

JAK/STAT in Bone Development

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The Janus kinase (JAK) signal transducer and activator of transcription (STAT) signaling pathway serves as an important downstream mediator for a variety of cytokines, hormones, and growth factors. Based on the knowledge gained from JAK and STAT knockout animals, the JAK/STAT signaling pathway was identified as important for bone development and homeostasis, recognizing that JAKs and STATs are not equally important for the biology of osteoblasts and osteoclasts. Moreover, their overall role in the musculoskeletal system is still not fully understood. Understanding the underlying mechanisms of how bone remodeling is regulated, how metabolic processes take place, and how bone responds to mechanical stimulation is central to maintaining the integrity of the skeletal system.

Keywords: JAK/STAT, osteoblast, osteoclast

1. Introduction

The sense of and reaction to external signals from the environment is essential for the survival of every living system. At the level of the whole organism, the sensory organs such as eyes, ears, and skin are specialized in perceiving the signals of the environment, processing the incoming signals, and passing on the information to finally trigger a reaction of the whole body. At the cellular level, external signals are primarily sensed and processed by biochemical receptors in the cell membrane and transmitted via signaling pathways and cascades that form a network with a variety of other pathways to further process the information. These signals initiate mechanisms that are responsible for controlling phenotypic and functional outcomes, e.g., proliferation or apoptosis. Among these signal transduction pathways, the Janus tyrosine kinase (JAK)- and signal transducers and activators of transcription (STAT)-mediated signaling are responsible for transducing signals of more than fifty cytokines, growth factors and hormones, regulated on multiple levels [1][2][3]. Loss- or gain-of-function mutations of genes encoding JAK/STAT components display dramatic immunological phenotypes in humans and mice underpinning the importance of the central communication hub for the immune system [1][3][4]. Regulation of cellular, molecular, and genomic processes via JAK and/or STAT proteins are inhibited by the suppressor of cytokine signaling (SOCS)—a family of intracellular negative feedback proteins (Figure 1). Some of these cytokines, growth factors, and hormones have been shown to regulate bone homeostasis via JAK and/or STAT proteins [5].

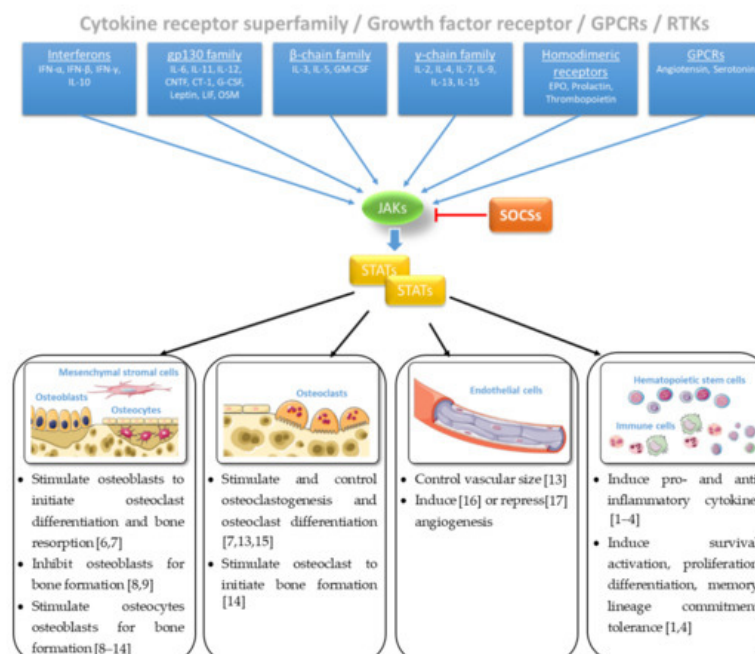


Figure 1. Janus tyrosine kinase (JAK)/signal transducers and activators of transcription (STAT) signaling in bone homeostasis [1][2][3][4][6][7][8][9][10][11][12][13][14][15][16][17]. Figure contains graphics from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. <http://smart.servier.com/>.

2. JAK/STAT Pathway at a Glance

In mammals, the JAK family contains four members (JAK1, JAK2, JAK3, and tyrosine kinase 2; TYK2). Their clinical importance has been highlighted by a human immunodeficiency syndrome caused by loss-of-function mutations in JAK3 [18][19]. Extracellular interaction of a cytokine with its transmembrane receptor initiates the canonical JAK/STAT signaling by inducing receptor oligomerization and trans-activation of JAKs. In turn, JAK trans-activation phosphorylates the cytoplasmic domains of the receptor, which assist as docking sites for STATs. Spatial proximity of JAK and STAT facilitates JAK-mediated tyrosine-phosphorylation of STAT that dimerizes and translocates to the nucleus. In the nucleus, all phosphorylated STAT dimers bind to interferon- γ (IFN- γ)-activated sequence (GAS) DNA motifs except STAT2, which forms a trimeric complex with STAT1 and Interferon Regulatory Factor 9 (IRF9). Finally, the STAT1–STAT2–IRF9 complex also known as Interferon-stimulated Gene Factor 3 (ISGF3) engages the Interferon-stimulated Response Element (ISRE) motif (Figure 2). While JAK1, JAK2, and TYK2 are ubiquitously expressed, JAK3 is expressed more restricted, regulated, and tissue specific and can be found in hematopoietic cells such as NK cells, thymocytes, T cells, B cells, and myeloid cells but also in vascular smooth muscle cells and endothelium [2]. The name of the Janus kinases is based on the depiction of the Roman gate and door god “Janus” with his two faces and is based on their two-sided character featured by the existence of tandem kinase and pseudokinase domains [2]. Seven JAK homology (JH) regions are described. While the catalytic JH1 domain or kinase domain, which has all the characteristics of a typical tyrosine kinase domain, is well described, the function of the other JH regions is still poorly understood [2]. The JH2 domain is a so called pseudokinase domain that contains all of the subdomains that correspond to those in the catalytic JH1 tyrosine kinase but being altered from the typical subdomain motifs. The exact function remains to be elusive although being important for full functionality of the kinase domain and providing a docking site that associates with STATs. Both, the JH2-like domain and the FERM domain facilitate the interaction between JAKs and multiple upstream receptors [20][21][22][23].

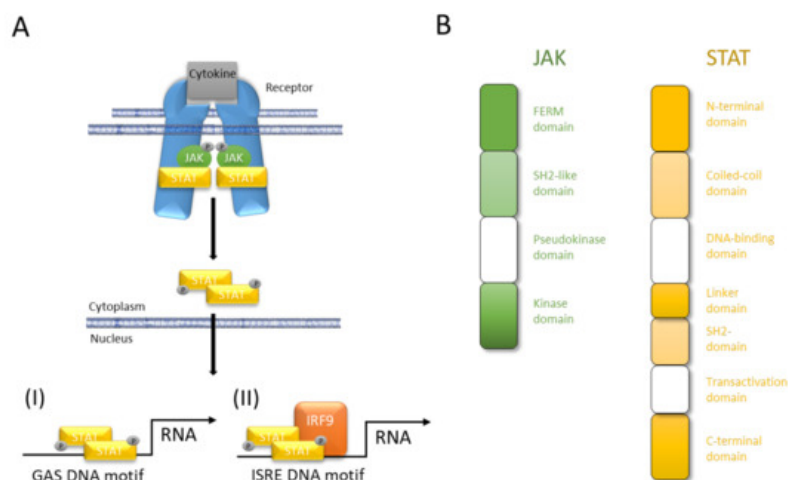


Figure 2. JAK/STAT pathway at a glance. **(A)** Cytokines interact with their corresponding receptor, which, after oligomerization, activates JAK and initiates JAK-mediated phosphorylation of its own cytoplasmic domain. Receptor phosphorylation causes STAT binding in close proximity to JAK that in turn mediates tyrosine-phosphorylation (p-Tyr) of the latter. STAT phosphorylation results in dimerization, nuclear translocation, DNA binding, and modulation of gene transcription. **(I)** All STAT can bind to interferon- γ (IFN- γ)-activated sequence (GAS) DNA motifs while **(II)** only STAT2 after forming a trimeric complex of STAT1–STAT2–IRF9 engages Interferon-stimulated Response Element (ISRE) DNA binding. **(B)** Four domains of JAK facilitate interaction with upstream receptors and promotion of kinase function (FERM domain), interaction with upstream receptors (SH2-like domain), control of kinase activity (pseudokinase domain), and trans-activation and tyrosine-phosphorylation of receptors, JAKs and STATs (kinase domain). The seven domains of STAT facilitate protein-protein interactions (N-terminal domain), protein–protein interactions and nuclear-localization (coiled-coil domain), nuclear import, DNA binding, and transcriptional activity (DNA-binding domain), structural organization and transcriptional activity (linker domain), dimerization and interaction with upstream receptors (SH2 domain), canonical signaling (transactivation domain), canonical and non-canonical functions (C-terminal domain).

The STAT family is composed of seven members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6), which share seven characteristic protein domains [2]. These domains interact with the upstream receptors, with each other (i.e., dimerization and tetramerization) and with certain DNA motifs. STATs mainly act as transcription factors that directly bind

to DNA regulatory elements and control the transcription of associated genes. STAT binding can be observed proximal to DNA responsive elements but also distal and far from protein-encoding genes [2]. These sites can be distinguished in majority as enhancers, epigenetic hotspots, and non-coding loci. Thus, it is noteworthy, that STATs bear the capability to bind DNA, to act as transcription factor, and to modify the epigenome; the latter by either controlling the expression of various chromatin modifiers, or by physical interactions between e.g., STATs and CBP/p300, which mediates histone acetylation [2]. However, all members of the STAT family are capable to directly bind to GAS elements but do also often bind to STAT-binding sites which do not contain GAS motifs or STATs physically interact with other transcriptional regulators without DNA binding. Moreover, different STATs tend to co-localize extensively as exemplified in the interleukin (IL)-2R α gene locus [2]. All the different modes of action and the various combinations of JAK and STAT proteins make an investigation on their targets almost impossible.

3. Guiding Bone Development by Combining JAKs and STATs

The skeletal system, one of the most important systems of the human body, serves as the structural support center of the body, provides a framework for the attachment of tissues, protects vital organs, and helps to direct the forces necessary for movement. The physiological bone development processes that lead to the structure, strength, and size of the bone are controlled by several pathways. These pathways regulate cellular functions within the skeletal system, which consists of bone-forming cells (osteoblasts), resident cells that form the regulatory network (osteocytes), and bone-resorbing cells (osteoclasts). During bone formation and remodeling processes, osteoblasts, osteocytes, osteoclasts, and chondrocytes are markedly influenced by various cytokines and their receptors such as the IL-6 receptor that is characterized by tyrosine kinases of the JAK family. Of note, many bone-related cytokines involved in bone development have been described, including those that signal through JAK and STAT pathways such as the IL-6 family of cytokines [3]. In bone, IL-6 family cytokines such as IL-6, IL-11, oncostatin M (OSM), cardiotrophin 1 (CT-1), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) act via the gp130 (glycoprotein 130) that activates gp130-associated JAKs [5][8]. This IL-6 receptor subunit has been demonstrated to be essential for the normal skeletal development, to stimulate bone formation of osteoblasts and to primarily act through STAT3 signaling. STAT3-dependent cytokines also suppress gene products that inhibit osteoblast differentiation, such as sclerostin [5]. Furthermore, the importance of the JAK/STAT signaling pathway for bone development is also highlighted by their involvement in mechanotransduction. Kido et al. showed that mechanical unloading suppresses, and reloading enhances the *IL11* expression in bone cells [24]. IL-11 has been shown to induce receptor activator of nuclear factor κ B ligand (*RANKL*) expression and stimulate bone resorption in vivo [25]. Moreover, the epidermal growth factor receptor (EGFR) and its ligands strongly inhibit osteoblast differentiation and mineralization, as determined by the decreased expression of the transcription factor *Runx2* and *Osterix* [26]. Based on the knowledge gained from JAK and STAT knockout animals, the JAK/STAT signaling pathway was identified as important for bone development and homeostasis, recognizing that JAKs and STATs are not equally important for the biology of osteoblasts and osteoclasts. Moreover, their overall role in the musculoskeletal system is still not fully understood. Understanding the underlying mechanisms of how bone remodeling is regulated, how metabolic processes take place, and how bone responds to mechanical stimulation is central to maintaining the integrity of the skeletal system, thus ensuring human health care. [Table 1](#) summarizes the influence of the JAK/STAT pathway in bone development using knockout animals.

Table 1. JAK/STAT pathway in bone development.

Model System	Genes Modified	Species	Bone Phenotype	References
Janus kinases (JAKs)				
<i>Jak1</i> ^{-/-}	<i>Jak1</i> deletion	Mouse	Small bone mass in contrast to wild-type mice; Perinatal lethal; Stunted embryos; Involved in bone formation	[27][28]
<i>MMTV-Cre.Jak1</i> ^{fl/fl}				
<i>Jak1</i> ^{S645P+/-}	<i>Jak1</i> activation	Mouse	Low bone mass levels in trabecular and cortical bone; Bone formation and resorption is increased	[29]
Tofacitinib treatment	<i>Jak1/3</i> inhibition	Mouse, rat	Protected against bone resorption by inflammation	[30][31][32]
Ruxolitinib treatment	<i>Jak1/2</i> inhibition	Mouse	Protected against age-related bone resorption	[33]

Model System	Genes Modified	Species	Bone Phenotype	References
Janus kinases (JAKs)				
<i>Jak2</i> ^{-/-}	<i>Jak2</i> deletion	Mouse	<i>Jak2</i> -null mice die before bone formation starts; Lethality of anemia at E12.5 (erythropoiesis is absent); Involved in bone formation	[34][35][36]
<i>Jak3</i> ^{-/-}	<i>Jak3</i> deletion	Mouse	Born normally; No gross abnormality	[37][38]
<i>Tyk2</i> ^{-/-}	<i>Tyk2</i> deletion	Mouse	Viable and fertile mice; No obvious phenotype; Involved in bone formation	[39][40]
Signal transducers and activators of transcription (STATs)				
<i>Stat1</i> ^{-/-}	<i>Stat1</i> deletion	Mouse	KO mice are indistinguishable compared to wild-type mice; Higher bone mass → osteopetrotic bone phenotype; Bone exhibits excessive osteoclastogenesis; Normal epiphyseal growth plate and longitudinal bone length; Characteristics: Pro-inflammatory, antagonize proliferation	[41][42][43]
<i>Stat2</i> ^{-/-}	<i>Stat2</i> deletion	Mouse	Viable and fertile mice; No gross abnormality	[44]
<i>Stat3</i> ^{-/-}	<i>Stat3</i> deletion in all cells	Mouse	Involved in early embryonic development; Lethality at E6.5–7.5; Selective inactivation causes osteoporosis; Surface mineralization reduced; Characteristics: Pro-proliferative, anti-inflammatory	[45][46][47][48]
Hyper-IgE syndrome	<i>Stat3</i> -DNA binding reduced in all cells	Mouse	Low bone mineral density; Recurrent fractures; Craniofacial and skeletal abnormalities	[49][50][51]
SA/SA and SA/-	Reduced <i>Stat3</i> phosphorylation in all cells	Mouse	Perinatal lethality: 75%; SA/SA phenotype is normal; <i>Stat3</i> phosphorylation in SA/- is reduced; Reduced skeletal size	[52]
<i>Dmp1Cre.Stat3</i> ^{fl/fl}	<i>Stat3</i> deletion in osteocytes	Mouse	Low bone mass and reduced bone formation rate; Bone formation response to mechanical forced reduced	[53]
<i>Col1α1(2.3 kb) Cre; Stat3</i> ^{fllox/fllox}	<i>Stat3</i> deletion in osteoblasts and osteocytes	Mouse	Low trabecular bone mass and bone formation rate reduced; Normal bone length; Bone formation response to mechanical forced reduced	[46][47][54][55]
<i>Col1α1(3.6 kb) Cre; Stat3</i> ^{fllox/fllox}	<i>Stat3</i> deletion in chondrocytes, osteoblasts, and osteocytes	Mouse	Skeletal size is very small with low trabecular bone mass; Bone formation rate reduced and osteoclast formation increased	[47][55]
<i>Prrx1Cre; Stat3</i> ^{fllox/fllox}	<i>Stat3</i> deletion in chondrocytes, osteoblasts, and osteocytes	Mouse	Skeletal size reduced; Postnatal limb curvature	[56]
<i>TCre.Stat3</i> ^{flf}	<i>Stat3</i> deletion in mesoderm-derived cells	Mouse	Shortened limbs at birth; Postnatal limb curvature	[56]
<i>Tie2(Tek)Cre.Stat3</i> ^{flf}	<i>Stat3</i> deletion in hematopoietic and endothelial cells	Mouse	Skeletal size and bone mass are reduced; Bone formation rate reduced with increased resorption	[57]

Model System	Genes Modified	Species	Bone Phenotype	References
Janus kinases (JAKs)				
<i>Socs3</i> ^{-/-}	<i>Socs3</i> deletion; elevated Stat3 signaling in all cells	Mouse	Embryonic lethality	[58][59]
<i>VavCre.Socs3</i> ^{fl/fl}	Elevated Stat3 signaling in endothelial and hematopoietic cells	Mouse	Joint inflammation; Low bone mass; Increased osteoblast and osteoclast formation	[60]
<i>Dmp1Cre.Socs3</i> ^{fl/fl}	Elevated Stat3 signaling in osteocytes	Mouse	Cortical porosity increased → delayed development of cortical bone; Increased bone formation and resorption	[61]
<i>Dmp1Cre.Socs3</i> ^{fl/fl} . <i>IL6</i> ^{-/-}	Elevated Stat3 signaling in osteocytes; no downstream of IL-6	Mouse	Cortical porosity increased → delayed development of cortical bone	[61]
<i>Col2Cre.Socs3</i> ^{fl/fl}	Elevated Stat3 signaling in chondrocytes, osteoblasts and osteocytes	Mouse	Cortical porosity increased; Bone size reduced	[62]
<i>Stat4</i> ^{-/-}	<i>Stat4</i> ^{-/-} deletion	Mouse	Viable and fertile mice; No gross abnormality	[63]
<i>Stat5a/b</i> ^{-/-}	Double mutation	Mouse	KO mice show obviously defective bone development; Smaller <i>Stat5a/5b</i> (male and female) KO mice and <i>Stat5b</i> (male) KO mice compared to wild-type mice	[64][65]
<i>Stat5a</i> ^{-/-}	<i>Stat5a</i> deletion	Mouse	Increased bone mass; Increased trabecular bone density and cortical bone formation; Prevented age-related bone loss	[66]
<i>Cathepsin K-Cre</i> ^{-/-} <i>-Stat5</i> ^{fl/fl}	Osteoclast-specific deletion	Mouse	Reduced bone mass	[67]
<i>Stat6</i> ^{-/-}	<i>Stat6</i> deletion	Mouse	Viable and fertile mice; No gross abnormality compared to their wild-type controls	[68][69][70]

All members of the JAK family—Jak1, Jak2, Jak3, and Tyk2—play a pleiotropic role in physiological processes such as bone development. While *Jak1*, *Jak2*, and *Tyk2* are ubiquitary, and expressed in bone cells, *Jak3* is typically expressed by hematopoietic, lymphoid, and myeloid cells as mentioned above. Among *Jak1* and *Jak2*, *Jak3* and *Tyk2* deficient mice show no obvious skeletal phenotype. These findings demonstrate that both Jak3 and Tyk2 are not clinically relevant for skeletal development. Most signaling cytokines depend on Jak1, and therefore it is unsurprisingly that *Jak1*-null mice die perinatally and weigh 40% less than the wild-type littermates, indicating that bone growth delays without Jak1 in embryos [28][71]. On the other hand, *Jak2*^{-/-} embryos are anemic and die at E12.5 before bone formation starts [72]. Unfortunately, the underlying mechanisms of how Jak1 and Jak2 affect osteoblasts and osteoclasts are of clinical relevance and highlight the importance of a deep understanding. Similar to Jaks, Stat proteins are located in bone tissue. The STAT family, first discovered in 1993 by James Darnell [73], consists of seven signal transducer and activator of transcription proteins. While Stat2, Stat4, and Stat6 do not play a crucial role in skeletal development, indicated by a normal skeletal phenotype, Stat1 is a critical regulator of both osteoclastogenesis and osteoblast differentiation. Therefore, *Stat1* depletion leads to excessive osteoclastogenesis and inhibition of the transcription factor *Runx2* as well as suppression of *Osterix* transcription in osteoblasts [43]. Although *Stat1*^{-/-} mice are indistinguishable from their normal controls, depletion leads to an osteopetrotic bone phenotype characterized by an increased bone mass [42]. These findings suggest that Stat1 has negative effects on bone formation in vivo. Based on the normal epiphyseal growth plate, Kim et al. suggest that physiological chondrocyte proliferation is not significantly increased due to *Stat1* depletion [42]. Among the seven, Stat3, Stat5a, and Stat5b have been shown to be directly involved in bone development. Stat3 was first described as a DNA-binding protein that is activated in IL-6-stimulated hepatocytes [74]. In humans, STAT3 is probably the most important transcription factor. Studies suggest that Stat3 plays a central role in early embryonic bone formation, is involved in bone metabolism, and reduces mechanical load-driven bone development [46][47]. Since Stat3 mediates intracellular signal transduction in osteoblasts and osteoclasts, depletion reduces bone mass and impairs bone development. Thus, the incidence of bone fractures increases [46][47]. Along with other members of the STAT family, Stat5 was originally identified as a cytosolic signal molecule involved in the proliferation, differentiation, and progression of solid tumor cells [75]. Recent

evidence suggests that STATs, especially Stat5 play a central role in growth hormone signaling, osteoblast differentiation, inhibition of osteoclast differentiation, and therefore bone homeostasis [76][77]. The depletion of both *Stat5a* and *Stat5b* in mice therefore lead to apparently defective bone formation in vivo. This delayed skeletal development is consistent with insulin like growth factor (IGF)-1 function in bone, which were significantly reduced by *Stat5a/b* mutation [67]. Moreover, the genetic mapping of the STAT gene family should be comment. Indeed, studies suggest that Stat1, Stat2, Stat3, Stat4, and Stat6 arose by chromosome duplications from Stat5 [78]. Therefore, both Stat5a and Stat5b show extensive similarities regarding their sequence with isoform-specific functions. Deletion of Stat5a leads to increased bone mineral density, trabecular and cortical bone mass and prevents age-related bone loss in mice [66]. Lee et al. investigated the role of STAT5a in human bone marrow-derived mesenchymal stromal cells. Surprisingly, inhibition of STAT5a resulted in a significant increase of osteoblast differentiation, whereas inhibition of STAT5b showed no effect. This demonstrates the isoform-specific function of the STAT5s. In addition, STAT5b has been shown to apparently regulate the male pattern of long bone growth that is characteristic of many species, including humans [65]. Nevertheless, further studies are needed to gain a better understanding on the detailed mode of action.

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