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CLINICAL IMPLICATIONS

Osteoarthritis is what the people have

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Degenerative joint disease, osteoarthrosis (in Europe), osteoarthritis (in the USA), and elsewhere, results from breakdown of joint cartilage and underlying bone. Joint pain and stiffness are the most common symptoms. The complaints are worsened by exercise and commonly become constant. Joint swelling, loss of joint motion range, and resultant weakness, numbness, and disability occur. The condition is asymmetrical. The joints involved are commonly distal, ends of fingers, base of the thumb, neck, lower back, knees, and hips. The condition afflicts work and daily activity. Unlike other forms of arthritis, the condition is confined to joints. Trauma, genetic predisposition, and overweight contribute to the disease. Inflammatory processes are intimately involved so that the term "arthritis" is very justified. The primary driving force is aging; all of us who survive will develop this problem, the sole question is when.

Trauma seems to be a predisposing factor for specific and premature osteoarthritis. For instance, the long-term consequences of anterior cruciate ligament and meniscus injuries and consequences of their treatment have been reviewed [1]. However, substantial "evidence-based" information gaps remain. There is little evidence to support a protective role of repair or reconstructive surgery against osteoarthritis development. In instances in which a randomized clinical trial is not feasible, natural history and other observational cohort studies could yield useful information. Interestingly, despite this dearth of clinical information, specific therapies have been spawned to avoid subsequent osteoarthritis after knee injuries. Autologous activated platelets retained in fibrin matrices are used as a source of molecular signals that control cell fate, including cell growth, cell differentiation, and the synthesis of diverse functional proteins. The idea has been developed that platelet-rich therapies (rich in growth-factor technologies) could be the source of advantageous signals [2]. The issues involve not only joint function but also (and perhaps more so) the consequences of joint osteoarthritis, namely pain syndromes. Osteoarthritis, low back pain, and fibromyalgia are common chronic pain disorders that occur frequently in the general population that are associated with aging [3]. Admittedly, genetic, environmental, and psychosocial factors likely play an important role. However, the economics of medical practices is surely also a contributor.

Aside from basketball and soccer players (USA-football players are currently more concerned about head-injury dementia), other elite performers present a challenge in terms of osteoarthritis. A delightful review by a physician who dedicated his career to help dancers and musicians has been published [4]. Artists in general are intelligent and the time spent on extensive explanation and advice is well spent, concluded the author. In overuse injuries, relative rest supported by "mental practice" is effective, the author advised. In terms of general physical exercise, there are few studies. An impressive case–control study with long-term follow up has been reported. About 500 aging (50–72 years) runners were compared to 247 never-runner "couch potato" controls. The study showed that "older persons" who engage in vigorous running and other aerobic activities have lower mortality and slower development of disability (including osteoarthritis) than do members of the general population [5, 6]. The association was probably related to increased aerobic activity, strength, fitness, and increased organ reserve rather than to an effect of postponed osteoarthritis development.

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We are less concerned about violinists, dancers, soccer players, and runners—what about the rest of us? Cell stress, damage, initiators of inflammation, and a host of age-related mechanisms (related to protein, carbohydrate, and lipid metabolism all abbreviated under the umbrella of "reactive oxygen species") have been implicated [7]. The appearance of cytokines such as tumor necrosis factor-alpha (TNFα), interleukin-1 (IL-1), transforming growth factor beta (TGFβ), as well as disturbed sirtuin-1 function, will not surprise you.

Treatment options aside from platelet therapy and non-proven operative interventions are suboptimal and nonspecific. Nonsteroidal anti-inflammatory drugs (NSAIDS), cyclooxygenase-1 and 2 inhibitors, acetaminophen, and aspirin are all employed. Not surprisingly, an anti-cytokine treatment similar as used in rheumatoid arthritis has also been advocated [8]. The entire "pain" industry is largely fed by osteoarthritis. Thus, the ramifications of this underappreciated condition are tremendous.

The pannexins are a family of vertebrate proteins with homology to the innexins. Innexins are responsible for forming gap junctions, while pannexins predominantly exist as large transmembrane channels that connect the intracellular and extracellular space [9]. Pannexin glycoproteins allow the passage of ions and small molecules including adenosine triphosphate (ATP) [10]. The pannexins have been implicated in purinergic receptor signaling and in the process of tumor development. Perhaps mouse models could provide more insight [11].

In this issue of J Mol Med, Moon et al. have done exactly that [12]. Pannexin-3 (Panx3) mediates ATP release in chondrocytes. The process accelerates hypertrophic differentiation. Chondrocyte hypertrophy is responsible for cartilage reabsorption in preparation for bone deposition. The master hypertrophic regulator RUNX2 targets Panx3. The transcription factor also drives matrix metalloproteinase-13 (MMP13) expression. MMP13 is a partner of Panx3. The authors generated both *Panx3* gene-deleted (−/−) mice and cartilage-specific *Panx3* gene-deleted mice. *Panx3* −/− mice had no specific phenotype. The authors performed surgical destabilization of the medial meniscus (DMM). The DMM procedure that is analogous to a traumatic joint injury-induced osteoarthritis provides a reproducible model of osteoarthritis in mice [13]. Elimination of *Pnx3* in cartilage led to a dramatic decrease in medial tibial plateau, medial-femoral condyle, and whole joint osteoarthritis with remarkable improvements in osteoarthritis-research-society-international (OARSI) joint injury scores. These findings potentially link pannexin channels to a human disease [14]. How could the process work?

The authors observed reduced MMP13 immunostaining after *Panx3* deletion [12]. Mechanistically, Runx2 could mediate induction of *Panx3* leading to increased ATP release from chondrocytes. Extracellular ATP could signal by means of the purine receptors, P2Y a G protein-coupled receptor, and P2X a gated ion channel. The resulting signals could lead to calcium signaling and ERK1/2 stimulated signaling thereby further activating *Runx2*. This state-of-affairs could begin a vicious cycle leading to further *Runx2* and MMP13 expression facilitating additional joint destruction. Pathway suggestions are clearly speculative (Fig. 1).

Information on pannexins in human tissues is rather sparse. Panx1 and Panx3 channels regulate skeletal muscle myoblast proliferation and differentiation including cells from humans [15]. The channels are expressed in human cartilage [16]. Panx3-transfected chondrocytic ATDC5 cells reduced parathyroid hormone-induced cell proliferation and promoted the release of ATP into the extracellular space, possibly by action of Panx3 as a hemichannel. Panx3 expression in chondrogenic ATDC5 cells reduced intracellular cAMP levels and the activation of cAMP-response element-binding, a protein kinase A downstream effector. The Panx3 activities were blocked by anti-Panx3 antibody. These results suggest that Panx3 functions to switch the chondrocyte cell fate from proliferation to differentiation by regulating the intracellular ATP/cAMP levels [17]. The current studies will undoubtedly stimulate much human PANX3 research and possibly target purinergic receptors as potential treatment avenues for osteoarthritis. The clinical ramifications of this research area are enormous and the field should be watched with extreme interest!

Respectfully,

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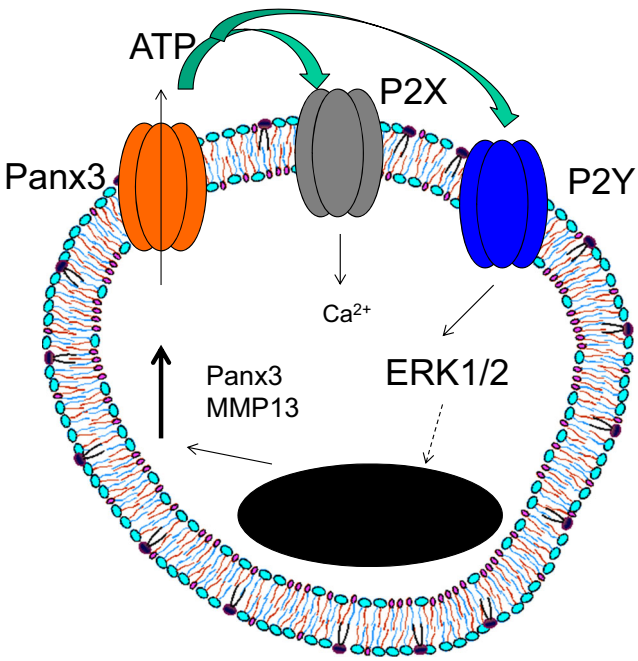

Fig 1 Entirely speculative notion on how the authors' findings might work. Panx3 is a glycoprotein ATP transporter, regulated by Runx2. ATP could signal over P2X and P2Y resulting in a positive feedback situation upregulating Panx3 and MMP13. MMP13 could contribute to osteoarthritis

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