SH3BP2 is a Critical Regulator of Macrophage and Osteoclast Response to M-CSF and RANKL Stimulation

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Abstract The protein Src homology 3 domain-binding protein 2 (SH3BP2) is a regulator of tumor necrosis factor (TNF)-alpha generation in macrophages and of osteoclast differentiation. SH3BP2 regulates bone marrow monocyte responses to macrophage and osteoclast differentiation signals downstream of the receptors for macrophage colony-stimulating factor and receptor activator of nuclear factor kappaB ligand. SH3BP2 is a potential target for the development of novel anti-TNF-alpha therapeutic interventions as well as a target for suppression of osteoclastogenesis.

Keywords SH3BP2 · macrophage · osteoclast · M-CSF · RANKL

Brief review

The signaling adapter protein, Src homology 3 domain-binding protein 2 (SH3BP2), is a previously unrecognized regulator of tumor necrosis factor (TNF)-alpha generation in macrophages and of osteoclast differentiation [1]. An adapter protein regulates the functions of protein binding partners. Adapter proteins are key components of signal transduction pathways by regulating the assembly of large molecular complexes [2]. Molecular scaffolds composed of adapter proteins and enzymes are assembled and activated at the plasma membrane. The scaffolds transduce signals to

the cytoplasm, cytoskeleton, and nucleus to activate gene expression and metabolic changes [2].

SH3BP2 plays a crucial role in signaling pathways during cell differentiation and function [2]. SH3BP2 is ubiquitously but dominantly expressed in hematopoietic cells (macrophages, NK, T, and B cells) and contains three domains, N-terminal pleckstrin homology domain, central proline-rich SH3-binding domain, and C-terminal SH2 domain [1]. SH3BP2 is highly expressed in osteoclasts [3]. SH3BP2 was originally isolated by a screen for proteins that could bind to the SH3 domain of the tyrosine kinase, c-Abl [4]. Interactions between SH3BP2 and a variety of other proteins have been reported in lymphocytes, mast cells, and NK cells [5–8].

Cherubism is a fibrous dysplasia-like syndrome characterized by excessive bone resorption in the jaw with accumulation of inflammatory/fibrous tissue. Pathological facial changes, reminiscent of cherubs portrayed in Renaissance art, appear 2–4 years after birth and regress after puberty. The disorder has been mapped to chromosome 4p. Amino acid missense mutations in SH3BP2 have been identified in several cherubism patients [3].

A recent study demonstrated that SH3BP2 regulates the bone marrow monocyte responses to macrophage and osteoclast differentiation signals downstream of the receptors for macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappaB ligand (RANKL) through mechanisms that involve control of extracellular signal-regulated kinase (ERK) and spleen tyrosine kinase (SYK) activity, respectively [1]. Whereas NF-kappaB directly stimulates TNF-alpha transcription, ERK enhances TNF-alpha mRNA transport from the nucleus to the cytoplasm [9]. SH3BP2 is required for optimum SYK phosphorylation and calcium flux [10]. SH3BP2 missense mutations cause bone loss and inflammation in patients with cherubism. The mouse model of cherubism indicated that mutant myeloid cells show increased responses to M-CSF and RANKL stimulation, and, through mechanisms of increased ERK and SYK

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phosphorylation/activation, they form macrophages that express high levels of TNF- α and large numbers of osteoclasts that are unusually large [1].

The position of the adaptor protein in the two signal cascades that are involved in the skeletal defects that are associated with cherubism can be summarized as follows: (1) RANKL–osteoclast–RANK–SH3BP2–SYK–activation–bone loss–cherubism and (2) M-CSF–macrophage receptors–SH3BP2–ERK–TNF- α –inflammation–cherubism. Phosphorylation of SH3BP2 plays an important role in activation of T and B cells [7, 8]. A recent study of SH3BP2 deficiency in T and B cells suggests that SH3BP2 is particularly important for signaling in B cells [11]. Activation of ERK was impaired after B cell receptor ligation in B cells from mice lacking SH3BP2 [11]. In SH3BP2 deficient mice, no impairment of T cell processes have been noted [11]. Therefore, SH3BP2 is unlikely to be important for setting the basic response threshold to incoming signals in wild-type myeloid cells but may serve to enhance responses under conditions of increased macrophage and osteoclast differentiation.

The identification of the proteins that control TNF- α production would provide new targets for the development of more effective and safer drugs for the treatment of inflammatory diseases of children such as juvenile rheumatoid arthritis. SH3BP2 and its associated proteins are potential targets for the development of novel anti-TNF- α therapeutic interventions as well as targets for suppression of osteoclastogenesis in the treatment of osteoporosis [12].

References

1. Ueki Y, Lin C, Senoo M, Ebihara T, Agata N, Onji M, Saheki Y, Kawai T, Mukherjee PM, Reichenberger E, Olsen B (2007) Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 “cherubism” mice. *Cell* 128:71–83
2. LeBras S, Moon C, Foucault I, Breittmayer J, Deckert M (2007) Abl-SH3 binding protein 2, 3BP2, interacts with CIN85 and HIP-55. *FEBS Lett* 581:967–974
3. Ueki Y, Tiziani V, Santanna C, Fukai N, Maulik C, Garfinkle J, Ninomiya C, doAmaral C, Peters H, Habal M, Rhee-Morris L, Doss JB, Kreiborg S, Olsen BR, Reichenberger E (2001) Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. *Nat Genet* 28:125–126
4. Ren R, Mayer BJ, Cicchetti P, Baltimore D (1993) Identification of a ten-amino acid proline-rich SH3 binding site. *Science* 259:1157–1161
5. Deckert M, Tartare-Deckert S, Hernandez J, Rottapel R, Altman A (1996) Adapter function for the Syk kinases-interacting protein 3BP2 in IL-2 gene activation. *Immunity* 9:595–605
6. Foucault I, Liu YC, Bernard A, Deckert M (2003) The chaperone protein 14–3–3 interacts with 3BP2/SH3BP2 and regulates its adapter function. *J Biol Chem* 278:7146–7153
7. Maeno K, Sada K, Kyo S, Miah SM, Kawauchi-Kamata K, Qu X, Shi Y, Yamamura H (2003) Adapter protein 3BP2 is a potential ligand of Src homology 2 and 3 domains of Lyn protein-tyrosine kinase. *J Biol Chem* 278:24912–24920
8. Foucault I, LeBras S, Charvet C, Moon C, Altman A, Deckert M (2005) The adapter protein 3BP2 associates with VAV guanine nucleotide exchange factors to regulate NFAT activation by the B-cell antigen receptor. *Blood* 105:1106–1113
9. Dumitru CD, Ceci JD, Tsatsanis C, Kontoyiannis D, Stamatakis K, Lin JH, Patriotis C, Jenkins NA, Copeland NG, Kollias G, Tsichlis PN (2000) TNF- α induction by LPS is regulated posttranscriptionally via a Tpl2/ERK-dependent pathway. *Cell* 103:1071–1083
10. Chen G, Dimitriou ID, LaRose J, Ilangumaran S, Yeh W, Doody G, Turner M, Gommerman J, Rottapel R (2007) The 3BP2 adapter protein is required for optimal B-cell activation and thymus-independent type 2 humoral response. *Mol Cell Biol* 27(8):3109–3122
11. Fuente MA de la, Kumar L, Lu B, Geha RS (2006) 3BP2 deficiency impairs response of B cells, but not T cells, to antigen receptor ligation. *Mol Cell Biol* 26:5214–5225
12. Leitman SA, Yin L, Levine MA (2008) SH3BP2 is an activator of NFAT activity and osteoclastogenesis. *Biochem Biophys Res Commun* 371(4):644–648