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REVIEW

A review of crosstalk between MAPK and Wnt signals and its impact on cartilage regeneration

Ying Zhang · Tyler Pizzute · Ming Pei

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Abstract Chondrogenesis is a developmental process that is controlled and coordinated by many growth and differentiation factors, in addition to environmental factors that initiate or suppress cellular signaling pathways and the transcription of specific genes in a temporal-spatial manner. As key signaling molecules in regulating cell proliferation, homeostasis and development, both mitogen-activated protein kinases (MAPK) and the Wnt family participate in morphogenesis and tissue patterning, playing important roles in skeletal development, especially chondrogenesis. Recent findings suggest that both signals are also actively involved in arthritis and related diseases. Despite the implication that crosstalk between MAPK and Wnt signaling has a significant function in cancer, few studies have summarized this interaction and its regulation of chondrogenesis. In this review, we focus on MAPK and Wnt signaling, referencing their relationships in various types of cells and particularly to their influence on chondrogenesis and cartilage development. We also discuss the interactions between MAPK and Wnt signaling with respect to cartilage-related diseases such as osteoarthritis and explore potential therapeutic targets for disease treatments.

Keywords Chondrogenesis · Mitogen-activated protein kinase (MAPK) · MAPK signal · Wnt signal · Stem cell · Osteoarthritis

Introduction

Chondrogenesis is a morphogenetic event that includes proliferation, condensation and differentiation of mesenchymal cells into chondrocytes with the production of a cartilage-specific extracellular matrix (ECM) rich in type II collagen and sulfated proteoglycans (Cancedda et al. 2000). Mitogen-activated protein kinase (MAPK) is one of the conserved signal transduction systems in cartilage and plays a crucial role in chondrogenic differentiation. The MAPK cascades constituting three sequentially activated kinase complexes, which include p38 MAPK, c-Jun N-terminal kinase (JNK) and extracellular regulated kinase (ERK), are substrates for phosphorylation by MAPK kinases (MKKs; Fig. 1). The MKKs are, in turn, phosphorylated by MAPK kinase kinases (MEKKs). With regard to chondrogenesis and chondrocyte differentiation, ERK and p38 MAPK have central roles in mediating chondrocyte proliferation and related gene expression (Krens et al. 2006), whereas JNK has a minor role in chondrogenesis, as JNK phosphorylation is not affected during the process (Nakamura et al. 1999; Stanton et al. 2003). p38 MAPK is usually phosphorylated during chondrogenesis and is generally accepted as a positive regulator in chondrogenesis and chondrocyte differentiation (Oh et al. 2000; Stanton et al. 2003; Watanabe et al. 2001); however, the role of the ERK MAPK pathway (also known as the MEK-ERK kinase cascade) is still controversial. Murakami et al. (2000) reported that ERK is a positive

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Y. Zhang · T. Pizzute · M. Pei (✉)
Stem Cell and Tissue Engineering Laboratory, Department of Orthopaedics, West Virginia University, PO Box 9196, One Medical Center Drive, Morgantown WV 26506-9196, USA
e-mail: mpei@hsc.wvu.edu

T. Pizzute · M. Pei
Exercise Physiology, West Virginia University, Morgantown WV 26506, USA

Y. Zhang · M. Pei
Mechanical & Aerospace Engineering, West Virginia University, Morgantown WV 26506, USA

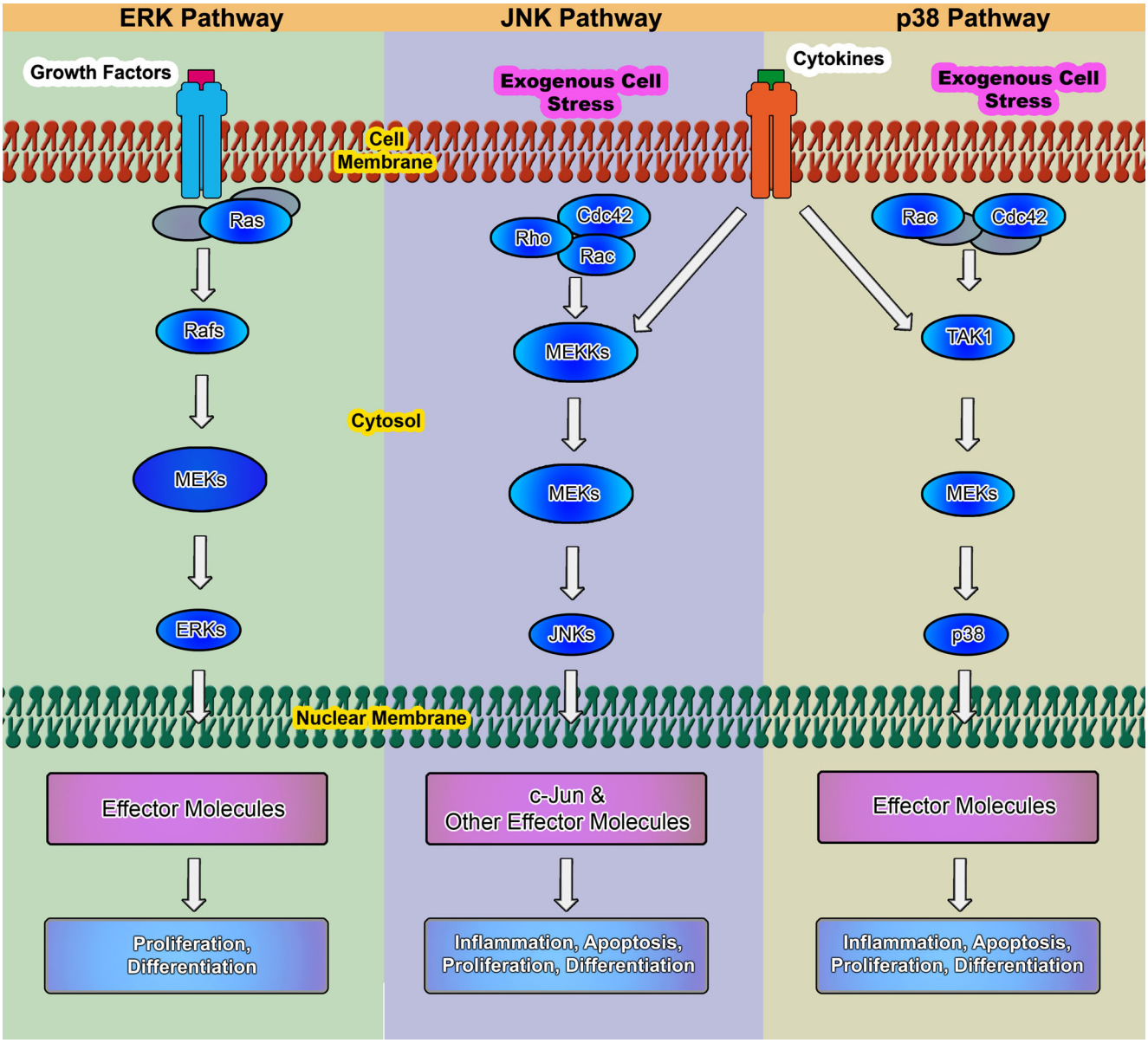

Fig. 1 The best characterized mitogen-activated protein kinase (*MAPK*) modules are the extracellular regulated kinase (*ERK*) pathway, the stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (*JNK*) pathway and the p38 MAPK pathway. The MAPK cascades consist in an MAPK kinase kinase (*MEKK*), an ERK kinase (*MEK*) and an MAPK. MEKKs are activated through a large variety of extracellular signals such as growth factors, cytokine factors and stress. The activated MEKKs can phosphorylate and activate one or several MEKs, which, in turn, phosphorylate and activate a specific MAPK. Activated MAPK phosphorylates and activates various substrates in the cytoplasm and the nucleus of the cell, including transcription factors. These downstream targets control cellular responses (e.g., apoptosis, proliferation and differentiation)

regulator in chondrogenesis, as the increase in SRY (sex-determining region Y)-box 9 (*SOX9*) levels induced by basic fibroblast growth factor (FGF2) is inhibited by a specific ERK kinase (MEK) inhibitor (U0126) in primary chondrocytes. Co-expression of a constitutively active mutant of MEK1 increases the activity of the Sox9-dependent enhancer in primary chondrocytes and C3H10T1/2 cells (Murakami et al.2000). However, the authors of some studies interpreted MEK-ERK as a negative factor for chondrogenesis. For example, ERK1/2 activities have been observed to decrease as chondrogenesis proceeds and the inhibition of ERK1/2 with PD98059 enhances chondrogenesis (Oh et al. 2000); other studies have also shown similar results (Bobick and Kulyk 2006; Chang et al. 1998).

The Wnt family of secreted glycoproteins are signaling molecules that play important roles in controlling a wide range of developmental processes, including tissue patterning, cell proliferation and cell fate, through two distinct canonical and non-canonical Wnt pathways (Fig. 2). In the canonical Wnt signaling pathway, the binding of secreted Wnts to the

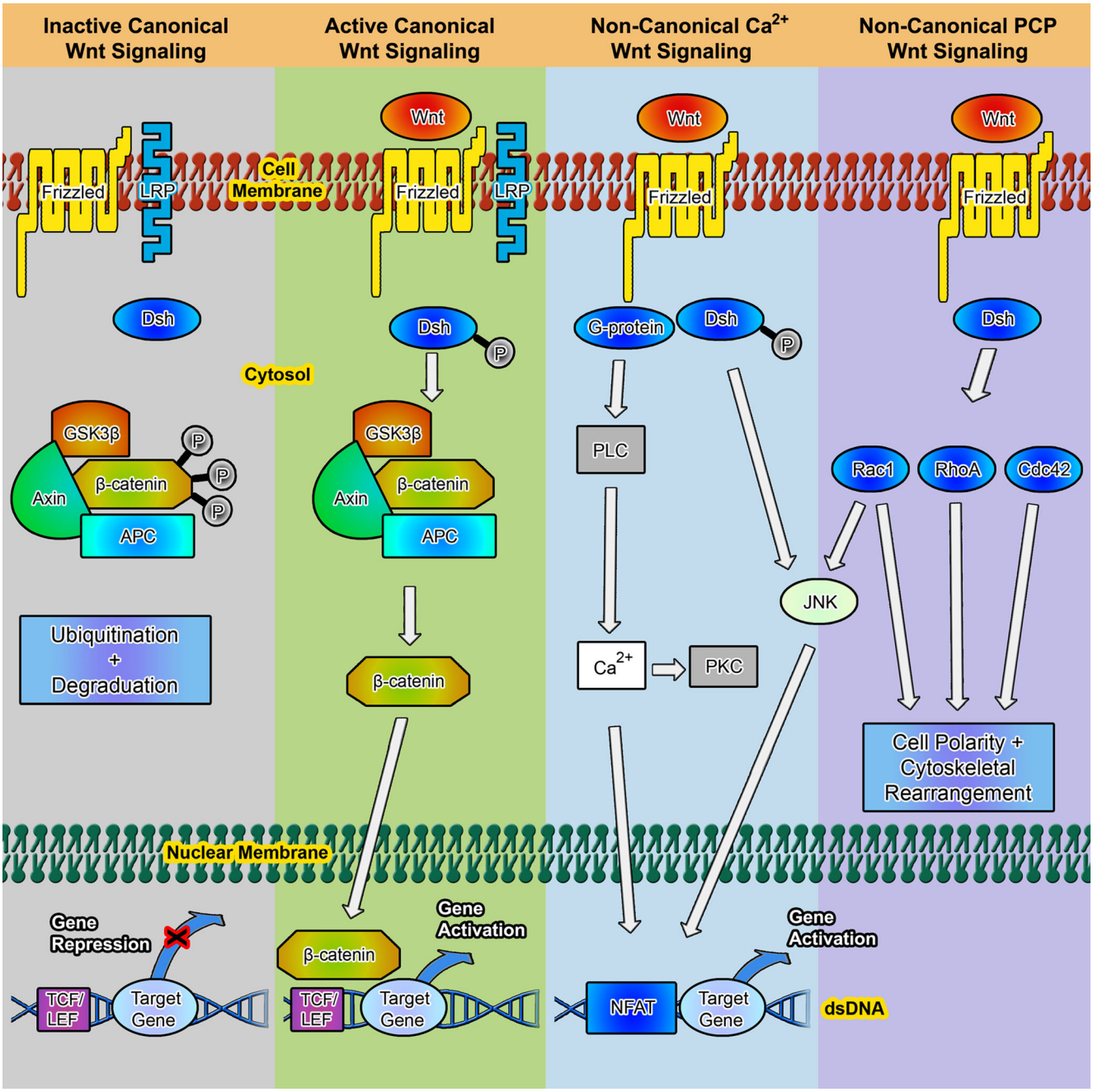

Fig. 2 Three Wnt-dependent pathways have been categorized: canonical Wnt/β-catenin and non-canonical Wnt/planar cell polarity (*PCP*) and Wnt/Ca^{2+} pathways. Canonical Wnt/β-catenin pathway: In cells, with an inactive state of canonical Wnt signaling, cytosolic β-catenin is targeted to proteolytic degradation through phosphorylation by the adenomatous polyposis coli (*APC*)–Axin–glycogen synthase kinase 3beta (*GSK3β*) complex and further ubiquitination through the action of the beta-transducin repeat containing the protein (βTrCP)-dependent E3 ubiquitin ligase complex. On stimulation by Wnt ligands, through binding to Frizzled (Fzd) receptors and its co-receptor LDL-related protein (*LRP*), Fzd recruits and phosphorates Dishevelled (*Dsh*) and inhibits APC–Axin–GSK3β complex formation by the recruitment and inhibition of GSK3β. Consequently, β-catenin can accumulate in the cytoplasm and enter the nucleus, activating the transcription of target genes through an association with the lymphoid enhancer-binding factor-1 (*LEF*)/T-cell factor (*TCF*) transcription factor family. Non-canonical Wnt/Ca^{2+} pathway: Interaction of Wnt ligands with Fzd receptors can lead to an increase in the intracellular calcium level, possibly through the activation of phospholipase C (*PLC*). Intracellular calcium will subsequently activate Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) and protein kinase C (PKC) in cells, and the transcription factor called nuclear factor of activated T cells (*NFAT*). This pathway is particularly important for convergent-extension movements during gastrulation. Additionally, Fzd receptors can also activate JNK, promoting the expression of specific genes through the activation of activator protein-1 (AP-1). Non-canonical Wnt/PCP pathway: This pathway is characterized by an asymmetric distribution of Fzd and related receptors, resulting in the polarization of the cell. Moreover, Wnt-signaling activates Cdc42, RhoA and Rac1 leading to cytoskeleton rearrangement. Rac1 can also activate JNK, activating specific gene transcription through the modulation of the AP-1 protein complex (*dsDNA* double-stranded DNA)

Frizzled family of cell-surface receptors inactivates glycogen synthase kinase 3beta (GSK3β), resulting in stabilization and nuclear translocation of β-catenin and activation of Wnt target genes. The non-canonical pathways also signal through the Frizzled receptors; the planar cell polarity (PCP) pathway activates the Rho family of GTPases and JNK and modifies cytoskeletal organization and epithelial cell polarization. The Wnt/Ca^{2+} pathway stimulates the intracellular increase of Ca^{2+} through the activation of protein kinase C (PKC) and calmodulin-dependent kinase II (CaMKII; Akiyama et al. 2004). During embryonic skeletogenesis, Wnt components act as both positive and negative regulators of key events, including chondroblast differentiation, chondrocyte maturation and joint formation (Church and Francis-West 2002).

In embryos, low levels of Wnt/β-catenin signaling stimulate chondrogenic differentiation of stem cells, whereas high levels of Wnt/β-catenin signaling inhibit that process (Hartmann 2006; Johnson and Rajamannan 2006; Westendorf et al. 2004). Wnts have also been shown to both inhibit and stimulate chondrogenic differentiation of adult progenitor cells (Day et al. 2005; Hill et al. 2005; Hu et al. 2005). Removal of β-catenin early in mesenchymal progenitor cells promotes chondrocyte differentiation, whereas ectopic expression of an activated form of β-catenin in early differentiating chondrocytes induces ectopic joint formation both morphologically and molecularly (Guo et al. 2004). In adult progenitor cells, osteoblast precursors lacking β-catenin are blocked in their differentiation and develop into chondrocytes instead. Detailed in vivo and in vitro loss- and gain-of-function analyses have revealed that β-catenin activity is necessary and sufficient to repress the differentiation of mesenchymal cells into runt-related transcription factor 2 (*RUNX2*)- and *SOX9*-positive skeletal precursors (Hill et al. 2005), suggesting that Wnt/β-catenin signaling controls osteoblast and chondrocyte formation when they differentiate from mesenchymal progenitors.

The MAPK pathway has also been reported to regulate Wnt/β-catenin signaling. Wnt/β-catenin signaling is activated by *LIT1* and *MOM4*, which separately encode a homolog of the MAPK-related Nemo-like Kinase (NLK) and a homolog of transforming growth factor beta (TGFβ)-activated kinase (TAK-1; Meneghini et al. 1999). TAK-1, which is a MEKK activated by TGFβ, by bone morphogenetic protein (BMP) and by other MAPK signaling components, plays a critical role in chondrogenesis. Deletion of *TAK1* in chondrocytes results in novel embryonic developmental cartilage defects including decreased chondrocyte proliferation, reduced proliferating chondrocyte survival, delayed onset of hypertrophy and reduced matrix metalloproteinase-13 (*MMP13*) expression (Gunnell et al. 2010). Since both MAPK and Wnt signaling pathways have crucial regulatory functions in the development of cartilage and bone formation, studies of their interactions and crosstalk are of extreme importance for the elucidation of the complex signaling networks in chondrogenesis and for the exploration of potential therapeutic targets for related diseases such as osteoarthritis (OA).

Influence of canonical Wnt signals on MAPK pathway

In totipotent mouse F9 teratocarcinoma cells, the canonical Wnt-β-catenin-JNK signaling pathway has been found to be activated by G-proteins, which can propagate the signals downstream through Dishevelled isoforms. Suppression of Dishevelled-1 or Dishevelled-3 abolished the Wnt3a activation of JNK (Bikkavilli et al. 2008a). Wnt3a treatment enhances the mRNA and protein expression of c-Jun and stimulates the phosphorylation of c-Jun and JNK. Furthermore, Wnt3a activation of activator protein-1 (AP-1) is blocked by the inhibition of JNK with SP600125 and by the inhibition of AP-1 with N-acetyl-L-cysteine and nordihydroguaiaretic acid (Hwang et al. 2005). AP-1 is also activated by ERK1/2 in C3H10T1/2 cells (Seghatoleslami et al. 2003). In NIH3T3 fibroblast cells, ERK pathway activation by Wnt signaling can occur at multiple levels, including β-catenin-independent direct signaling resulting from a Wnt3a (Wnt3a-Raf-1-MEK-ERK) and a β-catenin-/Tcf-4-dependent post gene transcription event (Yun et al. 2005). In addition to JNK and ERK, p38 MAPK is strongly activated by Wnt3a in mouse F9 teratocarcinoma cells and the activated p38 MAPK regulates canonical Wnt-β-catenin signaling through the regulation of GSK3β. Chemical inhibitors of p38 MAPK (SB203580) and the expression of a dominant-negative version of p38 MAPK attenuates the Wnt3a-induced accumulation of β-catenin, lymphoid enhancer-binding factor-1/T-cell factor (Lef/Tcf)-sensitive gene activation and primitive endoderm formation (Bikkavilli et al. 2008b). The above evidence indicates the influence of canonical Wnt signals on the MAPK pathway (Fig. 3).

The reduced expression of adhesion molecules is known to be associated with the formation and differentiation of cartilage nodules; this is supported by the finding that N-cadherin is expressed in prechondrogenic mesenchymes during cell condensation but not in differentiated chondrocytes (Oberlender and Tuan 1994; Tavella et al. 1994). One study has indicated that the inhibition of p38 MAPK results in the sustained expression of N-cadherin and eventually inhibits chondrogenic differentiation in chick limb mesenchymal micromass cultures (Oh et al. 2000). Wnt regulation of limb mesenchymal chondrogenesis is also involved in the modulation of N-cadherin. Wnt7a signaling has been shown to inhibit the chondrogenic differentiation of limb mesenchymal cells in vitro by modulating the expression of N-cadherin and the turnover of N-cadherin-dependent cell-cell adhesion complexes (Tufan and Tuan 2001). The combination of Wnt7a

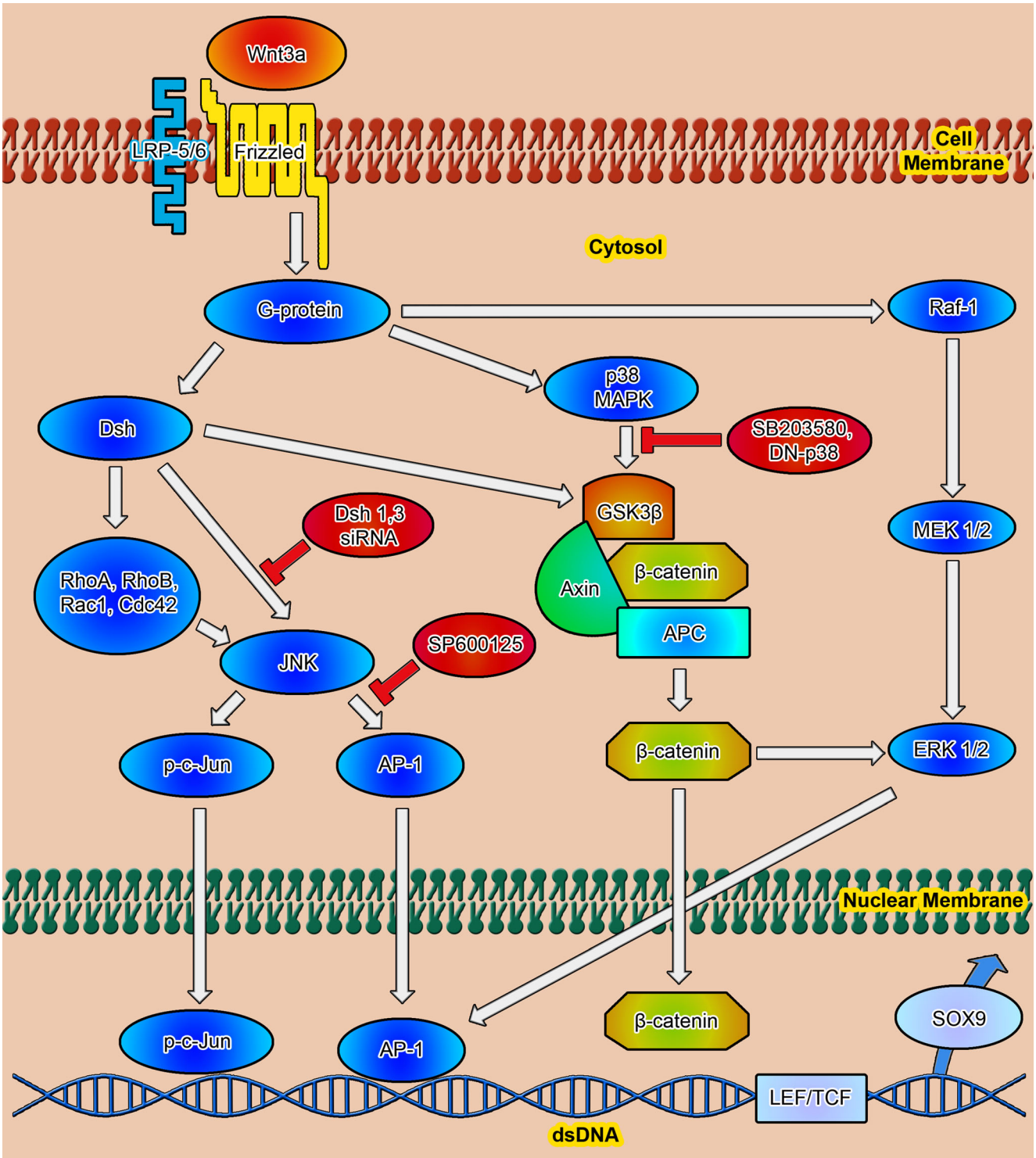

Fig. 3 Influence of canonical Wnt signals on the MAPK pathway. Wnt3a treatment activates the Raf-1-MEK-ERK cascade (Yun et al. 2005) and the JNK pathways (Bikkavilli et al. 2008a). Wnt3a activation of activator protein-1 (*AP-1*) is blocked by the inhibition of JNK with SP600125 and by the inhibition of AP-1 with N-acetyl-L-cysteine and nordihydroguaiaretic acid (Hwang et al. 2005). In C3H10T1/2 cells, AP-1 is activated by ERK1/2 (Seghatoleslami et al. 2003). In totipotent mouse F9 teratocarcinoma cells, canonical Wnt-β-catenin-JNK signaling is activated by G-proteins, which propagate the signals downstream through Dishevelled (*Dsh*) isoforms; suppression of Dsh-1 or Dsh-3 abolishes Wnt3a activation of JNK (Bikkavilli et al. 2008a). In addition to JNK and ERK, p38 MAPK is strongly activated by Wnt3a and the activated p38 MAPK regulates canonical Wnt-β-catenin signaling through the regulation of GSK3β. Chemical inhibitors of p38 MAPK (SB203580) and expression of a dominant-negative version of p38 MAPK attenuate Wnt3a-induced accumulation of β-catenin, Lef/Tcf-sensitive gene activation and primitive endoderm formation (Bikkavilli et al. 2008b)

misexpression and ERK inhibition partially recovers the Wnt7a inhibition of chondrogenic differentiation, whereas the combination of Wnt7a misexpression and p38 inhibition acts in a synergistic chondro-inhibitory fashion (Tufan et al. 2002).

Wnt3a can also induce a rapid and transient activation of p38 MAPK, which in turn regulates alkaline phosphatase activity and mineralization of nodules, directing the differentiation of mesenchymal cells into osteoprogenitors. Dickkopf1, a selective antagonist of Wnt proteins, does not influence the activation of p38 MAPK and ERK induced by Wnt3a (Caverzasio and Manen 2007), implying that non-canonical Wnt pathways participate in the regulatory process of mesenchymal cell differentiation into osteogenic cells.

Influence of non-canonical Wnt signals on MAPK pathway

As a non-canonical Wnt signal, Wnt5a specifically promotes entry into the prehypertrophic phase, whereas it conversely blocks chondrocyte hypertrophy, acting in a stage-specific context (Kawakami et al. 1999; Yang et al. 2003). This finding was confirmed by a study showing that Wnt5a misexpression delays the maturation of chondrocytes and the onset of bone collar formation (Hartmann and Tabin 2000). Wnt5a increases chondrocyte differentiation at an early stage through the CaMK/calcineurin (CaN)/nuclear factor of activated T cells (NFAT)-dependent induction of Sox9, while repressing chondrocyte hypertrophy via the IκB kinase (IKK)/nuclear factor-κB (NF-κB)-dependent inhibition of Runx2 expression (Bradley and Drissi 2010). In mouse F9 embryonal teratocarcinoma cells, strong activation of p38 MAPK has been observed in response to Wnt5a; treatment with SB203580 effectively abolishes the stimulatory effects of Wnt5a (Ma and Wang 2007). Both exogenous TGFβ3 and the overexpression of Wnt5a stimulates PKCα and p38 MAPK activation early in culture, resulting in cellular condensation and chondrogenesis. Comparatively, the inhibition of PKCα or p38 MAPK activity abolishes the promotion of chondrogenic differentiation by overexpressing Wnt5a or exogenous TGFβ3. On the other hand, the partial reduction of endogenous *WNT5A* by small interfering RNA diminishes TGFβ3-stimulated chondrogenesis through the inhibition of PKCα and p38 MAPK activity (Jin et al. 2006a). Wnt5a has also been found to promote ERK1/2 phosphorylation in endothelial cells (Masckauchán et al. 2006); the expression of Wnt5a blocks canonical Wnt signaling in endothelial cells and other cell types (Topol et al. 2003) (Fig. 4).

However, non-canonical Wnt signaling more commonly functions through the Wnt-JNK pathways (Logan and Nusse 2004). Activation of Wnt5a signaling by interleukin 1beta (IL-1β) induces the expression of MMPs via the JNK pathways in rabbit temporomandibular joint (TMJ) condylar chondrocytes, whereas blockage of JNK signaling impairs the Wnt5a-induced up-regulation of MMPs (Ge et al. 2009). The highly homologous non-canonical Wnt signals, Wnt5a and Wnt5b, have differential effects on cartilage development with regard to cell proliferation and the expression of type II collagen. Unlike Wnt5a, Wnt5b represses chondrocyte differentiation in both the initial stages of cartilage condensation and the late hypertrophic stage (Yang et al. 2003). Wnt5b activates JNK, a component of the PCP pathway, thereby contributing to an increase in cellular migration and Wnt5b-mediated decreases in cell-cell adhesion through the activation of Src and subsequent cadherin receptor turnover (Bradley and Drissi 2011; Fig. 4).

Wnt5a also plays an important role in osteoblast differentiation. The MAPK pathway is altered in Wnt5a-deficient mouse calvarial cells, suggesting that Wnt5a signaling influences the MAPK/JNK pathway (Guo et al. 2008). Other studies provide evidence for crosstalk between Wnt5a and MAPK. Ishitani et al. (2003) found that the overexpression of Wnt5a in HEK293 cells activates NLK MAPK through TAK-1; furthermore, the overexpression of Wnt5a antagonizes the canonical Wnt/β-catenin pathway (Ishitani et al. 2003). Through CaMKII-TAK1-TAB2-NLK, non-canonical Wnt signaling transcriptionally represses the transactivation of peroxisome proliferator-activated receptor gamma (*PPARG*) and induces *RUNX2* expression, promoting osteoblastogenesis in preference to adipogenesis in bone marrow mesenchymal progenitors (Takada et al. 2007). Wnt4, conventionally regarded as a non-canonical Wnt class (Wong et al. 1994), has been found potently to enhance the osteogenic differentiation of mesenchymal stem cells (MSCs) isolated from human adult craniofacial tissue in vitro and bone formation in vivo, through the activation of p38 MAPK, which is known positively to regulate the osteogenic differentiation induced by BMPs and other growth factors (Gallea et al. 2001; Guicheux et al. 2003). The inhibition of p38 MAPK abolishes the osteogenic differentiation of MSCs promoted by Wnt4.

Wnt11 belongs to the Wnt5a subclass that exerts diverse effects through the activation of the non-canonical Wnt signaling pathway (Du et al. 1995). Recently, Rye and Chun (2006) demonstrated that Wnt11 stimulates the accumulation of type II collagen in articular chondrocytes. In three-dimensional alginate gels, *WNT11* expression peaks at the late stage of chondrogenic differentiation of human MSCs (Xu et al. 2008). In *Xenopus laevis* and mouse P19 cells, signaling cascades activated by Wnt11 are crucial for the initiation of cardiogenesis; furthermore, Wnt11 not only inhibits β-catenin signaling but also activates JNK, suggesting crosstalk between Wnt11 and MAPK signals (Pandur et al. 2002). In human hepatocellular carcinoma (HCC) cell lines, the overexpression of

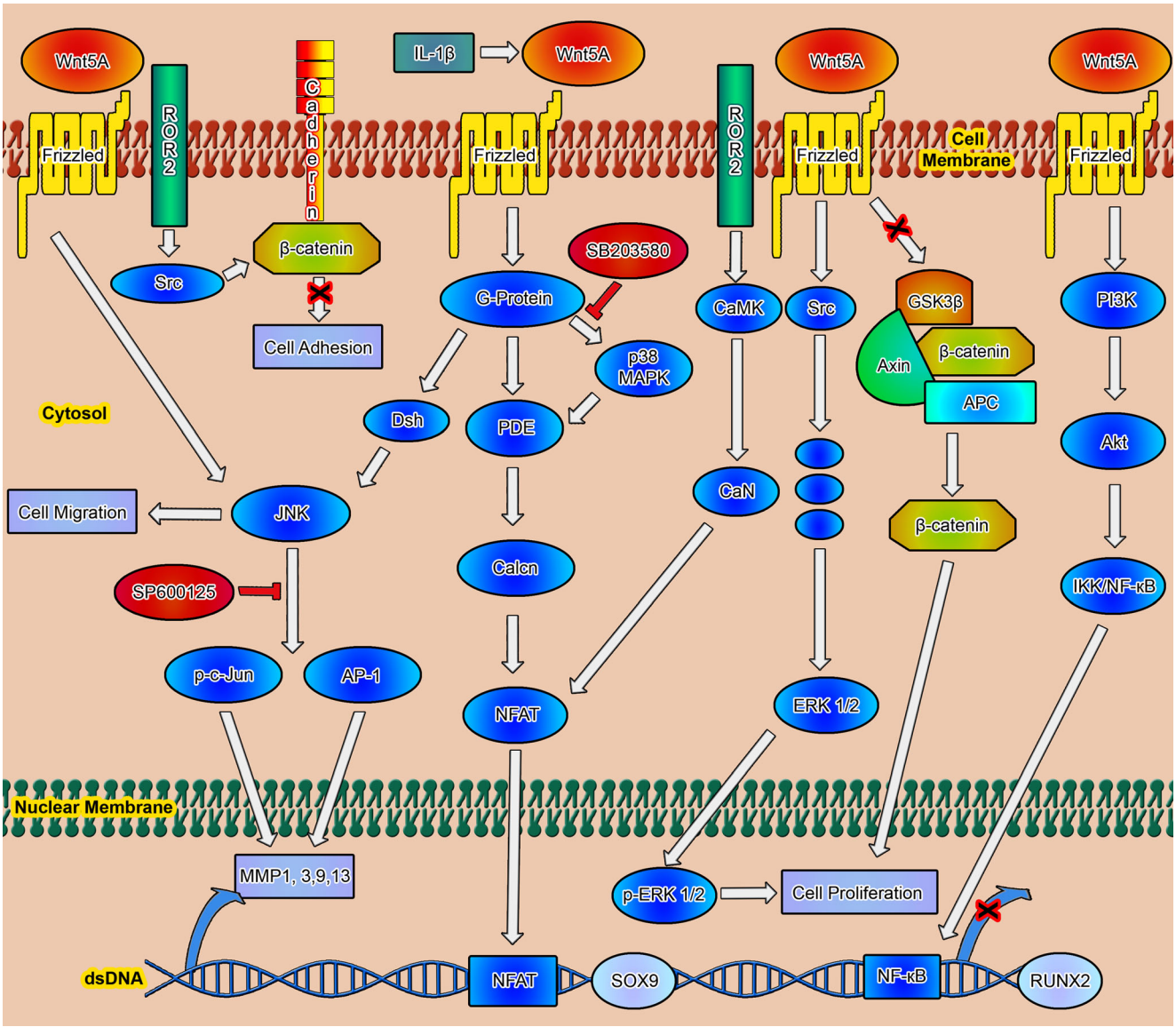

Fig. 4 Influence of non-canonical Wnt signals on the MAPK pathway. In mouse F9 teratocarcinoma embryonal cells, p38 MAPK is strongly activated in response to Wnt5a, and treatment with SB203580 effectively abolishes the stimulatory effects of Wnt5a (Ma and Wang 2007). Wnt5a also promotes ERK1/2 phosphorylation, enhancing endothelial cell survival and proliferation (Masckauchán et al. 2006) and the expression of Wnt5a blocks canonical Wnt signaling in endothelial cells (Masckauchán et al. 2006) and other cell types (Topol et al. 2003). However, non-canonical Wnt signaling more commonly functions through the Wnt-JNK pathway. Activation of Wnt5a signaling by interleukin-1β (*IL-1β*) induces the expression of matrix metalloproteinase (*MMP*) via the JNK pathway in rabbit temporomandibular joint condylar chondrocytes, whereas blockage of JNK signaling impairs the Wnt5a-induced up-regulation of MMPs (Ge et al. 2009). Wnt5a increases chondrocyte differentiation at an early stage through the CaMK/NFAT-dependent induction of Sox9, while repressing chondrocyte hypertrophy via the nuclear factor-κB (*NF-κB*)-dependent inhibition of Runx2 expression (Bradley and Drissi 2010). Wnt5b activates JNK, a component of the PCP pathway and contributes to an increase in cellular migration but Wnt5b also decreases cell-cell adhesion through the activation of Src and subsequent cadherin receptor turnover (Bradley and Drissi 2011)

Wnt11 activates PKC signaling, which antagonizes canonical Wnt signaling through the phosphorylation of β-catenin and the reduction of T-cell factor (TCF)-mediated transcriptional activity (Toyama et al. 2010). However, few studies have been reported about the interplay between Wnt11 and MAPK signaling in the regulation of chondrogenesis.

Influence of MAPK signals on Wnt pathway

Many studies have shown that MAPKs participate in the regulation of Wnt pathway activities (Fig. 5). Expression of constitutively active MKK6, an upstream activator of p38 MAPK, in 293T cells is sufficient to increase the expression of β-catenin proteins through the direct phosphorylation of

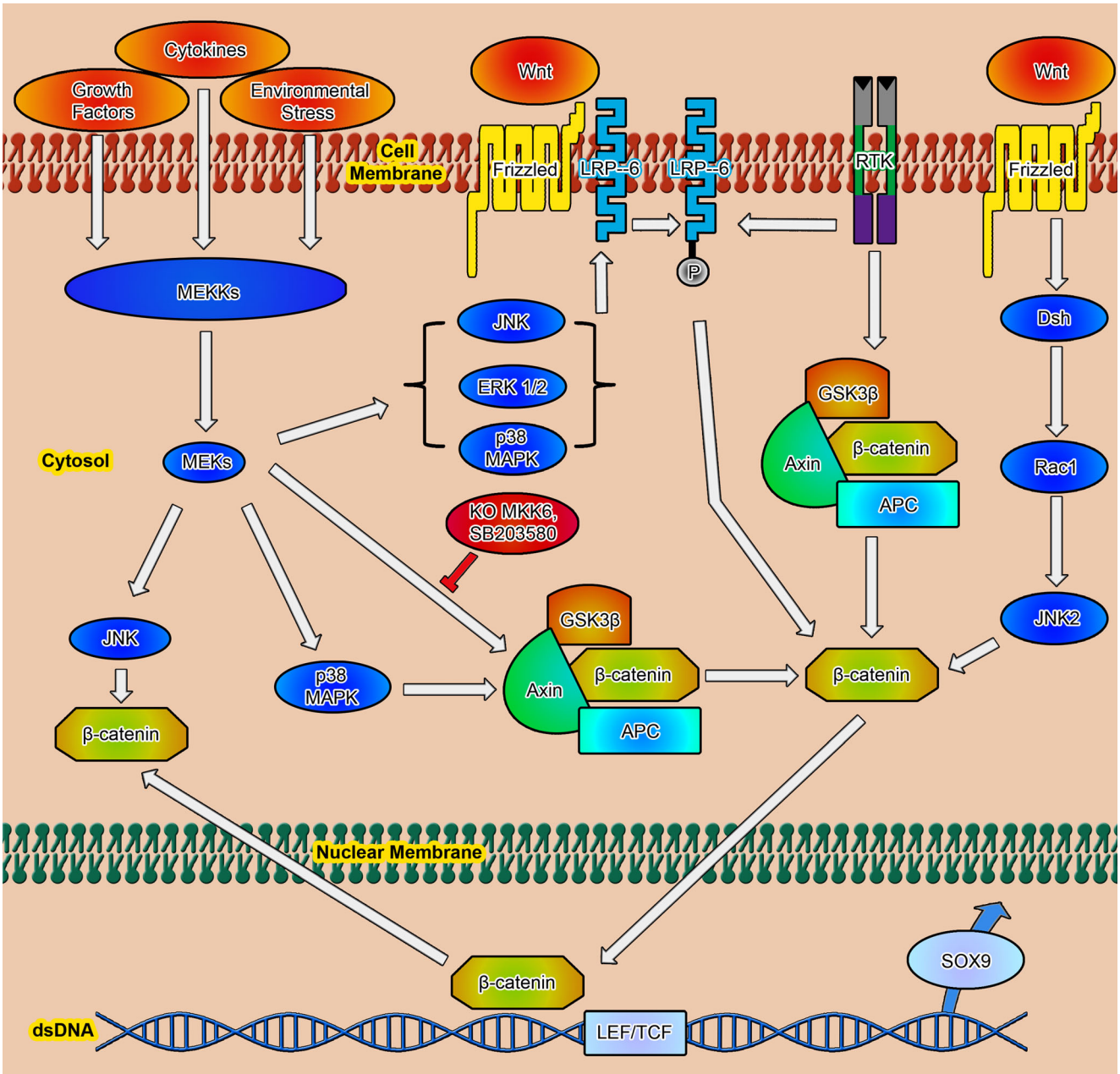

Fig. 5 Influence of MAPK signals on the Wnt pathway. Expression of constitutively active MKK6, an upstream activator of p38 MAPK, in 293 T cells increases the expression of β-catenin proteins through the direct phosphorylation of GSK3β protein, both in vitro and in vivo; this phosphorylation is blocked by SB203580 or the knock-out of MKK3 and MKK6 (Thornton et al. 2008). Members of MAPKs such as ERK1/2, p38 MAPK and JNK contribute to the phosphorylation of PPPS/TP clusters of endogenous LDL-related protein 6 (*LRP6*) phosphorylation, stimulating Wnt/β-catenin expression. Rac1, a small signaling G protein, can activate JNK2 to phosphorylate β-catenin (Wu et al. 2008). In *Xenopus* embryos, activation of JNK antagonizes the canonical Wnt pathway through activating the nuclear export of β-catenin instead of maintaining its cytoplasmic stability (Liao et al. 2006). Receptor tyrosine kinase (*RTK*) systems facilitate Wnt/β-catenin signaling by the phosphatidylinositol 3-kinase (PI3K)/AKT pathway through the inhibition of GSK3 activities (Dailey et al. 2005); RTKs can also phosphorylate β-catenin by involving ERK/LRP6 pathways to activate Wnt/β-catenin signaling (Krejci et al. 2012)

GSK3β protein, both in vitro and in vivo; this phosphorylation is blocked by SB203580 or the knock-out of MKK3 and MKK6 (Ding et al. 2005; Thornton et al. 2008). Since MAPK signals are required for the phosphorylation of PPPS/TP motifs of endogenous LDL-related protein 6 (LRP6), Wnt3a-induced phosphorylation of endogenous LRP6 is significantly attenuated by the knock-down of JNK1 and p38β. These results are further confirmed by pharmacological inhibition of p38 MAPK by SB203580 and that of JNK by SP600125 (Červenka et al. 2011). Rac1 can activate JNK2 to phosphorylate β-catenin, which is responsible for controlling limb outgrowth in mouse embryos (Wu et al. 2008). In *Xenopus*

embryos, the activation of JNK antagonizes the canonical Wnt pathway through the activation of the nuclear export of β-catenin rather than its cytoplasmic stability (Liao et al. 2006). Many receptor tyrosine kinase (RTK) systems facilitate Wnt/β-catenin signaling by the phosphatidylinositol 3-kinase (PI3K)/AKT (or alternatively protein kinase B, PKB) pathway through the inhibition of GSK3 activity (Dailey et al. 2005). Interestingly, RTKs have also been found to utilize ERK/LRP6 pathways for the direct phosphorylation of β-catenin to activate WNT/β-catenin signaling (Krejci et al. 2012).

Some critical transcriptional factor activities such as Sox9 or Runx2 are regulated by changing key signals of the Wnt pathways and eventually determine the differentiation fate of cells. BMP2, for instance, promotes chondrogenesis by activating p38 MAPK, which in turn down-regulates Wnt7a/β-catenin signaling. Inhibition of p38 MAPK by using a dominant-negative mutant leads to a sustained Wnt7a increase and decreased Sox9 expression, with the consequent inhibition of pre-cartilage condensation and chondrogenic differentiation (Jin et al. 2006b). Similarly, TGFβ-1-mediated MAPK activation, which controls *WNT7A* gene expression and Wnt-mediated signaling through the intracellular β-catenin-TCF pathway, probably regulates N-cadherin expression and subsequent N-cadherin-mediated cell-adhesion complexes during the early steps of mesenchymal progenitor cell chondrogenesis (Tuli et al. 2003).

Environmental factors such as mechanical stress and cytokines might also activate the MAPK pathway. Static compressive loading of cartilage activates the MAPK pathway, which is also known as the stress-activated protein kinase (SAPK) pathway (Fanning et al. 2003; Tibbles and Woodgett 1999). Wnt/β-catenin signaling not only is involved in the bone response to mechanical loading (Robinson et al. 2006; Sawakami et al. 2006) but is also associated with the response to mechanical damage to cartilage, which results in an increase in Wnt16 expression (Dell'accio et al. 2008). In MC3T3-E1 osteoblastic cells, the activation of the pathway by treatment with a GSK3β inhibitor results in an anabolic bone formation response, whereas the application of an inhibitor combined with mechanical loading produces a synergistic effect on the expression of Wnt/β-catenin pathway target genes (Robinson et al. 2006). These results indicate that mechanical loading activates the Wnt/β-catenin signaling pathway, at least in part, through the MAPK signaling pathway (Thornton et al. 2008).

Crosstalk of MAPK and Wnt signals in cartilage inflammation and regeneration

OA is a common disease clinically manifested by joint pain, swelling and impairment of joint function and leads to disability and the need for joint replacement. Levels of β-catenin and cyclooxygenase 2 (COX2) are increased in osteoarthritic and rheumatoid arthritic cartilage, suggesting that the accumulation of β-catenin contributes to the inflammatory responses of cartilage by inducing *COX2* expression in the chondrocytes of arthritis-affected cartilage (Kim et al. 2002). Activation of β-catenin in mature chondrocytes stimulates hypertrophy and matrix mineralization, as evidenced by the expression of *MMP13* and vascular endothelial growth factor (*VEGF*; Day et al. 2005; Tamamura et al. 2005). Overexpression of β-catenin in chondrocytes markedly increases the expression of matrix degradation enzymes such as MMP-2, MMP-3, MMP-7, MMP-9, membrane-type 3 MMP (MT3-MMP) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5; Tamamura et al. 2005). Animals and in vitro models exhibiting the knock-out of *FRZB*, which encodes a secreted Frizzled-related protein that can bind Wnt proteins, are more prone to lose proteoglycans from the articular cartilage in the knee (Lories et al. 2007). Through β-catenin stabilization and its nuclear translocation, Wnt signaling is associated with the negative regulation of early chondrogenesis and the stimulation of chondrocyte hypertrophy during development. Overexpression of Frzb1 lowers the expression of β-catenin (Enomoto-Iwamoto et al. 2002). $FRZB^{-/-}$ mice can experience induced OA formation through the up-regulation and stabilization of β-catenin in the canonical Wnt pathway. Interestingly, Frzb deficiency also results in thicker cortical bone, with increased stiffness and higher cortical appositional bone formation after loading; this seems to support the hypothesized inverse relationship between OA and osteoporosis (Dequeker et al. 2003). In addition, canonical Wnt signaling is influenced by local factors, including alterations in glycosaminoglycan sulfation, cartilage matrix content, TGFβ and vitamin D. Notably, the MMPs and ADAMTSs boosted by the experimental activation of the Wnt/β-catenin pathway are similar to those triggered by treatment with IL-1β or tumor necrosis factor alpha (TNFα) in chondrocytes (Burrage et al. 2006). However, the role of β-catenin in the homeostasis of cartilage is still controversial; as suggested by Zhu et al. (2008), the inhibition of β-catenin signaling in articular chondrocytes causes increased cell apoptosis and articular cartilage destruction in COL2A1-ICAT-transgenic mice. The Wnt/β-catenin pathway is assumed to be part of integrated signal transduction mechanisms through which chondrocytes respond to deranging and catabolic cues, activate the expression of *MMP* and *ADAMTS* genes and corresponding proteolytic activity and undermine their phenotypic status and ultimate tissue function (Yuasa et al. 2008).

Accumulating evidence supports a central regulatory role of MAPK in mediating inflammatory and matrix-degrading processes that contribute to joint tissue destruction in OA. Both OA and normal chondrocytes express p38 MAPK; however, OA chondrocytes show a much higher phosphorylated

p38 MAPK level compared with normal chondrocytes (Fan et al. 2007; Takebe et al. 2011). Activated JNK has been detected in the cytoplasm of OA chondrocytes but not in healthy controls (Clancy et al. 2001). In a dog model of surgically induced OA, p38 MAPK, JNK and ERK1/2 are all activated to a greater degree compared with those in normal tissue (Boileau et al. 2006). Among the possible MAPK therapeutic targets for OA or rheumatoid arthritis (RA), p38 MAPK is generally considered to be the most promising, as p38 MAPK isoforms have been implicated in the regulation of processes (such as the migration and accumulation of leukocytes and the production of cytokines and pro-inflammatory mediators and angiogenesis) that promote disease pathogenesis (Korb et al. 2006; Schett et al. 2000). p38 MAPK inhibitors have been proven effective in reducing clinical severity, paw swelling, inflammation, cartilage breakdown and bone erosion in a rat streptococcal cell wall arthritis model (Mbalaviele et al. 2006; Mclay et al. 2001), a collagen-induced-arthritis (CIA) model in mice (Medicherla et al. 2006) and adjuvant and CIA models in rats (Badger et al. 2000; Nishikawa et al. 2003). JNK appears to be a critical MAPK pathway for IL-1-induced collagenase gene expression in synoviocytes and joint arthritis (Han et al. 1999, 2001). The JNK inhibitor SP600125 completely blocks not only IL-1-induced accumulation of phosphorylated Jun and induction of c-Jun transcription in synoviocytes but also AP-1 binding and collagenase mRNA accumulation (Han et al. 2001). ERK is known to be involved in the regulation of IL-6, IL-12, IL-23 and TNF-α synthesis, suggesting a possible involvement of ERK in joint damage associated with pro-inflammatory cytokine production by macrophages (Feng et al. 1999; Goodridge et al. 2003). ERK inhibitors have been found to be successful in reducing inflammation in an experimental OA model in rabbits (Pelletier et al. 2003); therapeutic intervention with the goal of MEK1/2 inhibition might have interesting potential for the development of agents for the treatment of OA. Because of their important roles in transducing inflammation and joint destruction, MAPK signals are key molecular targets for therapeutic intervention in inflammatory diseases such as OA and RA. However, inhibitors targeting the ablation or reduction of MAPK activity are likely to have serious side effects (Thalhamer et al. 2008).

Recently, several non-canonical Wnt isoforms such as Wnt5a and Wnt11 were reported to be involved in the IL-1β-induced dedifferentiation of articular chondrocytes (Ryu and Chun 2006). Wnt5a is detectably expressed in OA and RA and is involved in the IL-1β-induced up-regulation of MMP-1, MMP-3, MMP-9 and MMP-13 in primary TMJ condylar chondrocyte via the JNK pathway, suggesting the role of Wnt5a in arthritic pathology and the regulation of cartilage destruction. Furthermore, the blockage of JNK signaling impairs the Wnt5a-induced up-regulation of MMPs (Ge et al. 2009). This finding indicates that crosstalk between Wnt5a and JNK contributes to the pathogenesis of OA; meanwhile, the disturbance or intervention of the interaction between these signals might provide new targets for OA treatment. Several studies have indicated that signaling pathways involving MAPKs mediate the catabolic response of chondrocytes to these inflammatory cytokines; specific inhibitors to these pathways can counteract cytokine effects on matrix protease gene expression (Geng et al. 1996; Hwang et al. 2005; Kumar et al. 2001; Liacini et al. 2002; Ryu et al. 2002).

In addition to the activation of inflammatory cytokines such as IL-1, the occurrence of OA can also take the route whereby articular chondrocytes lose their differentiated phenotype and exhibit a behavior with similarities to that of terminal differentiating chondrocytes (hypertrophy-like), as can be found in the growth plate of growing individuals (Dreier 2010; von der Mark et al. 1992). Chondrocytes in OA cartilage show an aberrant phenotype and actively produce cartilage-degrading enzymes, such as MMP-13 and aggrecanases (Moldovan et al. 1997; Shlopov et al. 2000; Song et al. 2007). The higher expression of hypertrophic chondrocyte markers, type X collagen and MMP-13 (Kirsch and von der Mark 1992; Nurminskaya and Linsenmayer 1996) in OA suggests a correlation between hypertrophy and OA. Some studies have demonstrated that Wnt signaling promotes chick chondrocyte hypertrophy through the induction of the bone and cartilage-related transcription factor Runx2. Dong et al. (2006) reported that β-catenin is able to induce *RUNX2* and *COL10A1* transcription as the molecular mechanism through which Wnt signaling regulates chondrocyte hypertrophy. Protein levels of β-catenin, which accumulates in OA chondrocytes, are extremely low in differentiated articular chondrocytes; however, low levels of β-catenin are up-regulated during phenotypic loss after a serial monolayer culture. Ectopic expression or inhibition of β-catenin degradation causes the cessation of cartilage-specific ECM molecule synthesis via the activation of β-catenin-Tcf/Lef transcriptional activity (Ryu et al. 2002). The activation of Wnt/β-catenin signaling is usually accompanied by a shift in chondrocyte cytoarchitecture. This event might result from a reduction of proteoglycan pericellular matrix or interactions between chondrocyte surface and substrate or fibrillar components such as collagen or fibronectin, which could change intracellular signaling and up-regulate cell adhesion pathways such as that of MAPK (Gemba et al. 2002). Because the loss of a differentiated phenotype of chondrocytes is associated with cartilage destruction during arthritis (Sandell and Aigner 2001), the canonical Wnt pathway-mediated cell phenotype change via crosstalk with MAPK signals is another pathway through which OA forms. For the non-canonical Wnt signal pathway, Wnt5a has been reported as a key parameter influencing the phenotypic stability of chondrocytes (Benya and Shaffer 1982; Yuasa et al. 2008). Wnt5a inhibits type II

Table 1 Highlighted references related to the crosstalk between Wnt and mitogen-activated protein kinase (MAPK) pathways in various cell types, especially its influence in the regulation of chondrogenesis (*siRNA* short interfering RNA, *NFAT* nuclear factor of activated T cells, *JNK* c-Jun N-terminal kinase, *Dvl* dishevelled, *ERK* extracellular regulated kinase, *MEK* ERK kinase, *Tcf* T-cell factor, *Lef* lymphoid enhancer-binding factor, *Ap-1* activator protein-1, *PKC* protein kinase C, *TGF* transforming growth factor, *BMP* bone morphogenetic protein, *Sox* sex-determining region Y-box, *GSK* glycogen synthase kinase, *PI3K* phosphatidylinositol 3-kinase, *FGFR* fibroblast growth factor receptor, *LRP* LDL-related protein, *EGFR* endothelial growth factor receptor, *TRKA* tyrosine kinase receptor-A, *IL* interleukin, *MMP* matrix metalloproteinase, *MKK* MAPK kinase)

Cell type	Approach	Signal	Result	Reference
Mouse F9 teratocarcinoma cells	Gene knock-out (siRNAs targeting p38α MAPK) and chemical inhibitor (SB203580 targeting p38 MAPK)	P38 MAPK and Wnt5a	Wnt5a activates p38 MAPK pathway, which feeds into the Wnt5a/cyclic GMP/Ca^{2+}/NFAT pathway	Ma and Wang 2007
	Gene knock-out (siRNA targeting the dishevelled genes Dvl-1, Dvl-2 and Dvl-3) and chemical inhibitors (SB203580 targeting p38 MAPK, SP600125 targeting JNK)	Wnt3a and JNK	Suppression of either Dvl-1 or Dvl-3 but not Dvl-2 abolishes Wnt3a activation of JNK; SP600125 but not SB203580 blocks Wnt3a activation of JNK	Bikkavilli et al. 2008a
	Gene knock-out (siRNA targeting $G\alpha_0$, $G\alpha_s$, $G\alpha_q$, $G\alpha_{11}$, JNK1) and chemical inhibitor (SB203580 targeting p38 MAPK)	Wnt3a and JNK	Wnt3a activates p38 MAPK, whereas $G\alpha_s$, and $G\alpha_q$ knock-out attenuates this effect; SB203580 attenuates Wnt3a induced accumulation of β-catenin	Bikkavilli et al. 2008b
Mouse C3H10T1/2 mesenchymal cells	Gene transfection (dominant-negative p38, MEK3, and MEK6) and chemical inhibitors (SB203580 targeting p38 MAPK, MEK inhibitor U0126)	Wnt3a, ERK, and P38 MAPK	Wnt3a induces a rapid and transient activation of p38 MAPK and ERK; SB203580 and dominant-negative p38, MEK3 and MEK6 lead to inhibition of β-catenin expression	Caverzasio and Manen 2007
Mouse NIH3T3 cells	Gene transfection (recombinant Wnt3a) and gene knock-out (siRNA targeting β-catenin, ERK1, ERK2)	ERK and Wnt/β-catenin	Wnt3a stimulates the proliferation of fibroblast cells, at least in part, via activation of the ERK and Wnt/β-catenin pathways	Yun et al. 2005
Mouse stromal cell clone (ST2)	Gene transfection (retroviruses expressing GqI, Dkk1, Dvl-2 derivatives, N17Rac1, N17Cdc42 and V12Rac1) and gene knock-out (siRNA targeting β-catenin)	Wnt/β-catenin and JNK2	JNK2 kinase activates Rac1 resulting in β-catenin phosphorylation and canonical Wnt signaling activation	Wu et al. 2008
Chicken mesenchymal cells from embryo wing buds	Gene transfection (dominant-negative Tcf-4)	Wnt3a and JNK	Wnt3a inhibits chondrogenesis by stabilizing cell-cell adhesion; Wnt3a causes dedifferentiation of chondrocytes by activation of the β-catenin-Tcf/Lef transcriptional complex and the c-Jun/Ap-1 pathway	Hwang et al. 2005
	Gene transfection (retrovirus transfection targeting Wnt5a, Wnt7a)	N-cadherin (MAPKs) and Wnt7a, Wnt5a	Retrovirally mediated misexpression of Wnt7a inhibits in vitro chondrogenesis, whereas Wnt5a does not; Wnt signaling in chondrogenesis probably involves modulation of N-cadherin expression	Tufan and Tuan 2001
	Gene transfection (RCAS constructs of Wnt5a or RCAS vector); gene knock-out (siRNA targeting Wnt5a); and chemical	Wnt5a and p38 MAPK	Overexpression of Wnt5a or treatment with TGFβ3 stimulates the activation of PKC-α and p38 MAPK, which both	Jin et al. 2006a

Table 1 (continued)

Cell type	Approach	Signal	Result	Reference
	inhibitors (PD169316 targeting p38 MAPK, GF109203X targeting PKC-α)		positively regulate chondrogenic differentiation; inactivation of PKC-α and p38 MAPK by specific inhibitors abrogates chondrogenesis stimulated by both TGFβ3 and Wnt5a	
	Gene transfection (dominant-negative p38 MAPK)	Wnt7a/β-catenin and p38 MAPK	BMP2 promotes chondrogenesis by activating p38 MAPK, which in turn down-regulates Wnt7a/β-catenin signaling responsible for proteasomal degradation of Sox9	Jin et al. 2006b
	Chemical inhibitors (SP600125 targeting JNK, Src kinase inhibitor I targeting Src)	Wnt5b and JNK	Wnt5b not only inhibits chondrocyte hypertrophy but also promotes cellular migration through the JNK-dependent activation of Src and subsequent cadherin receptor turnover	Bradley and Drissi 2011
Human embryonic kidney 293 (HEK 293) cell line	Gene transfection (GSK3β mutant constructs, dominant-negative ERK1/2, constitutively active GSK3β); gene knock-out (siRNA targeting β-catenin, siRNA targeting ERK1/2); and chemical inhibitors (PD98059 targeting MEK1, LY294002 targeting PI3K, calphostin C targeting PKC)	P38 MAPK; ERK1/2; and Wnt/β-catenin	ERK activation leads to phosphorylation and inactivation of GSK3β, resulting in release of β-catenin, which is translocated into the nucleus and facilitates cell proliferation	Ding et al. 2005
	Gene transfection (plasmids for wild type p38 MAPK, constitutively active MEK6, mutant GSK3β) and chemical inhibitors (SB203580 targeting p38 MAPK, Wortmanin targeting PI3K)	Tak1 MAPK and Wnt/β-catenin	p38 MAPK inactivates GSK3β by direct phosphorylation at its C terminus; this inactivation leads to an accumulation of β-catenin in the nucleus	Thornton et al. 2008
	Gene transfection (FGFR3 vectors, LRP6 variant vectors, plasmids expressing V5-tagged FGFR2, EGFR and TRKA) and chemical inhibitor (U0126 targeting ERK1/2)	Wnt/β-catenin and ERK1/2	Wnt/β-catenin is activated by FGFR2/3, EGFR and TRKA kinases, which depend on ERK-mediated phosphorylation of Wnt co-receptor LRP6	Krejci et al. 2012
	Gene knock-out (siRNAs targeting MAPK1, MAPK3, MAPK8, MAPK11) and chemical inhibitors (BIRB796 and SB203580 targeting p38 MAPK, SP600125 targeting JNK, U0126 targeting ERK1/2)	MAPKs and Wnt/β-catenin	Several MAPKs, such as p38, ERK1/2 and JNK1, are sufficient and required for the phosphorylation of PPPS/TP motifs of LRP6, which is a co-receptor of Wnts and a key regulator of Wnt/β-catenin pathway	Červenka et al. 2011
Human trabecular bone-derived mesenchymalprogenitor cells (MPCs)	Gene transfection (plasmid containing human type II collagen α1, plasmid of pAGC1 containing human aggrecan promoter) and chemical inhibitors (SB203580 targeting p38 MAPK, PD98059 targeting ERK-1 specific MEK1, SP600125 targeting JNK)	MAPKs and Wnt7a	TGFβ1 treatment initiates and maintains chondrogenesis of MPCs through the differential chondro-stimulatory activities of p38, ERK1 and to a lesser extent, JNK; TGFβ1-mediated MAPK activation controls Wnt7a gene expression and Wnt-mediated signaling through the intracellular β-catenin-TCF pathway, which probably regulates N-cadherin expression and subsequent cell-	Tuli et al. 2003

Table 1 (continued)

Cell type	Approach	Signal	Result	Reference
			adhesion complexes during the early steps of MPC chondrogenesis	
Rabbit temporomandibular joint (TMJ) condylar chondrocytes	Gene transfection (β-catenin-Tcf/Lef expression plasmid, Wnt5a expression vector)	Wnt5a and JNK	Activation of Wnt5a signaling by IL-1β induces the expression of MMPs via the JNK pathway	Ge et al. 2009
Xenopus embryo	Gene transfection [constitutive-active JNK plasmid (Flag-MKK7-hJNK1), antisense oligo against Dishevelled] and chemical inhibitor (SP600125 targeting JNK)	Wnt/β-catenin and JNK	JNK antagonizes the canonical Wnt pathway by regulating the nucleocytoplasmic transport of β-catenin	Liao et al. 2006

collagen expression in rabbit TMJ condylar chondrocytes (Ge et al. 2009), suggesting that Wnt5a signaling regulates pathologic cartilage degeneration by inducing chondrocyte dedifferentiation (Ryu and Chun 2006). Increased p38 activity is accompanied by type X collagen staining in osteochondrocytes and marginal synovial cells in a mouse OA model (Seto et al. 2004). During monolayer culture, p38 MAPK is responsible for the loss of chondrocyte phenotypes including type II collagen and Sox9, whereas the blockade of p38 MAPK enhances chondrocyte phenotypes, which suggests a blockade of dedifferentiation (Rosenzweig et al. 2013). Inhibition of p38 signaling in chondrocytes results in decreased expression of the *COL10A1* gene (Beier and LuValle 1999; Stanton et al. 2003; Zhen et al. 2001).

Concluding remarks and future directions

Although awareness is increasing with regard to the importance of MAPK and Wnt signaling pathways in regulating cell activities and in relevant diseases such as cancer, their interaction networks and potential roles in disease are still not fully appreciated, especially in the cartilage regeneration area (Table 1). Cartilage differentiation and the maintenance of homeostasis are finely tuned by a complex network of signaling molecules; interplay of these signaling pathways leads to changes in cell activities and eventually influences their differentiation fates. Over the past two decades, extensive studies on the Wnt and MAPK regulation of chondrogenesis and cartilage development have shown that Wnt and MAPK signals have both positive and negative regulatory effects on cartilage development. Accumulating evidence indicates the involvement of Wnt and MAPK signals in the regulation of differentiated chondrocyte functions and cartilage disease.

Recent evidence from both animal experiments and clinical samples has demonstrated the role of both Wnt and MAPK signaling in OA pathology, making these pathways attractive targets for therapy. Some chemicals and drugs targeting MAPK or Wnt have been designed and applied clinically; whereas some are effective in the treatment of OA, their side effects have caused concern. Direct targeting to Wnt or MAPK has been reported to be too risky, because of the crucial role of these signals in the maintenance of articular chondrocyte stability. A promising method would be to identify the mis-regulated genes in the Wnt or MAPK pathways and to try to determine balanced therapeutic targets. The ideal therapeutic goal would be treatment with few or even no side effects in patients. In order to achieve the goal of clinical application, comprehensive appreciation and meticulous evaluation of the interactions of these signaling pathways are essential. Future research should focus on the elucidation of the network between MAPK and Wnt signaling, their

interplay and the exploration of clinical application in cartilage regeneration by intervention in specific signaling pathways.

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