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Chondrocyte Apoptosis in Rheumatoid Arthritis: Is Preventive Therapy Possible?

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Introduction

Rheumatoid arthritis (RA) is a systemic, chronic autoimmune disease of unknown etiology. At the tissue and organ level, respectively, RA is associated with sustained synovial joint inflammation which may also go on to affect other peripheral organs [1]. At the cellular level, RA is characterized by defective innate and adaptive immune responses [2]. Thus, experimental studies designed to dissect out the progression of RA changes have noted the extensive presence of activated T-lymphocytes with associated B-cell hyperactivity, as well as heightened migration, adhesion and retention of activated macrophages, dendritic cells and neutrophils emanating from the peripheral circulation and reaching synovial tissue [3]. These cellular events ultimately give rise to activate the normally quiescent synovial tissue fibroblasts which most often results from the action of pro-inflammatory cytokines and other soluble mediators of inflammation that are abundantly present in the RA synovial joint [4]. The clustering of these aberrant cellular events culminate in subchondral bone erosions. In this regard, bone erosions have also been associated with mechanically-deficient ligaments and tendons as well as a marked increase in the degradation of articular cartilage extracellular matrix proteins. The destruction of articular cartilage generally occurs under these conditions following the up-regulation matrix metalloproteinase (MMP) gene expression [5]. However, paradoxically this increase in MMP gene expression is also accompanied by a marked increase in the frequency of non-viable articular chondrocytes which can result from controlled cell death, also known as programmed cell death or apoptosis [6–8].

Significant clinical advances have been made in the therapeutic management of RA over the last 15–20 years, including the development of biologic drugs and small molecule inhibitors designed to either block the interaction between pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and IL-6 with their respective receptors on the plasma membrane of macrophages and other cell types involved in the progression of

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RA [9–16]. However, there has been little advancement in our understanding of whether these therapeutic strategies also ameliorate chondrocyte apoptosis.

TNF- α blockade fits prominently into the medical therapy of RA. In addition to its well-known role as a clinically efficacious treatment, TNF- α blockade [10–13] appears to ameliorate the progression of bone erosions in RA. In addition, because TNF- α is a potent inducer of apoptosis, TNF- α blockade is likely to reduce, but not totally eliminate, apoptosis by the complex network of activated immune cells in RA. Biologic drugs designed to neutralize T-cell [17] and B-cell hyperactivity [18,19] or the activity of various Janus kinases [20–23] have also been developed and approved for use in RA which may or may not affect chondrocyte apoptosis.

Importantly, no drugs have been developed for the clinical management of RA which specifically inhibit chondrocyte apoptosis. Thus, an advance in this field could become quite critical for maintaining the function of articular cartilage in the RA milieu, for in the absence of significant numbers of chondroprogenitor stem cells, which could theoretically replenish the population of chondrocytes lost via apoptosis, the death of articular chondrocytes in RA cartilage would appear to be an inevitable consequence of progressive RA disease. This appears to occur even under conditions of maximal therapeutic support. Therefore, an appropriate question one should ask is; could chondrocyte apoptosis be specifically blocked by preventive therapy?

Before designing drugs to specifically inhibit chondrocyte apoptosis in RA can be considered, it will be especially critical to also address at least one major conundrum characteristic of RA synovial joints. Thus, whereas there is ample evidence for the elevated frequency of chondrocyte apoptosis in RA cartilage, there is also compelling evidence for “apoptosis-resistance” in RA synovial tissue [24–26]. Therefore, any therapeutic strategy to be employed in RA to inhibit chondrocyte apoptosis will confront the possibility that aberrant survival of activated cells of the immune system would be potentially exacerbated. Mechanistically speaking, this might arise by activating signaling pathways known to be involved in apoptosis, [3,8,15,22,23]. Therefore, to thwart this event it is likely that “survival” signaling pathways such as PI3K/Akt/mTOR-mediated signaling may also have to be simultaneously targeted [27]. Potentially this would allow us to achieve the dual objective of inhibiting chondrocyte apoptosis while also blunting the aberrant survival of activated immune cells.

The impact of the epigenome and microRNAs activity on the RA process are also likely to fit into the developing a complete picture of how apoptosis can become deregulated in RA. Epigenetics has been characterized as “the DNA-templated process that results in heritable changes in gene activity and expression” [28]. Therefore, an understanding of how DNA methylation patterns alter RA pathogenesis and disease progression will be critical for designing future therapies for RA [29–31]. For example, altered methylome patterns were found in activated RA synovial fibroblasts which probably reflect the hyperactivity of these cells [30]. Moreover, reversing the impact of DNA hypomethylation by inhibiting the polyamine recycling pathway is strongly considered to be a potential therapeutic target for RA [31]. On the other hand, microRNAs form another component of epigenetics which

regulates many target genes considered critical to the development of RA [32]. In that regard, Churov et al. [33] reported that the many microRNAs are systemically (i.e., both peripherally and at the level of the joint) overexpressed in RA, including, microRNA (miR)-16, miR-146a/b, miR-150, miR-155 and miR-223. However, other miRs (e.g., miR-21, miR-125a, miR-223 and miR-451) are elevated principally in the plasma and serum of RA patients which suggest that these miRs may be useful biomarkers for assessing RA disease activity.

With respect to the potential role of miRs as regulators of apoptosis it was recently shown that the transcription factor, Twist1 which has a limiting effect on murine T-cell activation as well as another transcription factor, t-Bet, induces miR-148a gene expression. This, in turn, regulates the expression of the pro-apoptotic protein Bim. Thus, “antagomirs” of miR-148a when incubated with chronically activated murine Th1 cells increased the expression of Bim while also increasing the Th1 apoptotic response [34]. In contrast, Treg cells in RA synovial fluid were shown to express elevated levels of Bcl-2 and miR-21. These Treg cells showed little capacity to undergo apoptosis [35]. Although most of the miR manipulation studies to date have focused on regulating the apoptotic responses of chronically activated immune cells, it may be also be possible in RA to employ such strategies to prevent chondrocytes from undergoing apoptosis.

It is also germane for the future development of drugs to manage RA to briefly examine the evidence that has accumulated which directly implicates chondrocyte apoptosis as a critical pathophysiologic element in the progression of RA. In that regard, Kim and Song [36] were among the first group of investigators to compare the frequency of chondrocyte apoptosis in RA versus normal articular cartilage. In their study, they found about a 45-fold increase in the frequency of apoptotic chondrocytes in RA cartilage when compared to normal cartilage. They also reported a 1.85-times lower level of Bcl-2 gene expression with no differences in Fas gene expression between RA and normal cartilage. A subsequent analyses of RA cartilage reported several additional changes in RA cartilage which were consistent with an increased frequency of chondrocyte apoptosis. These included, evidence of natural killer activity in RA chondrocytes involving granzyme B activity [37], the latter enzyme having been implicated in poly-ADP-ribose polymerase degradation (PARP) [38] as well as high levels of TNF- α , IL-1 β [39], and IL-8 [40]. Importantly, TNF- α , IL-1 β , and interferon- γ were also associated with induction of chondrocyte apoptosis [9,41–44] whereas IL-6 and IL-4 were not [40]. Other cellular events which govern the development of acute and chronic inflammation have also been implicated in chondrocyte apoptosis [45]. These include, inducible nitric oxide, a potent inducer of chondrocyte apoptosis [46] which was also reported to be at increased levels in RA cartilage as were 2 apoptosis-related genes, namely, the c-myc and p53 genes [47]. However, the likelihood that a complex networking exists between these factors which have been implicated in chondrocyte apoptosis was at play in RA was suggested by the results of a study by Rel'ic et al. [48] who showed that TNF- α actually protected articular chondrocytes from nitric oxide-induced apoptosis by acting through the inhibition NF- κ B and cyclooxygenase-2 activity.

Interestingly, the association between clinically active periodontal disease and RA [49] may also be related to the elevated frequency of apoptotic chondrocytes in RA. Thus, Röhner et

al. [50] reported an increased frequency of TUNEL- and Annexin-V-positive chondrocytes (both are measures of DNA fragmentation and apoptosis) as well as up-regulation of caspase-3 in patients infected with *Porphyromonas gingivalis*. More recently, the results of an experimentally-based study showed that TNF- α potentially increased autophagy-related gene which was accompanied by activated autophagy both in vitro and in vivo [51]. Moreover, arthritic hTNF α -transgenic mice transplanted with Atg (fl/fl) \times LysMCRE (+) bone marrow cells showed evidence of fewer activated osteoclasts. In fact, these mice were also protected from TNF- α -induced bone erosions, loss of proteoglycan and chondrocyte death, thus indicating that autophagy was likely to play a crucial role in the progression of experimentally-induced RA disease [51] and perhaps in regulating the induction of chondrocyte apoptosis as well.

With regard to human RA, Wang et al. [52] showed that programmed cell death 5 (PDCD5), a novel apoptosis regulatory gene, was significantly elevated in the plasma and synovial fluid of RA patients where the level of PDCD5 was inversely correlated with TNF- α . Prior to the induction of apoptosis PDCD5 protein is distributed between the nucleus and cytoplasm. However, when apoptosis was induced, the level of PDCD5 protein was increased which was then translocated from the cytoplasm to the nucleus where PDCD5 accumulation occurred. Although the precise function of PDCD5 has not yet been defined, PDCD5 protein has been proposed as a regulator during the early phase of apoptosis [53]. These findings also suggested that although TNF- α may be an influential pro-inflammatory cytokine in the induction of apoptosis in RA joints, the abnormal expression of PDCD5 which was shown to play a role in regulating apoptosis in RA synoviocytes [54] may also be a fruitful target in RA for suppressing chondrocyte apoptosis.

Here, I want to propose a prudent strategy which would systematically investigate which of the many activated cells of the immune system known to be relevant in RA pathology is, in fact, responsible for producing those molecules which are likely to promote chondrocyte apoptosis. Although several novel targets have been previously proposed for further study in this regard, including, tumor necrosis factor-related apoptosis-inducing ligand receptor (TRAIL) [55], heat-shock protein-70 [56], NF- κ B [57], NF- κ B via bcl-3 [58], the BH3-family of proteins, especially, bcl-2 [59], TNF-related weak inducer of apoptosis (TWEAK) [60] and the forkhead box O family members of transcription factors [8,61] it still remains problematic as to which therapeutic strategies could be designed to independently target each of these potential critical apoptosis and anti-apoptosis-related factors. Importantly, this will have to be accomplished without compromising the therapeutic efficacy of drugs already FDA approved for the medical management of RA.

Finally, a clinical trial design which incorporated the acquisition of synovial tissue biopsies as a component for assessing the clinical efficacy of the JAK3-selective SMI, tofacitinib, reported by Boyle et al. [62] was a significant advance. This was because the results of this study verified that STAT1 and STAT3 activation was markedly reduced by tofacitinib measured *ex vivo* in these synovial tissue biopsies as well as confirming previously reported results of pre-clinical studies which had predicted that oral administration of tofacitinib would reduce synovial tissue MMP production. Indeed, MMP-1 and MMP-3 mRNA levels were reduced. In addition, treatment with tofacitinib significantly reduced synovial mRNA

expression of the CCL2, CXCL10 and CXCL13 group of chemokines. Of note, CCL2 and CXCL13 were previously implicated in RA as chemokines active in the chemotactic response of immune cells [9]. In that regard, CXCL10 was found to contribute to the recruitment of Th1 cells to synovial joints [63–65], whereas CCL2/MCP-1 was reported to be a ligand for CCR5 [63].

An extension this type of clinical trial study design to now include articular cartilage biopsies which could be analyzed *ex vivo*, although an admirable objective, would likely prove to be difficult after considering the long-standing standard of care guidelines for treating RA. Thus, any longitudinal sampling of articular cartilage would likely prove to be prohibitive. Nevertheless, the development of non-invasive imaging techniques that could theoretically be employed to assess the frequency of chondrocyte apoptosis following administration of experimental drugs in well-validated animal models of RA and then subsequently after employing approved therapies for RA (e.g., TNF blockade) would be a laudable goal going forward.

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