*MINI REVIEW ARTICLE*

A C G publications

*Bioorg. Med. Chem. Rep.* 1:1 (2018) 2-5

Bioorganic & Medicinal Chemistry Reports

# Immunomodulation of macrophages for bone formation

**Furkan Ayaz** *

*Mersin University, Faculty of Arts and Science, Department of Biotechnology, Türkiye*

*(Received September 13, 2018; Revised December 03, 2018 ; Accepted December 24, 2018)*

**Abstract:** Especially in elderly women osteoporosis leads to decline in the strength of the bone tissue by erosion of its mass. Weakened bone tissue is more prone to breaks. Patients mostly realize this situation after having a bone breakage especially with the wrist and hip fractures. There has not been an effective way of improving this debilitating condition. A new approach aiming to regulate the activities of the immune system cells in order to reverse osteoporosis and push the tissue for the formation of the bone structure gained attention due to its promising potential. In this review, I will be focusing on this approach by regulation of the macrophage activity, the major immune cell type that is involved in the bone formation. Immunomodulation of the macrophages enable formation and healing of the bone tissue in the patients and conducting more studies in this area would certainly improve the quality of the applicable medicines.

**Keywords:** Macrophages; immunomodulation; bone; bone formation; osteoporosis; immunomodulatory agents


## 1. Introduction

In this review, immunomodulation of macrophages as a medicinal tool to prevent osteoporesis and induce the bone formation in the patients, will be analyzed by conceptual detailing. Firstly, the bone structure will be presented with the crucial cell types involved in the formation and break of the tissue. Then, the role of the macrophages in the bone tissue formation will be given. Finally, the concept of immunomodulation of macrophages in order to increase the bone tissue mass as well as heal the wounded sections will be explained.

Osteogenesis is the process of bone formation and it is regulated mainly by two types of cells[1-5]. Osteblasts secrete osteoid[1-5]. Osteoid accumulates calcium and other mineral salts[1-5]. During this calcification process they entrap the osteoblasts which then differentiate and become osteocytes[1-5]. Whereas osteoclasts are at the other end of the spectrum during bone formation[6-8]. These cells break down the bone tissue in order to release the minerals such as calcium needed by the body or in some cases to remodel the bone tissue for growth and repair purposes[6-8]. Osteoclasts fulfill their function by producing acid and a type of collagenase to break down the bone matrix[6-8]. Osteoclasts are as crucial as osteoblasts to form the final shape of the bone[6-8].

*Corresponding author: E-mail: furkanayaz@mersin.edu.tr

The article was published by ACG Publications
http://www.acgpubs.org/journal/bioorganic-medicinal-chemistry-reports © January-December 2018
DOI: http://doi.org/10.25135/bmcr.11.18.09.899

Studies have indicated a balance of osteoclast and osteoblast cell types in order to maintain the bone structure. Manipulation of this balance is especially important in patients who need bone formation[6]. In skeletal diseases where patients lack proper bone formation such as Osteogenesis imperfecta (OI also called as brittle bone disease), therapeutics that would tilt the balance towards osteoblast generation over osteoclast generation would be beneficial[9]. There are other cases, in which, due to accidents the patients have fractured bones that need to be repaired. These patients either get replacement biomaterials that would reside in the patient's body for a long term (10-20 years) or regenerative biomaterials that would enable the function of the lost tissue andget degraded in several days to months after fulfilling their mission in the body[10].

Furthermore, in elderly people or pregnant women there is osteoclasis[11-12]. Osteoclasis occurs in these people mostly because of lack of minerals and closing this gap by using the supplies from the bone tissue, as well as due to lack of osteoblast formation in their bones to turn on the repair mechanisms later on[11-12].

Current applications to cope with these bone tissue related diseases or symptoms involve molecular manipulations of osteoclast and osteoblast ratio in the bone tissue[13-14]. Unfortunately, these manipulations do not possess high potential of success since these methods cannot generate an efficient and persistant effect[13-14]. A different and fairly new strategy is replacing this approach. Improvements in polymer science and generation of biomaterials with different properties enabled this new approach[13-14]. Immunomodulation of macrophages in the bone tissue is the emerging method of interest forindirect and steady manipulation of the osteoblast to osteoclast ratio[13-14].

*Immunomodulation as a novel approach to induce the bone formation:*

Immunomodulation is regulation of the immune system cells by outside factors to such an extent that we can determine the type, strength and state of the immune system's reaction depending on the disease case[15-16]. For example, in autoimmune diseases we would like to halt the excessive inflammatory reaction against our self molecules to prevent tissue injury[13-14]. In another case such as vaccination depending on the pathogen or danger we try to manipulate our immune system to generate a specific type, strength and eventually memory of response to enable immunity[13-14]. Studies have been focusing on generation of therapeutics that act as immunomodulators and these would enable a controlled immunomodulation of our immune cells depending on the disease that we are targetting[13-14].

Macropages are the main type of cells that are involved both in pro-inflammatory responses as well as after elimination of the danger in anti-inflammatory responses, wound healing and tissue repair processes[13-14]. Macrophages derive from monocytes that are circulating in the blood[13-14] . Precursor cells in the bone marrow develop into monocytes and these cells mature into macrophages once they get into tissue[13-14]. There is evidence supporting the idea of tissue resident macrophages from embryological development, that proliferate and expand if needed[13-14]. Therefore, there are two sources of tissue macrophages[13-14].

When there is a danger, these cells produce cytokines to create a microenvironment that would regulate the responses of other immune cell types[13-16]. Cytokines produced during this stage are TNFα, IL1β, GMCSF, IL12 and IL6[13-16]. These cytokines are pro-inflammatory[13-16]. At this stage macrophages act as antigen presenting cells as well[13-16]. Due to their phagocytic capacity, they can engulf the pathogens and present it to other immune system cells to form a proper response[13-16]. After elimination of danger macrophages use their phagocytic behavior to clear the tissue from cell debris, immune complexes as well as pathogenic molecules[13-16]. Macrophages play a crucial role at this point by starting wound healing process[13-16]. They produce IL10 cytokine to suppress inflammatory reponse[13-16]. Macrophages export iron to the tissue to help tissue remodelling and healing[13-16].

Studies suggest an interplay between macrophages and mesenchymal stem cells from the bone marrow[13-14]. During their direct interaction macrophages gain wound healing and tissue remodelling phenotype while mesenchymal stem cells differentiate into osteoblasts[13-14]. Osteoblasts can then form the bone tissue[13-14]. Macrophages produce oncostatin M to cue the differentiation of mesenchymal stem cells into osteoblasts[13-14]. Both cell types express COX2 at this point which leads to production of prostoglandin E2 (PGE2), that regulates the function and phenotype of both macrophages and mesenchymal stem cells[13-14]. These findings further suggest macrophages as a strong candidate to target for the formation of bone tissue.

## 2. Concluding remarks

Immunomodulatory molecules can regulate the macrophage responses[13-16]. There are molecules that are biocompatible and can cultivate macrophage response into more of a wound healing and tissue remodelling type[13-16]. It has been shown by previous studies that macrophages at this stage would enable bone formation and healing[13-14]. Therefore, either during the transfer of biocompatible materials to support the bone tissue after bone fracture or as a medicine in elderly and pregnant women who suffer from osteoclasis, immunomodulatory molecules that would generate a wound healing and tissue remodelling response in macrophages can be used[13-14]. This will enable a much efficient healing process for the bones.

Structures and shapes of biomaterials and their functional groups have been part of ongoing research in the field of immunomodulation[13-14]. PEG and polyacrylamide based gels have been widely used with modifications changing their charge and structure properties. Depending on their stiffness and surface properties these materials are able to change the behaviors of the macrophages and induce bone formation[13-14]. Macrophages are crucial targets to enable healing and remodelling of bone tissue[13-16]. More detailed research is needed in order to fully determine the effects of biomaterials on the macrophages as well as how this might lead to bone formation. Macrophages ability to produce different types of cytokines and phagocytic potential should be delineated in the presence of the immunomodulatory materials. Moreover, a detailed analysis of cell growth, bone formation and expression of bone forming factors should be analyzed after coculturing of the immunomodulated macrophages with the bone cells (osteoblasts or osteoclasts).

## Acknowledgements

I would like to thank Dr. Juan Anguita for his valuable contributions.

**ORCID**
FurkanAyaz:0000-0003-0271-0594

## References

[1] Tenenbaum, H.C.; Heersche, J.N.M. Differentiation of osteoblasts and formation of mineralized bone *in vitro*. *Calcif. Tissue Int*. **1982**, *34*,76-79.
[2] Binderman, I.; Duksin, D.; Harrell, A.; Katzir, E.; Sachs, L. Formation of bone tissue in culture from isolated bone cells. *J. Cell Biol*. **1974**, *61*, 427–439.
[3] Binderman, I.; Greene, R. M.; Pennypacker, J. P. Calcification of differentiating skeletal mesenchyme *in vitro*. *Science***1979**, *206*, 222–224.
[4] Thorogood, P. *In vitro* studies on skeletogenic potential of membrane bone periosteal cells. *J.Embryol. Exp.Morphol.* **1979**, *54*, 185–207.
[5] Nijweide, P. J.; Peren-Van Gent, A.S.; Kawilarang-De Haas, E. W. M.; Van Der Plas, A.; Wassenaar, A. M. Embryonic chicken periosteum in tissue culture: osteoid formation and calcium uptake. *Proc. Kon. Ned. Akad. Wet.***1975**, *C78*, 410–417.
[6] Teitelbaum, S.L. Osteoclasts: What do they do and how do they do it? *The Am. J.Pathol.* **2007**, *170(2)*, 427-435.
[7] Udagawa, N.; Takahashi, N.; Akatsu, T.; Tanaka, H.; Sasaki, T.; Nishihara, T.; Koga, T.; Martin, T.J.; Suda, T. Origin of osteoclasts: Mature monocytes and macrophages are capable of differentiating into osteoclasts under a suitable microenvironment prepared by bone marrow-derived stromal cells. *Proc. Natl. Acad. Sci.***1990**, *87*, 7260-7264.
[8] Fuller, K.; Kirstein, B.; Chambers, T.J. Murine osteoclast formation and function: Differential regulation by humoral agents. *Endocrinology* **2006**, *147*, 1979-1985.
[9] Van Dijk, F.S.; Cobben, J.M.; Kariminejad, A.; Maugeri, A.; Nikkels, P.G.; Van Rijn, R.R.; Pals, G. Osteogenesis Imperfecta: A Review with Clinical Examples. *Mol. Syndromol.* **2011**, 2(1), 1-20.
[10] Stevens, M.M. Biomaterials for bone tissue engineering. *Mater. Today* **2008**, *11*, 18-25.

[11] Stewart, R. J. C.; Sheppard, H.G.; Preece, R. F.; Exton-smtth, A. N. Bone resorption in the elderly. *Age Ageing***1972**,*1*, 1–13.
[12] Ettinger, A.S.; Lamadrid-Figueroa, H.; Mercado-García, A.; Kordas, K.; Wood, R.J.; Peterson, K.E.; Hu, H.; Hernández-Avila, M.; Téllez-Rojo, M.M. Effect of calcium supplementation on bone resorption in pregnancy and the early postpartum: a randomized controlled trial in Mexican Women. *Nutr. J.***2014**, *13*, 116 (9 pages).
[13] Sridharan, R.; Cameron, A.R.; Kelly, D.J.; Kearney, C.J; O'Brien, F.J. Biomaterial based modulation of macrophage polarization: A review and suggested design principles. *Mater. Today***2015**, *18*, 313-325.
[14] Horwood, N.J. Macrophage Polarization and Bone Formation: A review.*Clin. Rev. Allergy Immunol.***2016**, *51*, 79.
[15] Moyano, D.; Yuangchang, L.; Ayaz, F.; Hou, S.; Puangploy, P.; Duncan, B.; Osborne, B.A.; Rotello, V.M.Immunomodulatory effects of coated gold nanoparticles in LPS stimulated in vitro and in vivo Murine model systems. *Cell Press Chem.* **2016**, 1, 320-327.
[16] Thaker, H.; Som, A.; Ayaz, F.; Lui, D.; Pan, W.; Scott, R.; Anguita, J.; Tew, G. Synthetic mimics of antimicrobial peptides with immunomodulatory responses. *J. Am. Chem. Soc.* **2012**, *134*, 11088-11091.