



Role of microRNA-182 in skeletal diseases: new therapeutic approaches to prevent bone loss

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The onset of bone erosion is associated to several diseases, including metabolic processes as hyperparathyroidism, malignancies, chronic inflammation such as rheumatoid arthritis and osteoporosis (1). This condition leads to mobility loss, functional impairment, pains and fractures with a dramatically reduction of patients' life quality. The resulting bone loss reflects, basically, an imbalance of osteoclasts and osteoblasts activity where bone formation is replaced by its resorption (2).

In order to understand the mechanisms leading to bone erosion, further insights into the biology of bone homeostasis and the molecular pathways involved in the osteoclasts and osteoblasts differentiation and function is mandatory. In particular, osteoclasts are fundamental for normal bone function, but their activity must be monitored. In contrast to several other pathological conditions, no treatment progression has been made for skeletal diseases and so new therapeutic targets or biomarkers are urgently needed.

With the advance of high-throughput sequencing platforms, there have been an exponential interesting in the non-coding portion of the genome, fundamental for both normal conditions and disease development (3,4). During the last years, researchers have found evidences regarding the involvement of miRNAs in bone disease such as osteoporosis and rheumatoid arthritis (5). It's well known in literature that miRNAs are able to influence osteoclast, osteoblasts and osteocyte differentiation and proliferation in osteoporosis while they regulate immune cells (e.g., lymphocyte and monocyte) in rheumatoid arthritis (6).

In particular, miR-182 has been studied as negative regulator of osteoblast proliferation and differentiation through the expression of FOXO1, a transcription factor that regulates the reduction and oxidation balance in osteoblasts (7). Moreover, in 2016 Miller and colleagues, by using a high throughput sequencing approach (i.e., miRNA-seq), identified miR-182 as a novel positive regulator of inflammatory osteoclastogenesis under the control of RB-J and TNF- α (8). This miRNA was found to have a key role also in other biological backgrounds such as cell growth, cancer and helper T-lymphocytes expansion (9-11).

On this grounds, Inoue and colleagues recently tried to elucidate miR-182 role in bone homeostasis and disease (12). At first the authors showed evidences regarding the positive regulatory role of miR-182 in osteoclastogenesis. In fact, miR-182 inhibition leads to a significant decreased of key osteoclastogenic transcription factor and markers and osteoclast formation *in vivo* and *in vitro*. Moreover, the bone phenotype of the deficiency miR-182 mice showed lower osteoclast numbers and smaller osteoclast surface area compared to wild type controls. Moving into a pathological background such as osteoporosis and inflammatory arthritis, miR-182 inhibition appeared to prevent bone loss affecting osteoclast formation and bone erosion.

The potential of miRNAs as treatment targets in human diseases has been explored in many pathological settings (13,14). Inoue and colleagues demonstrated that miR-182 inhibition leads to control bone loss in absence of toxicity or effects on bone itself by using CH-nanoparticles as drug delivery vehicles. From a genetic

and pharmacological point of view, these data underlay how miR-182 is considerably involved in skeletal disease. Nevertheless, since miR182, may affect many mRNA targets several of which may be involved in skeletal diseases, the identification of specific pathological disease signaling pathway dysregulation was mandatory.

For this reason, the authors investigated miR-182 deficiency mice RNA profiling through a high throughput RNA-sequencing approach identifying the enrichment of type I IFN gene sets and PKR, an IFN pathway regulator, as a key miR-182 target. Thus, they first identified the miR182-PKR-IFN- β pathway as a crucial axis in osteoclastogenesis in mice and *in vitro*.

In the contest of miRNA-based therapy, several main challenges have to be overcome: at first, the identification of the best miRNA candidate or target for each specific disease, second, the application of suitable vehicles for miRNA candidate and finally to avoid toxic and off-target effects (15). It is also important to take in account the well known ability of miRNAs to target several genes leading to activation of multiple compensatory pathways especially in complex scenario such as resistance development. The paper of Inoue and colleagues has significantly contributed to highlight the biological pathways involved in skeletal disease providing preliminary promising data regarding miR-182 targeting as new therapeutic approach *in vivo* and *in vitro*. Further researches are needed to validate the biological and clinical relevance of miR-182 in human skeletal disease in order to develop new targeted efficient therapeutic approaches.

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