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MEETING REPORT

Cell interactions and signaling at the bone–cartilage interface (Sun Valley 2013)

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For decades it has been known that late-stage osteoarthritis is associated with increasing densification, or sclerosis, of the subchondral bone underlying the joint cartilage. In the early 1970s, Eric Radin and his colleagues[1,2] at Harvard and MIT hypothesized that this sclerotic subchondral bone initiated and drove the process of cartilage degeneration. The idea was that the very hard and stiff subchondral bone lost its capacity to serve as a 'shock absorber' so that stresses in the articular cartilage were greater than in healthy cartilage. This was a purely mechanical explanation for joint degeneration; it did not invoke a role for cells, other than as a response to mechanical stress, and did not suggest any communication between cell populations of the bone and cartilage.

Over the past 10–15 years, this view has changed. It is now clear that the processes occurring in the subchondral bone and cartilage are both temporally and spatially interdependent. Initiation and progression of joint deterioration are clearly separate processes, and associated with different remodeling effects in the subchondral bone. Initiation of cartilage damage is associated with increased bone remodeling and decreased subchondral bone volume and density (an osteopenia), whereas progression of disease to full cartilage loss is associated with decreased bone remodeling, an imbalance in favor of bone formation, and increased subchondral density (sclerosis). Questions remain, however, about how much of this is a purely mechanical phenomenon, and how much involves cellular coordination between bone and cartilage during the development of disease. There is also controversy about the roles that these changes play in the pathogenesis of osteoarthritis (OA).

The goal of this session at the Sun Valley Workshop was to consider cellular cross-talk between bone and cartilage, and its potential role in OA pathogenesis. There are numerous studies now showing convincing evidence of communication between bone and cartilage, making it difficult to argue against biological connections between these tissues during the development of OA. Differences in vascularity and tissue permeability are clearly present in OA, associated with aging and altered loading, although the precise role that these play and their importance is still unclear. The initial thinning and vessel-perforation of transport barriers (for example, the calcified cartilage and subchondral bone) should facilitate the cross-talk between bone and cartilage in developing OA, but whether transport of important proteins, metabolites and cytokines is altered in OA is still a question that has not been answered. Transport across the osteochondral junction and tidemark is dependent on the size of the signaling molecules (molecules $<10\,000$ Da are more likely candidates as messengers), and on their half-life. Tracer studies suggest that molecules less than 10 kDa can cross the osteochondral interface and calcified cartilage in 0.5–2 h. Molecules that are too short-lived do not have time to diffuse across the boundaries and still have an effect. It was proposed that a matrix of potential signaling proteins based on these two characteristics be developed. This would identify the most likely signaling candidates, which could then be targeted for study. Prostaglandins, nitric oxide and RANKL were determined not to be likely candidates, based on these two characteristics. However, specific Wnt proteins, those either in the canonical or the non-canonical pathways, could be candidates. It is known that there are changes in Dkk and sclerostin in osteoblasts derived from subchondral bone of OA patients, and also that Dkk and some Wnt proteins not only affect osteogenesis, but also can affect chondrocytes directly. In animal models, too little β-catenin appears to initiate OA-like features, whereas too much appears to promote progression of OA. Clearly, we need to know more about the differential effects of Wnt canonical signaling on cartilage and bone. In addition, we need to know more about non-canonical Wnt signaling, which is crucial for both osteogenesis and chondrogenesis.

Bisphosphonates (BPs) have been utilized as potential therapeutic agents to reduce the progression of OA, with very mixed results. Animal models suggest they may be effective, but clinical trials with primary OA have not been successful. Although BP use would be contraindicated if subchondral sclerosis were the driving characteristic for OA progression, they might be beneficial if angiogenesis (especially early in disease) is implicated as part of the pathogenesis. Angiogenesis potentially would increase transport of proteins that could act as paracrine agents, and BPs could regulate this. However, no study has been performed to determine whether transport is altered by BP treatment, which is the first step in assessing whether BP treatment might ultimately translate to the human clinical condition.

It is also possible that temporal considerations are paramount, and this may be one reason that BP treatment can be shown to work in animals, but has been ineffective in humans. If the positive effect of BPs occurs by reducing vasculogenesis, then BPs will only be effective if used in very early stage disease—perhaps before changes are evident. By the time disease is identified, it is already in an advanced stage with vascular invasion of the calcified and even articular cartilage, and it may be too late to do much about it. In animal models, BP treatment is started in early-phase disease, and therefore may be more effective at that stage. In humans, there is a need to study prevention, which means enrolling subjects who do not already have defined OA, and who may never get OA, but such studies are difficult, lengthy and expensive.

There may of course be other pathways that are just now being explored for the first time. CITED2, a mechanosensitive transcriptional repressor of several matrix metalloproteinases (MMPs), may protect cartilage from deterioration. Inhibiting CITED2 expression also leads to chondrocyte senescence through regulation of p21. Proteoglycan 4 (PRG4) appears to prevent age-related and post-traumatic cartilage degeneration, and overexpressing it is protective in preventing OA in animal models. PRG4 upregulates HIF3α, a post-translational inhibitor of HIF1α and HIF2α, which suppress collagen X, vascular endothelial growth factor and MMP13, all implicated in the progression of OA. It also alters boundary lubrication in the cartilage. How or whether either of these proteins affects the bone response is not yet clear.

The presence and role of bone marrow lesions (BMLs) in OA was extensively discussed. It is clear that we need to know more about what BMLs are, and how they are connected to the development of OA.

Thus, there are many avenues of investigation still open. OA remains something of a mystery, but may represent the next big challenge in preventing or reversing a significant and debilitating musculoskeletal disease.

Conflict of Interest

The author declares no conflict of interest.

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