Cellular Signalling 53 (2019) 212–223

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Interleukin-1β signaling in osteoarthritis – chondrocytes in focus

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ABSTRACT

Osteoarthritis (OA) can be regarded as a chronic, painful and degenerative disease that affects all tissues of a joint and one of the major endpoints being loss of articular cartilage. In most cases, OA is associated with a variable degree of synovial inflammation. A variety of different cell types including chondrocytes, synovial fibroblasts, adipocytes, osteoblasts and osteoclasts as well as stem and immune cells are involved in catabolic and inflammatory processes but also in attempts to counteract the cartilage loss. At the molecular level, these changes are regulated by a complex network of proteolytic enzymes, chemokines and cytokines (for review: [1]). Here, interleukin-1 signaling (IL-1) plays a central role and its effects on the different cell types involved in OA are discussed in this review with a special focus on the chondrocyte.

1. The interleukin superfamily

Interleukins (ILs) are a large family of cytokines that were first described to be expressed by monocytes and neutrophils. The term interleukin was coined in the late 1970's and indicated at that time that these substances were thought to be produced by and also to mainly act on leukocytes [2–4]. After many decades of intense research, more than 50 ILs and related proteins encoded in the human genome have been identified. ILs can be divided into four major groups based on structural and functional features [5].

2. The IL-1 superfamily

Today, the IL-1 superfamily comprises 11 members, which share a similar gene structure. Nine IL-1 superfamily members (IL-1α, IL-1β, IL-36α, IL-36β, IL-36γ, IL-36RA, IL-37, IL-38, and IL-1Ra) occur in a single cluster on human chromosome 2 and both their sequence and the chromosomal anatomy suggests that these genes developed through a series of duplications of a proto-IL-1β sharing a common lineage. In contrast, IL-18 and IL-33 are located on chromosomes 11 and 9 in humans, respectively, and there is insufficient evidence to suggest they share common ancestry with the other IL-1 superfamily members [6]. However, the latter two members were added into the IL-1 superfamily

Abbreviations: ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; AP-1, activator protein 1; BMP, bone morphogenetic protein; C/EBP, CCAAT-enhancer-binding protein; Ca^{2+}, Calcium ion; CCL, CC-chemokine ligand; cDNA, complementary DNA; c-Fos, v-fos FBJ murine osteosarcoma viral oncogene homolog; COL2A1, human type II collagen gene symbol; COX2, cyclo-oxygenase-2; ECM, extracellular matrix; EP4, prostaglandin E2 receptor 4; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; GLUT, glucose transporter; gp130, glycoprotein 130; IL, interleukin; IL-1R, interleukin-1 receptor; IL-1RAcP, interleukin-1 receptor accessory protein; iNOS, inducible nitric oxide synthase; IP3, inositol-1,4,5-trisphosphat; IRAK, interleukin-1 receptor-activated protein kinase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; kDa, kilodalton; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein 1; miRNA or miR, microRNA; MMP, matrix metalloproteinase; mRNA, messenger RNA; MYD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor k-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NICD, intracellular domain of the notch protein; NO, nitric oxide; Notch1, Notch homolog 1, translocation-associated (Drosophila); OA, osteoarthritis; p38, mitogen-activated protein kinase subfamily; PDK1, protein 3-phosphoinositide-dependent protein kinase-1; PGE, prostaglandin E2; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RANKL, Receptor Activator of NF-κB Ligand; RANTES, regulated on activation normal T cell expressed and secreted; Rho-GTPase, Ras homolog gene family member guanosinetriphosphatase; RIG, retinoic acid inducible gene; RLR, retinoic acid inducible gene-like receptors; RUNX2, Runt-related transcription factor 2; SNP, single nucleotide polymorphisms; Sox9, SRY-homeobOX - like gene 9-encoded protein; STAT, signal transducer and activator of transcription proteins; TAK-1, TGF-β-activated protein kinase; TGF-β, transforming growth factor β; Th1, pro-inflammatory T cells; TIMP, tissue inhibitor of matrix metalloproteinases; TIR, Toll/interleukin-1-Rezeptor; TLR, Toll-like receptors; TNFα, tumor necrosis factor alpha; TRAF, tumor necrosis factor receptor-associated factor; Treg, regulatory T cells; ubiquitin E3, ubiquitin enzyme3; VEGF, vascular endothelial growth factor; WNT, wingless-type protein

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https://doi.org/10.1016/j.cellsig.2018.10.005
Received 20 June 2018; Received in revised form 7 October 2018; Accepted 8 October 2018
Available online 09 October 2018
0898-6568/

due to structural similarities, overlapping functions and their corresponding receptors.

The nomenclature of the IL-1 superfamily was updated and revisited several times [7–9]. The members are now classified in subgroups mainly based on their activity. IL-1 family ligands include seven receptor agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36 IL-1α, IL-36β, and IL-36γ), three with antagonist activity (IL-1Ra, IL-36Ra, and IL-38) and one anti-inflammatory cytokine (IL-37). IL-1α and IL-1β were discovered first and are therefore the best investigated and characterized members. Their natural antagonist IL-1Ra inhibits the pro-inflammatory activity of IL-1α and IL-1β by competing for binding sites at the corresponding receptor. In this review, we focus primarily on IL-1 and mostly on IL-1β.

3. Polymorphisms in IL-1 genes and arthritic diseases associated with altered IL-1 levels

A large number of IL-1 gene polymorphisms has been identified over the last years and single nucleotide polymorphisms (SNP) of IL-1 genes linked to human diseases were reviewed very recently [10]. Newly identified SNPs in IL-1β are updated on a regular basis and can be followed here: https://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=3553. Even though IL-1 is mostly considered to be classical proinflammatory cytokine, its functions are not restricted to inflammation and, as a consequence, polymorphisms have been associated with a wide range of other physiological and pathological functions. Interestingly, also associations with skeletal conditions were described in different subpopulations, like e.g. with risk to hip and knee OA [11–13] and intervertebral disc degeneration [14,15]. Further, an 86-bp repeat polymorphism in the IL1-receptor antagonist gene has been associated with increased risk of osteoporotic fractures [16]. As mentioned earlier, increased IL-1 levels have been detected in synovial fluids from patients with both rheumatoid arthritis and OA [17,18]. Further, IL-1 is up-regulated in OA cartilage tissue and OA chondrocytes seem to express higher levels of IL-1 receptor type 1 [19,20]. In a recent study, Attur et al. investigated whether inflammatory events within joints are reflected in plasma of patients with symptomatic knee OA. Indeed, there was a modest association of IL1Ra plasma levels with the severity and progression of knee OA in a causal fashion, independent of other risk factors [21]. These results are promising with regard to the identification of prognostic biomarkers involved in IL-1 signaling as well as for the development of novel drugs for OA treatment.

4. Animal models

Needless to say, that the role of IL-1 signaling has been studied in various animal models. However, in this review we will only briefly touch on arthritis-related phenotypes in different mouse models. Several groups have shown that the complete absence of the IL-1Ra in mice leads to spontaneous development of arthritis. The observed phenotype was described as autoimmune arthritis [22], destructive arthritis [23] and chronic inflammatory arthropathy resembling rheumatoid arthritis, respectively [22]. Interestingly, IL-1Ra deficiency leads to spontaneous arthritis only in some strains of mice and the development of the phenotype strongly depends on the genetic background [24]. The molecular basis and the underlying signaling mechanisms for arthritis in these mice are still under investigation but it is obvious that T cells are important and that IL-17 is essential for disease development. In addition, an elevated IL-1 receptor expression has been described [25]. Several mouse models with experimentally induced arthritis underline the importance of IL-1 signaling [26]. However, in most models the form of arthritis investigated resembles more rheumatoid arthritis than OA. Interestingly, a recent study investigated the role of IL-1α and IL-1β in the pathology of collagenase-induced OA in a mouse model. Even though a clear inflammatory component was involved in this model, the authors could show by using IL-1 deficient mouse models that neither IL-1α nor IL-1β was involved in synovial inflammation and cartilage destruction [27]. The surprising finding that IL-1α and IL-1β are not key mediators of OA was confirmed in the murine meniscectomy model [28]. The authors concluded that this observation might explain the inefficiency of IL-1 targeted therapies in human OA. Nevertheless, the role of IL-1 signaling in different subytpes of OA definitely warrants further investigation.

5. Cloning, structure, expression and secretion of IL-1

The first human IL-1 cDNA was isolated in 1984 [29] and at the same time there was already evidence that two biochemically different forms of IL-1 exist [30]. Both IL-1α and IL-1β were then cloned [31,32] and a couple of years after purification their crystal structures have been solved [33–35]. Both proteins are synthesized as a precursor protein that is then activated by proteolytic cleavage resulting in a mature form. In contrast to IL-1α, IL-1β is synthesized only after stimulation. The induction of expression is best studied in innate immune cells after exposure to alarmins and activation of Toll-like receptors (TLRs) or RIG-like receptors (RLRs). Interestingly, IL-1β can also induce its own expression [36]. With regard to changes in biomechanical tissue properties in affected joints during development and progression of OA it is interesting to note that mechanical strain is also able to induce IL-1β mRNA expression not only in keratinocytes [37] but also in chondrocytes. Fujisawa et al. demonstrated that cyclic mechanical stress induces the production of IL-1β in human chondrosarcoma-derived chondrocyte cell line (HCS-2/8) [38]. In addition, Ozawa et al. have shown a mechanical stress-induced IL-1β upregulation in healthy human articular chondrocytes in vitro [39].

In contrast to IL-1Ra, all members of the IL-1 superfamily including IL-1α and IL-1β are synthesized without a typical hydrophobic signal sequence. Therefore, they are not secreted via the classical endoplasmic reticulum to Golgi apparatus pathway but by an unconventional protein secretion pathway of which details regarding mechanisms and regulation are still largely unknown. The so-called leaderless IL-1 s are synthesized in the soluble cytosol and must find their way out of the cell different from the classical secretory pathway. A recent review summarizes the different models of secretion [40] focussing mainly on externalization of IL-1 via different types of vesicles, including secretory lysosomes, microvesicles and exosomes [41]. All the vesicles are potential carriers of IL-1 and their use might also depend on the cell type and the functional state of the secreting cell. For instance, synovial fibroblasts or mesenchymal stem cells release exosomes containing IL-1β. In contrast, chondrocyte derived exosomes or microvesicles do not contain IL-1β, but other cytokines such as IL-6 and IL-8 [42,43] [44]. In addition to vesicular secretion, monocytes and macrophages can undergo caspase 1-induced pyroptotic cell death [45] and release mature IL-1 across hyper-permeable plasma membranes.

6. IL-1 receptors

The identification and first biochemical characterization of an IL-1 receptor was achieved in 1985. The biochemical characterization of this first receptor revealed a membrane protein with a molecular weight of around 80 kDa. IL-1Rs were found to be expressed in many different cell types including chondrocytes [46]. Today, the family of interleukin-1 receptors consists of at least 11 receptors including a variety of modifications and subtypes [47]. Also for the receptors, a simplified nomenclature has been proposed [7,48]. Both, IL-1α and IL-1β bind to the same receptor, named type I IL-1 receptor I (IL-1RI). A binding of other members of the IL-1 superfamily (IL-18, IL-33, IL-36, IL-37, and IL-38) has been demonstrated for IL-1R4, IL-1R5, IL-1R6, and IL-1R9. Ligands for the remaining receptors are still unknown. Structurally, the IL-1 receptors are type 1 transmembrane proteins with similar architecture. The extracellular part of the receptor where the ligand binding takes place consists of three immunoglobuline-like domains followed by a

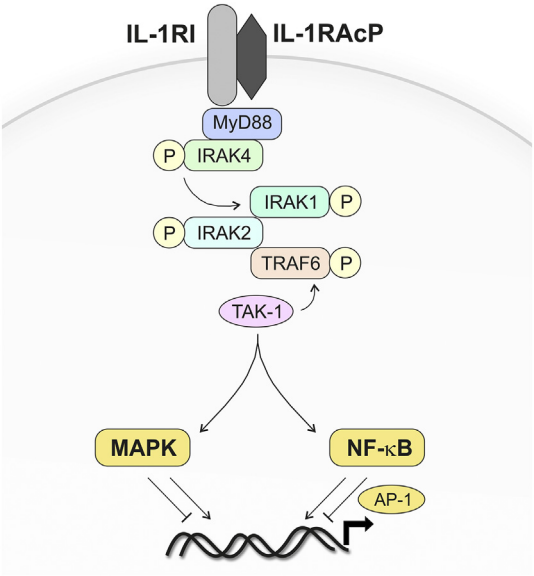

Fig. 1. Schematic representation of IL-1β-induced intracellular signal transduction with focus on downstream adaptor and associated proteins mediating signaling after IL-1β binding to the receptor IL-1RI. Detailed description of single signaling events is given in the text. Abbreviations: IL-1RI – interleukin-1 receptor type I, IL-1RAcP - interleukin-1 receptor accessory protein, MyD88 - myeloid differentiation primary response 88 protein, IRAK - interleukin-1 receptor-associated kinase, P – phosphorylation, TRAF - TNF receptor associated factor, TAK - TGF-β-activated kinase.

transmembrane domain and an intracellular part. This cytosolic region is called Toll- and IL-1R-like (TIR) domain and is crucial for the initiation of signal transduction. TIR domains are conserved among TLRs and IL-1Rs and contain 150–200 amino acids with a central five-stranded parallel β-sheet surrounded by five α-helices on both sides [49]. As already mentioned above, the IL-1 receptor antagonist (IL-1Ra) is a third ligand of this receptor that competes with IL-1α or IL-1β for binding sites at the receptor and inhibits their signaling. In addition to IL-1R1, some cell types, but not chondrocytes, express a second receptor IL-1RII. IL-1RII is a decoy receptor and binds IL-1 with high affinity. Since IL-1RII has no TIR domain, it does not signal and thus negatively regulates IL-1 activity [7]. All ligands bind first to the first extracellular domain of IL-1RI that recruits the IL-1 receptor accessory protein (IL-1RAcP) (Fig. 1). This protein serves as a co-receptor and is necessary and essential for interleukin signal transduction. IL-1RAcP is also needed for activation of IL-1RI by other IL-1 superfamily members, like e.g. IL-36Ra and IL-38. After the formation of a heterodimeric receptor complex, two intracellular adaptor proteins are recruited to the intracellular TIR domains: the myeloid differentiation primary response gene 88 (MYD88) and IL-1 receptor-activated protein kinase (IRAK) 4. Phosphorylation of IRAK4 is followed by phosphorylation of IRAK1, IRAK2 and the ubiquitin E3 ligase tumor necrosis factor receptor-associated factor (TRAF) 6. TRAF6 adds polyubiquitin chains to some IL-1 signaling intermediates, e.g. the TGF-β-activated protein kinase (TAK-1). That facilitates the association of TAK-1 with TRAF6 [47]. Activation of different mitogen-activated protein kinase (MAPK) pathways (ERK, c-Jun N-terminal kinase (JNK) and p38 MAPK) leads eventually to activation of transcription factors, such as NF-κB and AP-1 and thus to changes in gene expression and RNA stability (Fig. 1). The activation of these signaling pathways in different cell types relevant in OA is discussed below in greater detail.

7. microRNAs (miRNAs) and IL-1 receptor signaling

The impact of miRNAs on both TLR and IL-1 receptor signaling has been reviewed recently showing that distinct miRNAs can either activate or are regulated by these signaling pathways [50]. Over the last years, a large number of microRNAs were described that modulate IL-1β induced extracellular cartilage matrix degradation and thus might play an important role in the initiation and progression of OA [51]. Interestingly, recent studies have shown that activation and induction of the TLR/IL-1 signaling pathway can in turn regulate regulate the expression of several miRNAs. Some of them are able to regulate TLR/IL-1 signaling suggesting that these miRNAs might be involved in either positive or negative feedback mechanisms. Therefore, miRNAs were also referred to as the fine tuners of TLR signaling [52]. Recently, a signature of differentially expressed circulating microRNAs in OA patients was identified [53]. Interestingly, some of the miRNAs with aberrant expression levels in OA (miR-9, miR-27, miR-34a, miR-140, miR-146a, miR-558 and miR-602) have been shown to regulate expression of inflammatory pathways such as interleukin-mediated or matrix metalloproteinase-13 (MMP-13)-mediated degradation of the articular cartilage extracellular matrix [54].

8. IL-1β signaling pathways in different cell types involved in OA pathology

As mentioned above, all tissues in the joint potentially contribute to the initiation and progression of OA [55]. In the following part of this review, we summarize the cellular sources of IL-β1 and the effects of activated IL-1β signaling pathways in the different cell types present in a synovial joint.

9. Chondrocytes

Both healthy and OA articular chondrocytes express the type 1 receptor IL-1RI. However, in isolated human OA chondrocytes in vitro increased levels of IL-1RI were detected [56,57] suggesting that increased IL-1β concentrations during inflammatory processes induce IL-1RI expression. IL-1RI was mainly expressed at the cell membrane, but also nuclear staining was observed in human OA chondrocyte cultures [56]. Also interleukin-1 receptor accessory protein (IL-1RAcP) and further adaptor proteins like MyD88, IRAK1 and TRAF6, forming a complex with IL-1RI and initiating IL-1β-induced signaling have been detected in OA chondrocytes [58]. Potentiated IL-1β action does not only depend on increased IL-1β concentration and increased IL-1RI expression in OA chondrocytes, but also on the deficient expression of naturally occurring IL-1β inhibitors like the IL-1R antagonist or the soluble or membrane-associated IL-1RII [56,59]. In addition, chondrocytes express caspase-1, the IL-1β-converting enzyme that cleaves inactive pro IL-1β into its activated form [60]. In OA cartilage, increased caspase-1-positive chondrocytes and accordingly increased IL-1β-positive populations were detected, mainly in the superficial layer of articular cartilage [61,62]. Further studies confirmed that OA chondrocytes are able to secrete IL-1β by themselves in single-digit pg/ml range concentrations [36,63] and that IL-1β is able to upregulate itself in OA chondrocytes via a positive feedback mechanism [64]. Finally, one has to consider that most studies investigating IL-1β-mediated effects in chondrocytes were performed in expanded monolayer cultures and that under these in vitro conditions chondrocytes rapidly dedifferentiate. During in vitro dedifferentiation, polygonal chondrocytes show a characteristic shift towards a fibroblast-like shape and start to synthesize type I collagen instead of the most important hyaline cartilage-specific matrix components type II collagen and aggrecan [65]. Besides losing the chondrocytic phenotype also the upregulation of inflammatory mediators such as IL-1β takes place during dedifferentiation process [66].

The effect of IL-1β on chondrocytes can be generally described as catabolic and involves the upregulation of aggrecanases and matrix metalloproteinases (MMPs) [67], the induction of further inflammatory mediators as well as the downregulation of chondrogenic extracellular matrix synthesis. A decreased production of proteoglycans and

collagens promotes not only hypertrophic differentiation but also de-differentiation in the upper layers of cartilage as well as pro-apoptotic effects [68,69]. These molecular processes result in various pathological phenomena. Chondrocyte apoptosis plays an important role in OA manifestation, although it is not clear whether loss of chondrocytes is a result or an inducer of cartilage ECM degradation [70]. Increased expression and activity of aggrecanases and MMPs leads to massive hyaline cartilage matrix degradation and accordingly to loss of function characterized by lacking lubrication and insufficient transmission of mechanical loading in the joint. A similar malfunction is the result of downregulated biosynthesis of hyaline-cartilage specific proteoglycans and collagens. In addition, besides increased expression and activity of ECM-degrading enzymes also the down-regulation of their inhibitors play a role in perpetuating cartilage destruction. For instance, tissue inhibitor of matrix metalloproteinases 1 (TIMP1) is clearly decreased in OA [71]. Moreover, loss of the stable hyaline chondrocyte phenotype due to de-differentiation or hypertrophic terminal differentiation represents one important phenomenon during OA manifestation. These two completely different processes might appear concomitantly in different cartilage areas [69]. Chondrocyte de-differentiation is characterized by a fibroblastic-like phenotype with high type I production instead of high type II collagen synthetic activity, resulting in a soft and unstable fibrocartilage tissue [44]. In contrast, hypertrophic chondrocytes mainly produce type X collagen and were thought to undergo apoptosis after terminal differentiation. However, recent studies demonstrated that hypertrophic chondrocytes are able to trans-differentiate into osteoblast-like cells and due to increased VEGF and RUNX2 expression in OA articular cartilage becomes vascularized and finally mineralized. This results in thickened tidemark and osteophyte formation [72,73]. The induction of further inflammatory mediators including IL-6, TNF, LIF, PGE2, NO, COX2 or iNOS by IL-1β induces in chondrocytes most of the catabolic processes described above and contributes in addition to synovial inflammation perpetuating cartilage tissue degradation by activating synovial fibroblasts and immune cells.

The signaling pathways behind these chondrodestructive processes are multifaceted: IL-1β is capable of activating all three MAPK pathways (ERK, p38, JNK) as well as the NF-κB signal cascade [74] and inducing further factors such as NO, PGE2 and others, which in turn mediate the crosstalk between IL-1β and WNT, Notch1 or even TLR signaling [75–77]. Most of these intracellular signaling pathways target C/EBPβ in the nucleus, which in turn regulates diverse promotor activities for example promotors of MMP-3 and MMP-13. In addition, C/EBPβ activation inhibits type II collagen gene expression and induces hypertrophic differentiation process characterized by increased type X collagen biosynthesis as already mentioned above [78].

In the following section, we focus on what we believe are the best studied pathways in chondroctyes (Fig. 2) without stating that these are the most important ones. It is almost impossible to keep track of the large body of literature dealing with additional or seemingly minor signaling pathways in all cell types of the synovial joint. This review does also not imply any claim to completeness.

9.1. MAPK signaling pathways

9.1.1. ERK1/2-mediated effects

Once bound to IL-1RI at the chondrocyte cell membrane, IL-1β can activate different MAPK pathways simultaneously. In chondrocyte cultures, ERK activation by IL-1β leads on the one hand to the down-regulation of type II collagen and aggrecan gene expression [74,79–81]. On the other hand, IL-1β induces numerous extracellular matrix degrading enzymes via ERK, such as the collagenases and aggrecanases MMP-1 MMP-3, MMP-13 [74,79,82], as well as ADAMTS-4 [83]. Besides manipulating matrix synthesis and degradation, IL-1β also upregulates itself via ERK and induces the release of IL-6 and LIF [84], which not only exhibit similar effects on chondrocytes like IL-1β but also aggravate IL-1β effects [85]. IL-1β drives the production of the inflammatory and chemoattractive molecules PGE2 and NO by COX-2 and iNOS. These molecules are capable of inhibiting chondrogenic extracellular matrix synthesis and inducing apoptosis [86], interestingly also mediated by ERK [87,88], among other signaling pathways. In addition, chondrocyte proliferation has been shown to be inhibited by IL-1β-driven ERK signaling as well as apoptosis induction by cleavage of caspase-3 [89,90].

Again, it needs to be mentioned that chondrocytes grown in monolayer culture often respond differently to distinct extracellular stimuli than chondrocytes in three-dimensional cultures. IL-1β treatment of three-dimensional cultures resulted in lower but longer-lasting ERK activation suggesting that the surrounding extracellular matrix modulates the response of chondrocytes to IL-1β [91].

9.1.2. p38-mediated effects

Impaired synthesis of cartilage-specific extracellular matrix can also be mediated by signaling via p38 MAPK as shown for the down-regulation of aggrecan synthesis in chondrocytes after IL-1β treatment [80]. Similarly, IL-1β inhibited COL2A1 mRNA expression via p38, an effect that could be partially reversed using the p38-specific inhibitor SB203580 [92]. Interestingly, IL-1β can also exhibit anabolic effects by activating p38 similar to TGF-β via TAK1, namely the stimulation of BMP-2, which was shown to induce de novo synthesis of type II collagen [85,93]. However, the p38-mediated, dominating effects of IL-1β are still catabolic, reflected in enhanced MMP-1 and MMP-13 release after c-Fos and subsequent AP-1 activation in chondrocytes [74,81,85,94] or, similar to ERK signaling, in upregulated ADAMTS-4 gene expression [83]. In addition, p38 induction after IL-1β binding activates the RUNX2 pathway in chondrocytes being responsible for hypertrophic differentiation and upregulation of various catabolic enzymes [95,96]. Despite ERK signaling pathways are the major inducers of IL-1β-dependent upregulation of IL-6 or LIF, also p38 has been shown to be involved in the induction of other pro-inflammatory cytokines [84]. Furthermore, IL-1β-induced COX-2 expression and PGE2 increase can take place also via p38 in chondrocytes resulting in MMP-2 upregulation [97]. Further, IL-1β-induced signaling via p38 can influence chondrocyte metabolism by enhancing glucose transport due to upregulation of GLUT1 and GLUT6 expression. However, the contribution of this phenomenon to OA pathogenesis and progression has still remained unanswered until now [98,99]. Not less importantly, p38-dependent IL-1β signaling also plays a role in increased apoptosis of chondrocytes [100,101], which can occur directly or via PDK1-mediated activation of the p38 pathway [102].

9.1.3. JNK-mediated effects

In principle, the JNK pathway mediates similar effects on chondrocytes like the ERK and p38 pathway, but without a doubt the latter two exhibit more dominant effects after IL-1β stimulation. For instance, type II collagen expression is inhibited in chondrocytes due to Sox-9 suppression via JNK signaling [103] and also ADAMTS-4 expression increases after IL-1β-mediated activation of the JNK pathway [83]. However, unlike ERK and p38, JNK-2 pathway induction results in an upregulation of the aggrecanase ADAMTS-5 [104,105]. In addition JNK activation contributes to IL-1β-induced IL-6 secretion by chondrocytes potentiating the IL-6-inducing effects mediated by ERK and p38 [80]. Furthermore, also JNK induction results in enhanced MMP-1 and MMP-13 synthesis, which indeed has been shown to be inhibited via EP4 by PGE-2 induced by the other two MAPK or NF-κB pathways [106]. In addition, JNK signaling is also capable to upregulate MMP-1 and MMP-13 via induction of VEGF production [107] and the JNK phosphorylation state is involved in the regulation of chondrocyte apoptosis during OA pathogenesis [108,109].

9.2. NF-κB-mediated effects

One major difference between IL-1β-induced MAPK and NF-κB

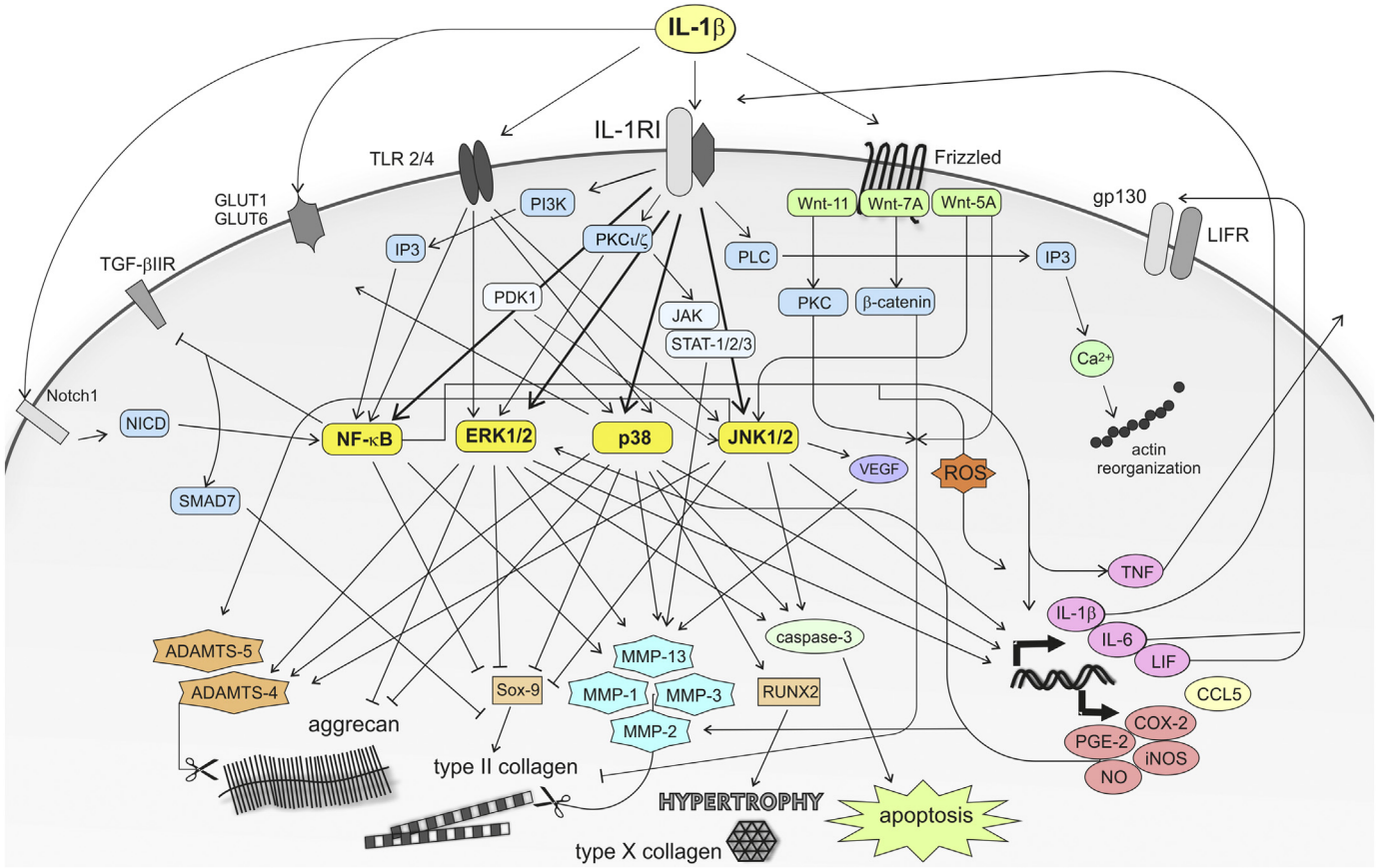

Fig. 2. IL-1β-induced intracellular signaling pathways in articular chondrocytes and their effect on metabolism, extracellular matrix components, and inflammatory mediators. Exact mechanisms and abbreviations are described in the section "Chondrocytes".

signaling is the fact that NF-κB has not yet been linked to the degradation of aggrecan [104]. However, inhibition of type II collagen expression can also be mediated via NF-κB signaling either by down-regulating Sox9 [110] or by inhibition of TGF-βII receptor by increasing the expression of SMAD7 [111]. In addition, like MAPK pathways, IL-1β-driven NF-κB induction increases the expression and release of MMP1 and MMP13 [74,81,112] and induces other cytokines like IL-6 via AP-1 in a PI3K-dependent manner [112] as well as the production of the inflammatory mediators NO and PGE2 via PI3K/AKT signaling [113]. Interestingly, NF-κB signaling is the only pathway until now that has been shown to induce TNF release in chondrocytes [77]. In addition, IL-1β increases reactive oxygen species (ROS) production, which in turn also upregulates the pro-inflammatory factors COX-2, iNOS, PGE2, and NO via NF-κB [114].

9.3. PKC-(JAK-STAT, ERK)-mediated effects

One of the most dominant effects of IL-1β on chondrocytes is the induction of MMPs. Growing evidence suggests that PKC, especially PKCζ or PKCι contribute to IL-1β-induced upregulation of the major collagenases in OA, namely MMP-1 and MMP-13, by activation of JAK-STAT1/2/3 or ERK signaling pathways, which then leads to AP1-mediated activation of the MMP promotors [94,115].

9.4. Wnt-mediated signaling

During the past years it became more and more apparent that Wnt proteins, especially Wnt-5A, Wnt-7A, and Wnt-11, play an important role in anabolic and catabolic processes in chondrocytes and thereby influence OA pathogenesis [116]. It has been recently described that IL-1β induces iNOS in chondrocytes, which then activates Wnt signaling via NO resulting in enhanced MMP expression [75]. In following studies IL-1β has been shown to upregulate Wnt-5A, which in turn induced MMP-1, MMP-3, MMP-9, and MMP-13 gene expression and inhibited type II collagen expression via JNK pathway activation [117]. Wnt-7A protein was also upregulated by IL-1β and inhibited type II collagen but via β-catenin signaling [118]. Interestingly, Wnt-11 exhibits an opposing effect after IL-1β stimulation and induces type II collagen expression by PKC pathway activation [118].

9.5. Notch1-mediated effects

Recent work showed that IL-1β increases the expression of Notch1 and NICD in chondrocytes with subsequent induction of MMPs and inflammatory mediators such as iNOS, IL-6 or TNFα as well as inhibition of TIMP-1 by activating the NF-κB pathway [77].

9.6. Crosstalk with TLR-signaling

It is also well known that the activation of toll-like receptors (TLR), especially TLR-2/4, increases the shift from an anabolic to a catabolic program in chondrocytes [76]. IL-1β has been shown to induce the expression of TLR 2/4, which then activates ERK/p38/JNK as well as NF-κB signaling pathways in chondrocytes leading to the effects described above [76] and to the secretion of further cytokines such as TNFα, IL-6, IL-8, and the chemokine ligand CCL5 [119].

9.7. PLC/IP3/Calcium-signaling

In response to IL-1β, also PLC can be activated in chondrocytes resulting in IP3- and Rho-GTPase-mediated increase of the intracellular Ca^{2+} concentration leading to F-actin reorganization in the cell. This

process has been described to be one of the very first signaling events in chondrocytes after IL-1β stimulation [120]. However, also here, the relation to OA remains to be determined.

10. Osteoblasts, osteocytes and osteoclasts

Subchondral osteoblasts are involved in pathological processes contributing to subchondral bone remodeling [121]. Osteoblasts express IL-1RI [122,123] and have been shown to produce elevated levels of IL-1 in an osteoarthritic joint [119]. When acute inflammation occurs, for example during fracture healing, increased IL-1β mediates anabolic effects in the bone [124]. For instance, IL-1β stimulates osteoblasts to produce more estrogen by converting androgen leading to a higher proliferation rate [125]. Furthermore, IL-1β induces COX-2 [126], NO [127,128], and PGE-2 [129,130] expression, which, in contrast to effects observed in chondrocytes, mediate anabolic effects leading to bone formation [131,132]. This could be one reason for the development of osteophytes in an OA joint, but the exact signaling pathways behind these effects have not been elucidated until now.

However, at least some forms of OA represent a chronic inflammatory situation in the joint with long-term IL-1β release, which also leads to catabolic activity reflected by upregulation of extracellular matrix degrading enzymes and other catabolic inflammatory mediators like IL-6 [133]. In osteoblast cultures, IL-1β increases the expression of MMP-2, MMP-3, MMP-9, MMP-13, ADAMTS-4, ADAMTS-5, and RANKL all playing a role not only in bone matrix degradation but also in cartilage catabolism in early OA [73,134–136]. Most of these matrix degrading enzymes seem to be induced primarily by ERK phosphorylation [137]. Interestingly, MMP-13 has not only a catabolic role, but has been shown to upregulate osteoblast proliferation after induction of Wnt16 signaling by IL-1β [138]. On the other hand, IL-1β is also capable to reduce osteoblast proliferation via decrease of the ζ isoform of PKC [139]. An indirect way of mediating catabolic effects in osteocytes is the IL-1β-dependent upregulation of FGF-2 and RANKL, downregulation of osteoprotegerin and subsequent induction of osteoclastogenesis [140–142]. Furthermore, in the late stage of OA, the IL-1β-induced matrix degrading enzymes and inflammatory mediators increase bone volume leading to subchondral bone sclerosis characterized by thickening of subchondral bone plate and altered subchondral trabecular structure [73].

Besides osteoblasts, osteoclasts are key players during subchondral bone remodeling in OA [121]. Since IL-1R is expressed on the osteoclast membrane [143], IL-1β can exert various effects. One of these effects is the inhibition of osteoclast apoptosis via activation of the NF-κB pathway [144]. In addition, IL-1β stimulates osteoclastogenesis either via enhancing RANKL expression by stromal cells [145,146] or by activating the gp130-STAT3 pathway, which is preferentially activated by IL-6 [147–149]. In isolated murine chondrocytes, osteoclast-conditioned media attenuated MMP-2 and MMP-9 activity, which was reversed by IL-1β via MAPK signaling [150]. Furthermore, in human osteophyte tissue isolated from hip and knee joints frfigom OA patients, osteoclasts releasing BMP-3 and -6 were detected at the bone remodeling sites suggesting that besides osteoblasts and osteocytes also osteoclast contribute to osteophyte formation [151]. However, the underlying signaling mechanisms are not completely understood.

11. Synovial fibroblasts

Since OA is a disease of the whole joint, synovial cells and first of all synovial fibroblasts, play a role in IL-1β-mediated processes of pathogenesis and perpetuation. Synovial fibroblasts express both IL-1RI and IL-1RII, but type I is the dominant receptor [152]. IL-1β is not a characteristic cytokine being produced by osteoarthritic synovial fibroblasts in contrast to IL-6 [153] that is increased upon stimulation with TNFα [154]. However, IL-1β is detectable in the synovial tissue and the concentration is dependent on OA grade [155], indicating that other cell types, namely monocytes and macrophages of the synovium, are responsible for IL-1β release [156].

IL-1β activates NF-κB does-dependently in synovial fibroblasts resulting in PGE2 induction, which in increases the proliferative response to IL-1β in human fibroblasts. This proliferative response is not as strong as in rheumatoid arthritis, where fibroblasts build a massively thickened synovial tissue the so-called pannus. However, also OA synovial fibroblasts form a similar thickened tissue in response to IL-1β in 70–80% of the OA cases [157]. This newly-formed tissue has been described as pannus-like fibrous tissue containing highly-proliferative fibroblasts, stem cells, macrophages, and other immune cells as described below more in detail [157,158].

The effects of IL-1β on the synovial fibroblast secretome are similar to those in chondrocytes and osteoblasts, mainly catabolic reflected by strong induction of MMP-2, MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, ADAMTS-7, and ADAMTS-12 via activation of RUNX-2 and Wnt/β-catenin as well as MAPK and NF-κB pathways [159–162]. Furthermore, IL-1β is responsible for the immunologic activation of synovial fibroblast leading to the expression and release of further pro-inflammatory cytokines such as IL-6, IL-8 as well as VEGF partly by NF-κB signaling pathways [163]. In addition, synovial fibroblasts have been also shown to be involved in pain perception in OA by producing elevated concentrations of NGF after IL-1β stimulation [164,165].

12. Stem cells

During the past years multipotent cells were detected in various tissues of the healthy as well as of the osteoarthritic joint including cartilage, subchondral bone and bone marrow, synovium and adipose tissue as well as synovial fluid. These progenitor cells have been shown to respond to injury and migrate to damaged cartilage areas and differentiate towards chondrocytes. However, their contribution to cartilage repair is limited and the quality of newly generated tissue is insufficient [166]. One reason for this limited regeneration capacity might be the presence of increased levels of IL-1β in the OA joint [167]. The expression of IL-1RI in stem cell cultures has been confirmed [122]. Although IL-1β-induced NGF in the joint was able to attract stem cells [168], their chondrogenic differentiation capacity was markedly inhibited by IL-1β reflected by decreased type II collagen and aggrecan expression as well as increased type X collagen synthesis [169,170]. However, in co-culture with chondrocytes, bone marrow derived mesenchymal stem cells were capable to antagonize IL-1β-mediated decrease of type II collagen and aggrecan synthesis and increase of MMP-13 and COX-2. Different trophic factors were able to inhibit IL-1β-induced ERK1/2, JNK, p38 MAPK and NF-κB signaling pathways [171]. A further study described that this stem cell secretome also reduces ADAMTS-5, NO, MMP-1 and MMP13 expression in synovial fibroblasts and induces IL-1Ra [172]. The intra-articular administration of mesenchymal stem cells in patients with knee osteoarthritis has been pursued with promising outcomes. However, the mechanism of action remains not well understood and it is unclear if modulation of IL-1 signaling by stem cells or stem cell derived vesicles plays a role in vivo.

13. Macrophages

Macrophages are attracted to the OA synovial tissue by cytokines and chemokines such as IL-8, PGE-2, VEGF, and IL-1β released by chondrocytes or fibroblasts. Macrophages become activated by these factors and the polarization into a pro-inflammatory M1 macrophage phenotype [173] leads to production of catabolic molecules such as IL-1β, TNFα and pro-MMPs [68,174,175] which perpetuate cartilage degeneration. Besides IL-1β and TNFα, also IL-6, IL-8, and MCP-1 production is increased in activated macrophages, mainly via NF-κB signaling pathways [174]. In the OA synovium, activated M1 macrophages represent the primary IL-1β source [156,176,177].

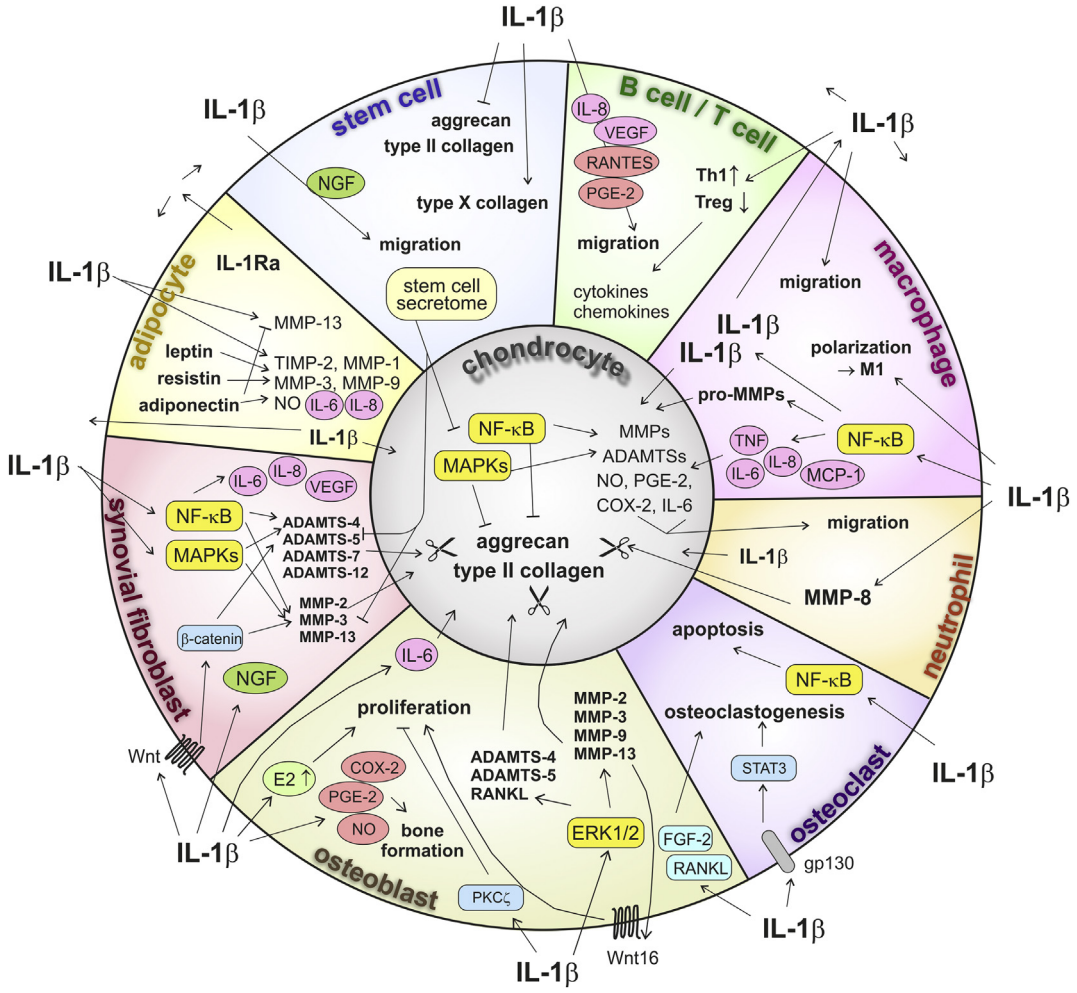

Fig. 3. The vicious circle of IL-1β-mediated cartilage degradation during OA pathogenesis and progression – involvement of different cell types and their interactions in the synovial joint. Details are described in the text.

14. Neutrophils

Although neutrophils mainly respond to bacterial infections, they have been detected in non-pathogen-induced acute inflammatory tissues such as the early inflamed synovium during OA manifestation [178]. Neutrophils are mainly attracted by COX-2 or IL-6 produced by chondrocytes, synovial fibroblasts, and macrophages induced by IL-1β [179]. Also neutrophils are capable to produce IL-1β, however, the released concentrations are low due to the low number of neutrophils in the OA synovium [172,173]. In addition, neutrophils have been shown to express the neutrophil-specific collagenase MMP-8, which is upregulated in the presence of IL-1β [180]. Neutrophils are the most abundant inflammatory cells in acute synovitis. However, the synovitis in OA has in general a more chronic character and is dominated by the presence of macrophages. Therefore, neutrophil-related IL-signaling might only play a minor role in OA.

15. Lymphocytes

There is accumulating evidence that besides macrophages, representing the major immune cell population in the OA synovium, also lymphocytes might contribute to OA pathogenesis [181], because B cells and different T cell subtypes were detected in OA synovial tissue. These lymphocytes are attracted by factors such as IL-1β, TNFα, IL-8, PGE-2 or RANTES produced by chondrocytes and synovial fibroblasts [88]. First studies indicated that B cells might play a role in the defective repair of subchondral bone in OA [182,183], however the exact mechanisms are unclear until now. Furthermore, changes in the T cell profile of the synovial tissue has been observed during OA progression, above all the increase of strong pro-inflammatory Th1 cells and the concomitant decrease of anti-inflammatory regulatory T (Treg) cells [181]. The knowledge of how different types of lymphocytes affect IL-1 signaling in OA is rather limited and further studies are needed to dissect their contribution.

16. Adipocytes

Subsynovial fat pad exhibits endocrine activity by releasing the adipokines adiponectin, leptin, and resistin, which have been shown to be involved in OA manifestation [184]. Adiponectin plays a dual role by inducing inflammatory mediators such as NO, IL-6, IL-8, MCP-1 as well as the matrix degrading enzymes MMP-1 and MMP-9 and on the other hand upregulating TIMP-2 and downregulating MMP-13 [185,186]. Overexpression of MMPs in general results in an imbalance between the activity of MMPs and TIMPs leading to accelerated cartilage damage. When MMP-specific TIMPs are also increased, the balance might be recovered [187], however, activity TIMP-2 released by adipose tissue seems to be insufficient in this regard. Leptin exhibits only destructive effects by inducing MMPs [186] just like resistin being shown to upregulate IL-6 as well as MMP-1 and MMP-3 [188]. Besides adipokines, adipocytes also secrete pro-inflammatory cytokines such as IL-1β and TNFα [184], which contribute to cartilage degradation. In addition,

adipose tissue has anti-inflammatory properties: adipocytes in the joint are the main source of IL-1Ra [189]. In summary, the contribution of adipocytes to IL-1 signaling in osteoarthritis is not well understood.

17. Therapeutic strategies targeting IL-1 signaling in OA

IL-1β is one of the major inflammatory and catabolic cytokines in the pathophysiology of OA. It has a pronounced catabolic effect on cartilage by increasing the expression and activity of key enzymes in matrix degradation. In addition, IL-1β decreases the synthesis of crucial extracellular cartilage matrix components like type II collagen and aggrecan. Therefore, it was attractive to speculate that interfering with IL-1 signaling pathways could be a successful treatment option in diseases affecting cartilage degeneration and, in particular, in OA. A variety of treatment strategies have been developed including the inhibition or modification of IL-1 action through the application of IL-1 receptor antagonist proteins, soluble IL-1 receptors, monoclonal antibodies against IL-1 or against IL-1 receptors, blocking the formation of active IL-1β and subsequent signaling. It is in the nature of things that such treatments are not cell type specific. A critical appraisal of all these treatment strategies targeting IL-1 signaling was published recently [190]. However, this review came to the conclusion that the results of treating OA with all these drugs were not entirely satisfactory, and that further research is required to achieve the desired goals of therapy. Administration of a monoclonal antibody (AMG 108) against the IL-1 receptor in patients with knee OA gave no clinical benefit [191]. Diacerein, a small-molecule IL-1 inhibitor leading to a reduction of functional IL-1 heterodimer receptor complexes, seems to lead to a significant reduction in joint space narrowing compared with placebo but the pain and functional impairment associated with OA remained unchanged [192,193]. In contrast to OA, where also the intraarticular injection of anakinra did not improve any of the OA symptoms [194], this interleukin-1 receptor antagonist had a strong protective effect on bone and cartilage degradation in rheumatoid arthritis. In a recent review and meta-analysis, the clinical efficacy and safety of this treatment was evaluated and significant improvement compared to placebo was found [195]. After acute joint injury, an intraarticular injection of anakinra significantly improved key outcomes of the Knee Injury and Osteoarthritis Outcome Score (KOOS) [196]. However, the promising effects of these early improvements after acute knee injury have to be evaluated in long-term follow up studies. Finally, treatment of patients with knee OA with an anti-IL-1 α/β dual variable domain immunoglobulin (ABT-981) in a randomized phase 1 study resulted in reduced IL-1 serum concentrations with significant suppression of tissue turnover [197]. The authors concluded that especially patients with inflammation-driven OA might benefit from this treatment.

18. Conclusion

In summary, the literature reviewed here and, a variety of additional studies that could not be mentioned due to space limitations, suggests that the chondrocyte might play a central role in OA pathogenesis and IL-1 signaling (Fig. 3). On the one hand, the chondrocyte contributes to degenerative changes as an IL-1 producing cell and on the other hand as an executioner that responds to IL-1 by both decreased anabolic and increased catabolic activity. Even though the efficacy of targeting IL-1 signaling in OA might depend on the presence and degree of inflammation, we still believe that components of IL-1 signaling pathways could represent attractive targets for the devolpment of novel drugs for OA treatment.

Acknowlegements

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG Research Unit 2407, JE 642/4-1 to ZJL and DFG Research Unit 2722 FZ) and by the European Community's Seventh Framework Programme under grant agreement no. 602300 (SYBIL) to FZ.

Disclosures

All authors state that they have no conflicts of interest.

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