone marrow microenvironment as the host of signals provided by stromal cells and required for hematopoiesis, and the pursuit of a "niche" for hematopoietic stem cells proper represent the developments over time of a third seminal observation; that is, that grafting of bone marrow in closed systems (diffusion chambers) would generate bone but bar the development of hematopoiesis, whereas transplantation in open systems would allow for both bone formation and development of marrow [2].

That all of these fundamental observations, which not only withstood the test of time, but also represented the seed for the subsequent flourishing of major fields of investigation, arose from the practice of heterotopic transplantation cannot escape notice. Considering the tremendous impact of establishing quail–chick chimeras (a kind of heterotopic transplantation in embryos) [8,9]in developmental biology and how much it contributed to further developments in lineage tracing, one is tempted by foolishly wondering what magic is inherent in putting tissues and cells where they do not belong (ectopic transplantation), and why is this practice so instructive. Perhaps all these simply highlightthe fundamental link between space (and time) and development (lineage, commitment, differentiation), a notion we owe, ultimately, to Alan Turing (the father, among many other things, of the diffusion–reaction model which established the chemical basis of morphogenesis [10]), and before him, to D'Arcy Thompson (a classicist and a morphologist renowned for his attention to the physical and mathematical laws underpinning morphogenesis) [11]. Heterotopic transplantation is instructive because it breaks the spatial and temporal constraints (the physics, one could naively argue) that drive development, and therefore reveals them in the most empirical way possible.

The fallout: post-World War II era

That these fundamental observations clustered in a specific stretch of time, on the other hand, is also intriguing. In the same, specific time interval, another major change in scientific trends arose. The idea of a hematopoietic stem cell, a common multipotent progenitor for all blood cells, had been formulated long before (reviewed in [12]), but had remained dormant without attracting interest and above all, experimental effort. The idea exited the realm of theoretical postulates in 1961, with the seminal work of Till et al.[13,14], admittedly the first experimental evidence for a common multipotent progenitor of blood cells. In essence, the fundamental discoveries of a dual system of stem cells in bone were not only almost synchronous, but also arose from efforts across the iron curtain that fell at the end of WWII, and are the direct result of the way WWII ended. It was the attempt to develop strategies for radioprotection that gave a new impetus to the science behind what was to become stem cell biology. Not casually, the front page of the famous New England Journal of Medicine paper by E. Donnall Thomas reporting in 1957 [15] the first attempt of bone marrow transplantation in humans both recounts the lethal effects of nuclear warfare, and acknowledges the support of the Atomic Energy Commission of the USA. Much more in bone science and science at large emanate from the same cradle: the biology of bone matrix [16,17] and the role of parathyroid glands [18], for example, and key techniques such as microradiography and autoradiography [16,17,19–21], to name a few.

At about the same time that something "osteogenic" was being discovered in bone marrow by Tavassoli and Crosby [3], and by Friedenstein and coworkers [2], it was exactly autoradiography that made it possible to trace the kinetics of bone cells in vivo, in a series of seminal studies by Owen and Macpherson [22–25]. This is how we learned about precursor cells of osteoblasts in the inner layer of the periosteum, about the origin of osteocytes from osteoblasts, and about the kinetics thereof. Not casually, the two independent lines of thinking about the origin and precursors of bone cells were to merge soon thereafter in the work of Owen, just like her background in physics and attention to biology had merged in her early work as a reflection of the post-war climate and strategic priorities. Even the work of Friedenstein and that of Owen united at one point [26], which was crucial to disseminate the significance of Friedenstein's work in the West (Figs. 1 and 2). That unification was also crucial to formulate the concept not only of a stem cell for bone, but also for different tissues together comprising the skeleton being connected to one another at the level of a common ancestor, rather than as separate entities as thought previously. For the first time, chondrocytes, osteoblasts and bone marrow adipocytes were brought together into a unified system. The "stromal system" comprising them all was conceived on the blueprint of the hematopoietic system, marking a major conceptual novelty in skeletal research [26,27].

The road to stem cells

Earliest experiments provided evidence for an inherent osteogenic potential of cells in bone marrow, and for its non-humoral nature. Subsequent steps involved the use of cell culture as a way to separate, at a time when no cell sorting tools were at hand, hematopoietic cells proper from non-hematopoietic (stromal cells), which in contrast to the former can adhere to a plastic substrate. Transplanting cultured stromal cells to the effect of generating heterotopic bone proved that it was the stromal fraction to be endowed with osteogenic potential. Using the same experimental approach, the same potential was later ascribed to the clonogenic fraction of stromal cells (i.e., to cells capable of density-insensitive clonal growth and therefore seen as progenitors), and to a subset of individual clonogenic cells [28–30]. The coexistence of multiple tissues within heterotopic "ossicles" generated by single clones proved the existence, first in rodents and much later in humans [31], of multipotent stromal progenitors, based on which the idea of an osteogenic stem cell was formulated as a working hypothesis [26,27,32]. Proving the existence of a bona fide stem cell also required proving the ability of the multipotent progenitor to self-renew, but this key question remained unaddressed for many years. Addressing this question required the identification of an anatomical in vivo counterpart of the multipotent clonogenic progenitor, and proof of its regeneration in heterotopic transplants. This only came with the demonstration that: a) the clonogenic fraction of bone marrow stromal cells in humans coincides with perisinusoidal reticular cells; which b) could be pinpointed using immunocytochemical markers both in the intact bone marrow and in the heterotopic graft; and c) could be secondarily isolated from the grafts, expanded and serially transplanted. First provided in humans [33], this type of evidence was later provided in the mouse [34]. Completion of this pursuit over 40 years leaves us with the notions that indeed, clonogenic, multipotent and self-renewing progenitors for

Fig. 1. Alexander Friedenstein.

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