STEM CELLS TRANSLATIONAL MEDICINE®

COMMENTARY

Perils and Promises of Therapeutic Approaches for the Stem Cell Disease Fibrous Dysplasia

ISABELLA SAGGIO

Department of Biology and Biotechnology, Sapienza University, Rome, Italy and Nanyang Technological University, Singapore

Correspondence: Isabella Saggio, Ph.D., Department of Biology and Biotechnology, Sapienza University, Piazzale Aldo Moro 5, 00185 Rome, Italy. Telephone: 390649912870; e-mail: isabella.saggio@uniroma1.it

A Commentary on
Jiang et al. in this issue

Received September 30, 2018; accepted for publication October 22, 2018; first published November 13, 2018.

http://dx.doi.org/10.1002/sctm.18-0213

In the article "HDAC8, a Potential Therapeutic Target, Regulates Proliferation and Differentiation of Bone Marrow Stromal Cells in Fibrous Dysplasia" [1], the authors fuse three elements of interest. First, and central, is the disease addressed: fibrous dysplasia (FD), a rare genetic condition associated with human bone marrow stromal cells (BMSCs), a population of adult stem cells whose specific biology and translational potential make the second element of interest in the story. Third, is the epigenetic component: the indication of histone deacetylase 8 (HDCA8), a zinc-dependent HDAC subtype, as potential therapeutic target for FD.

FD (OMIM#174800) is a rare postnatal disease linked to somatic mutations in the *GNAS* locus, modifying the encoded Gs-α product at residue 201, prevalently with R201C or R201H amino acidic substitutions [2]. These mutations convert the α subunit of the stimulatory G protein into a constitutively active engine, leading cells to overproduce cAMP, a central player in cell metabolism. Although the biochemistry of Gs-α mutations was dissected more than 15 years ago [3, 4], FD molecular pathophysiology is not yet fully defined. However, histological features of FD tissues are well-known, including bone with abnormal trabecular pattern, osteomalacia, enhanced resorption, and marrow fibrosis, which results from accumulation of osteogenic precursors, loss of adipocytes and hematopoiesis, and altered vascularity [2].

The contribution of bone marrow to the pathological process points to FD as a disease of the bone/bone marrow organ, in which context BMSCs play a pivotal role. Key experimental evidence of this principle came from the analysis of ectopic ossicles generated in mice implanted with FD patients' BMSCs or exogenously engineered, GNASR201C expressing, BMSCs [5, 6]. In both cases, it was demonstrated how bone and bone marrow alterations were detectable in the chimeric human/mouse organs generated in vivo. These data imply that the use of BMSCs is determinant for understanding FD, and for designing and testing innovative therapeutic strategies, but also suggest that FD studies are helpful for dissecting the role played by this adult stem cell population in the physiology of bone/bone marrow relationships. This concept makes FD one—among many—paradigmatic example underlying how science is synergic and interrelated in the advancement of knowledge, beyond boundaries established between applied and basic research.

Current FD therapies are not yet cures. FD patients, whose clinical symptoms can be highly invalidating, are treated with surgical interventions and with drugs controlling bone metabolism, such as bisphosphonates, derivatives of inorganic pyrophosphate, largely used for osteoporotic conditions. In the more recent years, antibodies have been investigated for treating FD. This approach has created new hopes, also based on the high success rate of immunotherapies for other diseases. A candidate route for FD therapy is based on the use of anti-RANKL humanized antibodies, as the Food and Drug Administration (FDA) approved Denosumab. RANKL is a key mediator in the response of bone cells to osteoclast precursors, is highly expressed in FD patient samples and in BMSCs expressing the GNASR201C mutation, which suggests a molecular explanation for excessive FD bone resorption along with pointing to this molecule as druggable target [5]. Other molecular approaches are also being investigated, albeit directed toward more generalized effects observed in FD, as the inhibitor of IL-6, Tocilizumab, which targets a disease-induced inflammatory condition paralleling strategies applied to rheumatoid arthritis.

Xiao et al. suggest another route for intervention on FD, based on the exploitation of epigenetic manipulation of cell metabolism via HDAC8 inhibitors [1]. HDACs control global chromatin organization and gene expression, contributing to multiple biological pathways and affecting numerous disease conditions including cancer, autoimmune diseases and neurodegenerative conditions. HDACs have robustly entered into the panoply of disease treatments. Clinicaltrials.com lists 653 studies based on histone deacetylases, mainly addressing cancer, but also targeting bone conditions. HDCA8 is a zinc-dependent class I, ubiquitously expressed

deacetylase, which affects multiple substrates and regulates diverse physiological and pathological processes [7]. Importantly for the FD setting, HDAC8 impinges on BMSCs osteogenic differentiation. Xiao et al. show that HDAC8 inhibition alters FD disease properties, by acting on the cAMP related cell phenotype and promoting osteogenesis in vivo [1]. Beyond this study, the implementation of epigenetic therapies for FD has solid bases in the fact that the differentiation properties and the related epigenetic status of FD BMSCs are profoundly implicated in the disease, since FD mutations, by inducing overproduction of cAMP, directly impact on cAMP responsive elements (CRE) and related transcription control by CRE binding proteins [8].

As outlined above, current strategies for FD include multiple treatments to control or rescue mutation consequences, including the use of bone metabolism affecting drugs, and approaches targeting single molecular interactions as in the case of anti-RANKL antibodies, or multiple molecular events as with HDAC8 inhibitors. However, the overview of current FD therapeutic options would not be complete if not integrated with the concept of tissue engineering approaches based on BMSCs. Genetic or metabolic correction of autologous FD BMSCs along with heterologous wild-type bone progenitors can be used to create bone grafts with potential dominant positive effects on clinical FD phenotypes. To this goal ex vivo or in vivo genetic manipulation of BMSCs is particularly relevant. Xiao et al. demonstrate that they can use vectors to inhibit HDAC8 overproduction observed in FD cells by expressing RNA interfering encoded sequences [1]. We used RNA interference to correct FD BMSCs identifying allele specific sequences targeting the GNASR01C mutation [5]. Furthermore, evolution of these concepts will be the use in FD of CrisprCas genome editing for in situ disease mutation correction [9].

If therapies for human diseases have always to be evaluated as a success versus risk ratio, there are some important *caveat* linked to the specific elements highlighted above. These include off targets effect of epigenetic manipulation. HDACs affect the epigenome at large impinging in unpredictable ways on the overall organismal biology. However, highly targeted, disease correction frontier tools require precaution too. CrisprCas technology, for example, is dealing with undesired editing and off target mutations [9]. Lastly, but certainly not least, perils in tissue engineering strategies involving BMSCs are also to be taken into account. Although the regeneration potential of adult stem cell is robustly assessed, the specific nature of cells possessing this potential, purification protocols, tissues into which cells can differentiate, are elements complexity [10]. Latest data show that there is a fine developmental hierarchy in adult stem cell progenitors generating bone, with the most up to date phenotype identifiable via differential expression of PDPN, CD146, CD73, and CD164 markers [11]. Usage of BMSCs for clinical application (or of *mesenchymal stem cells*) requires strict purification protocols and full marker phenotyping. Along with this, such experimental therapeutic strategies need systematic assessment of efficacy and safety in preclinical settings, as human ossicles described by Xiao et al., but also animal models, now available for FD [12, 13].

Disclosure of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

References

1 Xiao T, Fu Y, Zhu W et al. HDAC8, a potential therapeutic target, regulates proliferation and differentiation of bone marrow stromal cells in fibrous dysplasia. Stem Cells Translational Medicine 2019;8:148-161.

2 Bianco P, Wientroub S, Dysplasia F. Fibrous dysplasia. In: Glorieux FH, Pettifor JM, Juppner H, eds. Pediatric Bone: Biology and Disease. 2nd ed. New York, NY: Elsevier, 2012: 589-624.

3 Landis CA, Masters SB, Spada A et al. GTPase inhibiting mutations activate the alpha chain of Gs and stimulate adenylyl cyclase in human pituitary tumours. Nature 1989;340:692-696.

4 Bourne HR, Landis CA, Masters SB. Hydrolysis of GTP by the alpha-chain of Gs and other GTP binding proteins. Proteins 1989;6:222-230.

5 Piersanti S, Remoli C, Saggio I et al. Transfer, analysis, and reversion of the fibrous dysplasia cellular phenotype in human skeletal progenitors. J Bone Miner Res 2010; 25:1103-1116.

6 Riminucci M, Saggio I, Robey PG et al. Fibrous dysplasia as a stem cell disease. J Bone Miner Res 2006;21:P125-P131.

7 Chakrabarti A, O'ehme I, Witt O et al. HDAC8: A multifaceted target for therapeutic interventions. Trends Pharmacol Sci 2015;36:481-492.

8 Mayr B, Montminy M. Transcriptional regulation by the phosphorylation-dependent factor CREB. Nat Rev Mol Cell Biol 2001;2: 599-609.

9 Knott GJ, Jennifer AD. CRISPR-Cas guides the future of genetic engineering. Science 2018;361:866-869.

10 Sipp D, Robey P, Turner L. Clear up this stem-cell mess. Nature 2018;561:455-457.

11 Chan CKF, Gulati GS, Sinha RT et al. Identification of the human skeletal stem cell. Cell 2018;175:43-56.

12 Saggio I, Remoli C, Spica E et al. Constitutive expression of Gsalpha(R201C) in mice produces a heritable, direct replica of human fibrous dysplasia bone pathology and demonstrates its natural history. J Bone Miner Res 2014;29:2357-2368.

13 Khan SK, Yadav PS, Elliott G et al. Induced Gnas(R201H) expression from the endogenous Gnas locus causes fibrous dysplasia by up-regulating Wnt/beta-catenin signaling. Proc Natl Acad Sci USA 2018;115:E418-E427.