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Pharmacologic Interventions for Preventing Chondrocyte Apoptosis in Rheumatoid Arthritis and Osteoarthritis

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Abstract

Chronic inflammation drives the progression of rheumatoid arthritis (RA) and osteoarthritis (OA) to synovial joint failure. The inflammatory state in both musculoskeletal diseases is associated with significantly elevated levels of pro-inflammatory cytokines in joint synovial fluid, which is best exemplified by increases in interleukin-1β (IL-1β), IL-6, IL-17, tumor necrosis factor-α, among others, as well as increased activity of soluble mediators such as nitric oxide and certain growth factors including vascular endothelial growth factor and fibroblast growth factor. The multitude of these factors activate chondrocyte signal transduction pathways resulting in programmed cell death, otherwise known as apoptosis as well as compromising chondrocyte autophagy. Importantly, chondrocyte apoptosis causes a loss of articular cartilage vitality which dampens cartilage repair mechanisms because at present, the possibility that chondrocyte progenitor cells could replace those differentiated chondrocytes lost via apoptosis remains debatable. Certain pharmacologic interventions which have been proven to induce apoptosis in various cancer cell studies *in vitro* suggest the possibility that drugs could be developed to specifically suppress or completely inhibit chondrocyte apoptosis in RA and OA cartilage. This review supports that contention and indicates that apoptosis can be inhibited by identifying novel cellular targets which promote apoptosis and autophagy.

Keywords: apoptosis, chondrocyte, osteoarthritis, rheumatoid arthritis, signal transduction

1. Introduction

Controlled cell death otherwise known as programmed cell death or apoptosis constitutes a critical event which is germane to the normal development of the immune system, the appropriate

integration of cells within tissues and organs and organ homeostasis [1–7]. However, the aberrant frequency of apoptotic cells can compromise normal tissue architecture and, in doing so, contribute to the loss of cell vitality [8–10]. This is especially the case in explaining the loss of chondrocyte viability in arthritic conditions of synovial joints, such as rheumatoid arthritis (RA) and osteoarthritis (OA).

Significant progress has been achieved over the previous decade or so in furthering our understanding of the cellular and molecular events that trigger the increased frequency of chondrocyte apoptosis in RA and OA [11–16]. These advances include (1) an appreciation that the significant increase in the levels of pro-inflammatory cytokines in synovial fluid from RA and OA patients also can induce chondrocyte apoptosis *in vitro* [17–21]; (2) that the elevated frequency of chondrocyte apoptosis by these cytokines is deregulated by altered signal transduction which can involve continuous activation of stress-activated/mitogen-activated protein kinases (SAPK/MAPK) [22–25], the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway [26–31], the phosphatidylinositide-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway [32–36], and other protein kinase pathways [37–40]; (3) that specific co-factors are capable of regulating the activation of these signaling pathways [41–44]; and (4) that micro-RNAs (mi-RNAs) can regulate the activity of these co-factors and, in this manner, control the induction of apoptosis via these signaling pathways [45–48].

Furthermore, the increased frequency of chondrocyte apoptosis now confirmed in guinea pig OA cartilage [49] as well as human RA and OA articular cartilage [50–53] presents a particularly onerous scenario for the survival of synovial joints under these conditions. Although a population of chondroprogenitor cells was identified in several studies of adult normal and diseased articular cartilage [54–56], significant repair of damaged articular cartilage in RA and OA by these cells is effete. This effect on cartilage repair may result from elevated levels of pro-inflammatory cytokines such as IL-17, which was recently shown to inhibit the chondrocyte maturation lineage emanating from progenitor cells in RA [57]. Therefore, even if chondrocyte precursor cells exist in adult articular cartilage which could potentially become authentic chondrocytes lost from articular cartilage via apoptosis or chondrocytes lost via diffusion of cartilage extracellular matrix fragments into synovial fluid, the reduction in chondrocyte vitality via apoptosis would be a challenging event to overcome, especially in a synovial joint microenvironment replete with pro-inflammatory cytokines.

In this chapter, we have systematically examined the mechanistic underpinning for identifying novel targets in order to suppress or even inhibit chondrocyte apoptosis in RA and OA. However, the scenario in RA, in particular, is even more complex than in OA because in the context of devising therapeutic strategies designed to inhibit chondrocyte apoptosis in RA, one must also take into account the fact that in the hyperplastic RA synovial tissue, comprised of activated synoviocytes, immune cells, macrophages and other inflammatory cells are generally considered to be relatively "apoptosis-resistant" [58, 59]. Thus, this characteristic of the RA joint ensures a plentiful source of immune-mediated cells and non-immune inflammatory cells which drive the progression of RA. It is also likely that at

some time during the course of the progression of OA, immune-mediated inflammation may also cause a similar chronic inflammatory microenvironment, as found in RA, to arise and persist in OA synovial tissue [55] resulting, in part, in an increased frequency of apoptotic chondrocytes [60].

2. Compelling evidence that many factors relevant to RA and OA promote or induce chondrocyte apoptosis *in vitro*

Analyses of synovial fluids and sera from RA and OA patients with active disease showed that these samples contained significantly elevated levels of various pro-inflammatory cytokines and growth factors when compared to a control group [52–68]. Of note, incubation of rat [69], non-arthritic or human chondrocytes from OA cartilage [70–76] or immortalized lines of human chondrocytes [77] with physiological levels of these cytokines, growth factors (e.g., VEGF and FGF) or additional soluble mediators (e.g., nitric oxide) were shown to induce apoptosis, which was accompanied by activation of SAPK/MAPK, JAK/STAT or PI3K/Akt/mTor signaling in these cells [78–81]. In addition, mediators of inflammation, including prostaglandin E_2 and neuropeptides (e.g., Substance P), are also implicated in perpetuating chronic inflammation [38]. The induction of apoptosis was also shown to be related to altered levels of various down-regulators of apoptosis. These included BCL-2-like protein-11 (Bim) [18], B-cell lymphoma-2 (Bcl-2) [75], cell-derived inhibitors of apoptosis proteins (IAPs) [81–84] and Suppressor of Cytokine Synthesis (SOCS) [85, 86]. Furthermore, alterations in the functions of mitochondria [87] and endoplasmic reticulum (ER) [88–91] related to cell stress, the generation of reactive oxygen species [92] and the recently described advanced oxidation protein products [93] with respect to their capacity to induce apoptosis were reported as well. Taken together, these results provided compelling evidence that pro-inflammatory cytokines, growth factors and soluble mediators germane to the progression of RA and OA are responsible for inducing chondrocyte apoptosis in these conditions.

3. The relationship between apoptosis and autophagy

A recent review of RA pathogenesis by Angelotti et al. [94] emphasized the view that numerous cells comprising the innate immune system, including macrophages, dendritic cells, mast cells, natural killer cells and neutrophils as well as T-cells and B-cells, regulators of adaptive immunity, are primarily responsible for perpetuating the state of chronic inflammation through their capacity to alter the survival of resident synovial fibroblasts. It is also likely that such cell combinations are also involved in the progression of OA as well, as evidenced by the skewing of cartilage homeostasis toward catabolism, and the loss of chondrocyte vitality via the induction of apoptosis [95–97]. However, it was previously shown that the classical apoptosis cascade can be activated by various pro-inflammatory cytokines, and certain growth factors, chemokines, chemokine receptors (**Table 1**) and other interleukins, including

IL-8 (CXCL8) and adhesion molecules [64]. Thus, these factors are likely to be the most influential in inducing apoptosis pathway RA. However, a non-classical form of apoptosis, termed, "chondroptosis" is just as likely to be activated in OA. In that regard, "chondroptosis" involves an increase in the number of ER and Golgi apparatus reflecting an increase in protein synthesis that accompanies the loss of viable chondrocytes [98].

Furthermore, changes in the number of viable articular chondrocytes in experimentally induced arthritis [99], human RA [100], and OA are almost certainly associated with the autophagic-mediated cell death of chondrocytes [101–105], which occurs in concert with the activation of the extrinsic apoptosis pathway, the latter mediated by Tumor necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), Death Receptor-5 (DR5) and caspase-3 [106, 107]. In that regard, it was noteworthy that Huang et al. [108] reported that exogenous leptin promoted chondrocyte apoptosis while inhibiting chondrocyte autophagy via the up-regulation of lysyl oxidase-like 3 (LOXL3). Thus, in their study [108], overexpression of LOXL3 inhibited chondrocyte autophagy by activating mechanistic target of rapamycin complex-1 (mTORC1) [36]. In contrast, cartilage-specific

Cytokine, chemokine, chemokine receptors and growth factors	Reference
IL-17, IL-18BP	[62]
IL-17, IL-20, IL-21	[63]
IL-7	[64]
IL-12/IL-23	[64]
IL-15/IL-16	[64]
IL-17/IL-18	[64]
IL-19/-20/-21	[64]
IL-32	[64]
VEGF[1]; TGF-β_1[2]; Leptin; FGF[3]	[64–66]
CXCR3; CXCR4,-5; CXCR-1,-5,-6; IL-8; MIP-1α[4]; GRO-α[5](CXCL1); GRO-$\beta\gamma$[6]; MCP-1[7]; RANTES[8]; Eotaxin-1	[65, 68]
IL-6	[64, 67, 68]
TNF-α	[64, 67, 69]
IL-1β	[64]

[1]Vascular endothelial growth factor.
[2]Transforming growth factor-β_1.
[3]Fibroblast growth factor.
[4]Macrophage inflammatory protein-1 (CCL3).
[5]Growth-related oncogene-α.
[6]GRO-$\beta\gamma$.
[7]Monocyte chemotactic protein-1.
[8]Regulated on activation, normal T-cell expressed and secreted.

Table 1. Cytokines, chemokines, chemokine receptors and growth factors in RA and OA.

deletion of mTOR resulted in the up-regulation of autophagy [102]. Autophagy protected mouse cartilage from degeneration [109]. Autophagy was also shown to protect chondrocytes from glucocorticoid-induced apoptosis via reactive oxygen species, Akt and FOXO3 signaling [110] as well as from advanced glycation end-product-induced apoptosis which was accompanied by lower levels of MMP-3 and MMP-13 in rat chondrocyte cultures [111].

4. Do micro-RNAs play a critical role in chondrocyte apoptosis?

Micro-RNAs (miRs) are critical mediators of mRNA degradation as well acting as repressors of translation. MiRs have been implicated in the development of skeletal long bones via their multiple effects on osteogenesis [112]. However, recent evidence has also improved the recognized role of miRs in RA pathology as a result of evidence that many miRs including miR-16, miR-146a/b, miR-150, miR-155 and miR-223 are over-expressed both in the peripheral circulation of RA patients and in the RA synovial joint [113], although other miRs relevant to RA, such as miR-21, miR-125a, miR-223, and miR-451 are principally found to be at elevated levels in the plasma and sera of RA patients.

Additional evidence has been presented to show that several of these miRs also regulate apoptosis. For example, the level of the pro-apoptotic protein, Bim, was increased when activated T-cells were incubated with a repressor of miR-148a resulting in an increase in the Th1 apoptotic response [114]. Thus, accumulating evidence showed that both the immune cells and chondrocyte apoptotic and autophagic response can be manipulated by either experimental overexpression or repression of various miRs which are relevant to OA [115] and RA [116] pathophysiology.

The results of numerous studies have confirmed the role of specific miRs as directly affecting apoptosis or indirectly affecting apoptosis through their activity on other molecules that regulate chondrocyte apoptosis. For example, mIR-146a was reported to be over-expressed in OA [117]. In that regard, mIR-146a was shown to promote human OA chondrocyte proliferation and to inhibit apoptosis by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6) via NF-κB [118, 119]. By contrast, mIR-146a was also shown to target IL-1β, to induce VEGF production, and to promote rat chondrocyte apoptosis via Smad4 [120]. On the other hand, silencing of miR-34a inhibited rat chondrocyte apoptosis [121], whereas overexpression of mIR-34a promoted apoptosis in normal human chondrocytes by targeting SIRT1/p53 signaling [122], although other evidences indicated that miR-34a was increased in intervertebral disc degeneration and was associated with an elevated frequency of apoptotic cartilage end plate chondrocytes [123]. In another study, glycerol-3-phosphate dehydrogenase 1-like protein was shown to be a target for mIR-181a, which is deregulated in OA wherein human chondrocyte apoptosis was increased [124]. In yet another study, phosphatase and tensin homolog deleted on chromosome 10 (PTEN) [36] was identified as the target for mIR-181 whereby mIR-181 up-regulated the expression of proteins associated with apoptosis, including caspase-3 and PARP. However, mIR-181 also up-regulated MMP-2 (gelatinase A; 72 kDa gelatinase) and MMP-9 (gelatinase B; 92 kDa gelatinase) [125] which are two MMPs directly relevant to cartilage matrix protein degradation in arthritis [126].

Of note, several miRs were identified as potential targets for inducing chondrocyte survival and therefore could be considered anti-apoptosis factors; these included mIR-98 [127–129], mIR-9 [130], mIR-15a-5p [131], mIR-142-3p [132] and mIR-502-5p [133]. Additional mIRs, exemplified by miR-195 [134], mIR-139 [135], mIR-29b-3p [136], mIR-488-3p [137] and mIR-203 [138] could very well be included in this group. For example, by employing the C28/I2 line of immortalized human chondrocytes, Zhao et al. [138] showed that knockdown of mIR-203 targeting the myeloid cell leukemia-1 (MCL-1) protein activated Wnt/β-catenin and JAK/STAT signaling promoted chondrocyte survival.

To summarize this section, gaining a further understanding of how to manipulate specific mIRs to achieve increased or decreased synthesis of specific targets known to influence chondrocyte apoptosis may signal the next major advance in targeted OA and RA therapy designed to promote chondrocyte survival.

5. Pharmacologic interventions designed to specifically inhibit chondrocyte apoptosis

5.1. Signal transduction pathways

Lewis and Malemud [82] previously reviewed several potential pharmacologic strategies designed to limit the loss of chondrocyte vitality via apoptosis. These included, targeting x-linked inhibitor of apoptosis (XIAP), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), TRAIL, decoy-receptor-3 (DcR3), tumor necrosis factor receptor protein-like molecules, p53 up-regulated modulator of apoptosis (PUMA), and apoptosis-signal-regulating kinases. In that regard, we proposed several interventional strategies which we acknowledged involved developing a deeper understanding of which signal transduction pathways were altered in RA and OA chondrocytes [19, 28, 36, 77, 82, 106]. For example, XIAP, an inhibitor of activated caspase-9, and caspases-3 and -7 [82] was also shown to interact with mitogen-activated protein kinase kinase 2 (MEKK2) [139]. The interaction between XIAP and MEKK2 resulted in a biphasic activation of NF-κB, a known downstream effector of TNF-α-mediated apoptosis. This finding is relevant to the regulation of chondrocyte apoptosis in both RA and OA primarily because XIAP is a well-known inhibitor of apoptosis protein-3 (IAP3) [140]. In fact, we had previously shown that recombinant human TNF-α (rhTNF-α) induced human chondrocyte apoptosis via activation of p38, JNK1/2 and STAT3 [72], whereas apoptosis of the immortalized human chondrocyte line, C-28/I2 induced by rhTNF-α, but not by rhIL-6, was dependent on upstream MEK1/2 [77]. Therefore, we posit that in order to consider using potential drug interventions that alter the activation of various signaling pathways it will be useful to consider what we know about how alterations in receptor-mediated signaling pathways (reviewed in [19]) may influence apoptosis.

Activation of SAPK/MAPK signaling is most often associated with induction of chondrocyte apoptosis. Thus, induction of rabbit articular chondrocyte apoptosis by the nitric oxide (NO) donor sodium nitroprusside (SNP) was linked to inhibition of c-Jun-amino-terminal kinase (JNK) by virtue of the finding that the JNK small molecule inhibitor (SMI) SP600125, reduced

the frequency of apoptotic chondrocytes along with NO-induced NF-κB, p53 and caspase-3 [141]. IL-1β, another potent inducer of chondrocyte apoptosis, was also shown to be JNK-dependent as both chemical inhibitors of JNK as well as RNA interference with Bim, the latter up-regulated by IL-1β, were shown to be phosphorylated-JNK-dependent [142]. In other studies, chondrocyte apoptosis was again linked to IL-1β-induced activation of p38 kinase [143–145], along with JNK [145], and MMP-3 gene expression with IL-1β negatively regulating chondrocyte autophagy [145]. Of note, AG490, a pan-JAK SMI significantly reduced leptin-induced chondrocyte apoptosis *in vitro* as well as reducing STAT3 phosphorylation, reactive oxygen species, MMP-13 and B-cell lymphoma 2-associated X protein [146]. Interestingly, Li et al. [147] showed that the PI3K/NF-κB pathway was activated by TNF-α in human chondrocytes. However, the effect of leptin did not involve mTOR, suggesting that newly developed small molecule mTOR inhibitors (reviewed in [36]) might not be useful for neutralizing activated PI3K/NF-κB in response to leptin-induced apoptosis.

Several attempts to employ various compounds and/or natural products to inhibit chondrocyte apoptosis have taken advantage of various findings related to the role of these compounds and natural products in many of the aforementioned signal transduction pathways. For example, IL-1β-induced chondrocyte apoptosis was inhibited by oligomeric proanthocyanidin, a water-soluble plant polyphenolic compound [148]. Thus, the over-expression of peroxiredoxin 4 (PRDX4), a member of the PRDX family (a molecule essential for scavenging free radicals and reducing reactive oxygen species) reduced IL-1β-induced rat chondrocyte apoptosis [149]. Importantly, AZD5363, an inhibitor of Akt activation also reduced the apoptosis protective effect of PRDX4. In another aspect, chondrocyte apoptosis induced by IL-1β not only involved reduced Bcl-2 levels, activated (i.e., phosphorylated) Akt, and activated PRAS40, a proline-rich 40 kDa Akt substrate and an inhibitor of mTORC1 kinase activity, but was also linked to increasing the levels of Bax, and activated caspase-3/-9 [149].

Shikonin, a compound with anti-tumor, anti-inflammatory, anti-viral and pharmacological efficacy significantly inhibited apoptosis by decreasing IL-1β, TNF-α and inducible NO synthase (iNOS) in rats with experimentally induced OA [150]. The effect of shikonin in this animal model of OA was accompanied not only by reduced caspase-3 and cyclooxygenase-2 activity but also by increased activation of Akt, indicating a prominent role for PI3K/Akt signaling in this rat model of OA. Finally, a few novel targets, including protein kinase R-like endoplasmic reticulum kinase and activating transcription factor 6, were identified as potent regulators of chondrocyte apoptosis *in vitro* and *in vivo* [151], although the precise signaling mechanisms attributed to these molecules have yet to be completely established.

5.2. Additional potential targets related to apoptosis

Several experimental studies, of note, have focused on several cellular components which may eventually become suitable pharmacologic targets for altering chondrocyte apoptosis and/or autophagy in osteoarthritis (**Table 2**). However, the results of these mainly *in vitro* studies point out why it will be necessary to determine the underlying mechanisms regarding how these factors work to inhibit apoptosis. Thus, only after successful evaluation in animal models of RA and OA, can we envision that these targets could eventually be employed in a clinical setting.

Factor	Target	Reference
HIF-1α/HIF-2α[1]	HIF-1α—SOX9; HIF-2α—Fas	[152]
Integrin-β1	G1T1[2]	[153]
IGFBP-3[3]	Nur77[4]	[154]
SGBT[5]	Caspase-3/Hsp70[6]	[155]
UCP4[7]	ROS[8]	[156]
DEL1[9]	Caspase-3/Caspase-7	[157]
Rela[10]	Pik3r1[11]	[158]
Beclin[12]	Bcl-2; Bcl-2 associated X	[159]
AST[13]	LC3-II/I[14]; P62/SQSTM1[15]	[160]
AQP-1[16]	Caspase-3	[161]
Mt1/Mt2[17]	ROS[8]	[162]
Sirt1[18]	Bcl-2; Bax	[163]

[1]Hypoxia-inducible factor-1α/-2α.

[2]G-protein-coupled receptor kinase interacting protein-1.

[3]Insulin-like growth factor-1 binding protein-3.

[4]Nerve growth factor 1B.

[5]Small glutamine-rich tetratricopeptide repeat-containing β.

[6]Heat shock protein-70.

[7]Uncoupling protein-4.

[8]Reactive oxygen species.

[9]Developmental endothelial locus-1.

[10]RelA/p65 of NF-κB complex.

[11]Pik3r1 encodes a p85α regulatory protein that is a subunit of phosphatidylinositol 3-kinase (PI3K).

[12]Beclin-1, a product of the *BECN1* gene is a mammalian ortholog of the yeast autophagy-related gene 6 (Atg6) and BEC-1 in the *C. elegans* nematode.

[13]Astragaloside IV.

[14]Microtubule-associated protein 1A/1B-light chain-I/II.

[15]P62/sequestosome-1.

[16]Aquaporin-1.

[17]Metallothionein-1/metallothionein-2.

[18]Silent information regulation of transcription 1.

Table 2. Cellular factors that regulate chondrocyte apoptosis and/or autophagy *in vitro*.

6. Conclusions and future perspectives

It is now generally agreed upon by many investigators that a chronic state of inflammation is, in part, responsible for driving and perpetuating the progression of RA (reviewed in [94]) and OA (reviewed in [58, 164]). Moreover, additional recent evidence has indicated that both apoptosis and an altered state of autophagy are critical events in chronic musculoskeletal disorders, such as RA and OA [60, 102–105, 164–167]. Although the loss of chondrocyte vitality

is a common pathological finding in RA and OA, cellular mechanisms that result in synovial fibroblast and immune-cell-mediated "apoptosis-resistance," such as those that were found to underlie B-cell activity in RA [168–171], aids in distinguishing between the fundamental underpinning responsible for bony abnormalities in the two conditions. However, equally important is that the increased frequency of apoptotic chondrocytes in both RA and OA constitutes a major contributor to inefficient cartilage repair and synovial joint failure. We contend that any pharmacologic strategies designed to simultaneously target the "apoptosis-resistance" in the RA hyperplastic synovial tissue and the elevated frequency of chondrocyte apoptosis would be an onerous undertaking. So for the present, concentrating on developing agents that suppress or inhibit chondrocyte apoptosis might be the initial way to proceed. For example, the current literature on this subject has already indicated that certain drugs used in the medical therapy of RA suppress chondrocyte apoptosis *in vitro*. In that regard, the drug sulphasalazine, commonly employed in combination with methotrexate, for treating RA [172] was found to inhibit rabbit chondrocyte apoptosis induced by SNP [173]. In this study, the reduced frequency of chondrocyte apoptosis was accompanied by an increase in phosphorylated p38 kinase and ERK1/2 expression compared to treatment of chondrocytes with SNP alone.

Another area worthy of consideration is to employ *in vitro* studies to, in effect, rule out for further considerations for developing drugs for treating potential targets of chondrocyte apoptosis. A suitable example of this strategy was a recent finding by Nasi et al. [174] that the NALP3 inflammasome (reviewed in [175]) was not involved in chondrocyte apoptosis characteristic of several alterations in cartilage characteristically found in a murine menisectomy model of OA. Although alterations in the structure of articular cartilage such as cartilage destruction, synovial inflammation, cell death and calcification were seen in this OA animal model, a deficiency in IL-1α had no impact on these features. Importantly, deficiencies in IL-1β and NALP3 actually resulted in an enhancement of cartilage damage in this OA animal model.

The suppression or more favorably the complete inhibition of chondrocyte apoptosis in RA and OA using pharmacologic interventional strategies would be a laudable achievement in the continuing search for novel disease-modifying-anti-rheumatic drugs. A variety of potential novel targets have now been identified during the previous 3 years that at least employing cancer cells induces the frequency of apoptosis. Thus, targets have been identified to induce apoptosis in these cancers and therefore, may be eventually exploited for blocking chondrocyte apoptosis. For example, the activity of 2,5-dihydroxy-3-undecyl-1,4 benzoquinone, 6 g, also known as embelin was reviewed [82] as an inducer of apoptosis in inflammatory breast cancer cells and pancreatic cancer cells. Embelin was also shown to block the transcription of several gene products relevant to tumor cell survival, proliferation, invasiveness and metastatic cancer cell proliferation. Of note, treatment with non-toxic concentrations of embelin could also sensitize cultured malignant glioma to TRAIL-induced apoptosis [176]. Lewis and Malemud [82] reviewed the findings showing that embelin blocked the activation of NF-κB, RANKL and, STAT3, the latter finding demonstrating "proof-of-principle" that STAT3-activated transcription could also be employed to probe the extent to which this signaling pathway was required for maintaining chondrocyte survival *in vitro* [177]. In that regard, these pre-clinical results may provide a suitable platform for exploiting the overall objective of preventing synovial joint failure in RA and OA through the maintenance of normal articular chondrocyte viability and cartilage integrity.

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