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Environment and bone regeneration: how biomaterials, host mediators and even bacterial products can boost bone cells towards better clinical outcomes.

Dear Readers,

Studies focused on bone biology and pathology have been recurrent in the Journal of Applied of Science, highlighting the growing interest of the researchers in this expanding field. Interestingly, in recent editorials of the JAOS the impact of tissue environment and host response to regenerative processes were independently discussed[6,7,9], and in this issue, three studies bring new pieces to the multifaceted puzzle comprised by bone regeneration process, allowing a more interconnected analysis of this process.

Starting from the study by Jung, et al.[11] (2015), the authors demonstrate that the socket preservation mediated by a biomaterial composed of 60% hydroxyapatite and 40% beta-tricalcium phosphate involves the modulation of host response at the socket. The authors demonstrate that a moderated host response is associated with a favorable biomaterial grafting outcome, involving host inflammatory and immunological factors, such as chemokines and cytokines. Importantly, such data cope with the constructive inflammation concept, where the host response plays a central role in regenerative process providing signals that allow a transitory and selective migration of leukocytes to the repair site. Interestingly, after the trigger of host response that leads to cells mobilization to the repair site, the biomaterial is supposed to act as a substrate that supports cell migration, providing an adequate environment to all adhesive process that plays essential roles in cell mobilization[4,15].

Accordingly, biomaterials such as alginate hydrogels can effectively mimic extracellular matrices, and consequently improve cell migration process and regeneration outcome[3,5]. In fact, in this issue of the JAOS Li, et al.[13] (2015) demonstrate that an injectable thermo-sensitive alginate scaffold can enhance alveolar ridge augmentation in a minimally traumatic technique. In addition, alginate hydrogels have additional significant properties; such as the potential as drug delivery vehicles, and indeed, the sustained delivery of BMP-2 was demonstrated to improve the material properties *in vivo*, increasing the local activity of bone formation marker alkaline phosphatase. Taken together, the studies by Jung, et al.[11] (2015) and Li, et al.[13] (2015) demonstrate that environmental conditions that support cell migration and differentiation towards osteoblastic phenotype can be associated with desirable clinical response, and a moderate and transitory expression of host inflammatory immunological mediators seems to play a constructive role in the regenerative process[2,10].

Still in the "regenerative environment" context, additional *in vitro* data from this issue support the concept that some degree of host response can cope with bone regeneration. Albiero, et al.[1] (2015) demonstrate that periodontal ligament mesenchymal stem cells (PDLMSCs) cultures can sense microbial products (i.e. LPS), probably due to the significant expression of TLR4 and respond with the production of inflammatory molecules (interestingly, the same set of molecules analyzed by Jung, et al.[11] (2015). The authors also demonstrate that under optimal osteogenic cell culture conditions, the microbial antigen and the associated cellular response resulted in the increase of mineralized matrix deposition and higher RUNX2 and ALP mRNA levels by CD105+ cells when compared to the control group. Interestingly, usually the presence of microbial agents is associated with an exacerbated host response, and consequently with impaired wound healing bone regeneration *in vivo*, such as during alveolitis[14,16]. In accordance, Jung, et al.[11] (2015) demonstrate in this issue that the extension of the inflammatory and immunological response seems to be key in the regenerative process, since exacerbated host response results in a less favorable clinical outcome in the experimental model. Indeed, different patterns of host immune inflammatory mediators have been described to be associated with wound healing in active and inactive osteolytic lesions, contributing to the determination of lesions activity via the modulation of healing mechanisms[8,12]. Therefore, in the view of the positive effect of PDLMSCs stimulation and response in the osteogenic differentiation, it is possible to consider that the microbial challenge used *in vitro* by Albiero, et al.[1] (2015) may be equivalent to a moderated and transitory response *in vivo*. However, further studies are required to determine the exact degree of PDLMSCs responsiveness to LPS, and the impact of different microbial stimuli (different LPS concentrations and transient vs persistent stimulation) on osteoblastic differentiation, as well to test such hypothesis *in vivo*.

In summary, the aforementioned studies published in this issue of the JAOS showed interesting viewpoints on how biomaterials, host mediators and even bacterial products can influence bone cells *in vitro* and *in vivo*, and how these new data can be important to direct the development of bone regenerative strategies.

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