Immunity, Vol. 23, 461–464, November, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.10.004

An IL-1 Family Member Requires Caspase-1 Processing and Signals through the ST2 Receptor

Activation of ST2, an orphan member of the IL-1 receptor family for 16 years, drives T helper type 2 (T_H2) responses. The cytokine IL-33 is the specific ligand for ST2. IL-33 recapitulates much of the existing data that ST2 promotes T_H2-type responses. The caspase-1 processing of precursor IL-33 provides a therapeutic target to control allergic diseases.

The receptor termed ST2 is a member of the IL-1 receptor family and was first reported as regulated by the estrogen-inducible transcription factor Fos (Bergers et al., 1994). This receptor is very similar to the IL-1 receptor type I and the IL-18 receptor α chain in that ST2 also has three extracellular Ig domains and an intracellular Toll domain (Figure 1). Described more than 16 years ago, the search for its cognate ligand did not reveal a convincingly specific candidate. Although some members of the IL-1 family of ligands remain without known receptors, none of these bind to or signal the cell via ST2. It was always assumed that the ligand for ST2 would be a member of the IL-1 family. But it is not unusual to learn of the functions of an orphan receptor before the discovery of its ligand. And so it was the case with ST2. There was no dearth of studies on ST2 tissue-specific localization, regulation of its expression, and effects in transgenic mice overexpressing ST2, as well as deletion, neutralization, and antibody crosslinking of ST2. We learned that elevated levels of the soluble form of ST2 were present in the circulation of patients with a various inflammatory diseases and that exogenous administration of pharmacologic doses of soluble ST2 neutralized the putative ligand and reduced inflammation (Leung et al., 2004). Furthermore, several studies suggested that whatever the ligand for this orphan receptor, it was playing a role in allergic type diseases, often called T helper type 2 (T_H2) diseases. In fact, it became clear that activation of ST2 was uniquely driving T_H2 responses. Of the T_H2-driven diseases, asthma continues to be difficult to treat. In this issue of *Immunity*, a member of the IL-1 family, IL-33, is reported to be the specific ligand for ST2 (Schmitz et al., 2005). Structurally, IL-33 is closest to IL-18, rather than IL-1β. With the discovery of IL-33, the door appears to close on the 16-year-long search. But the discovery of IL-33 also raises the curtain on a new round of investigation on the immunological as well as inflammatory consequences of engagement of ST2. In this case, the dominant property of IL-33 is the induction of IL-4, IL-5, and IL-13 as well as properties anticipated for a T_H2-type cytokine. Diseases thought to be due to increased immunoglobulin production may also be related to IL-33.

Lacking an IL-33 knockout mouse, the investigators injected mice with human IL-33 and observed rather impressive pathological changes in the arterial walls, lungs, and intestinal tissues. Of particular relevance to the concept that IL-33 drives a T_H2 response, esosinophilic infiltration was a prominent finding. In addition, copious amounts of mucus were observed in the upper airways of the lung. Again, this finding is consistent with the classic T_H2 disease, asthma. Large amounts of mucus were also seen in the lumen of the intestine associated with hypertrophy of the mucus-producing goblet cells. Although the interpretation of in vivo effects following the administration of an exogenous cytokine should be conservative, the findings are clearly consistent with IL-33 being a proinflammatory ligand of the IL-1 receptor family. Even before the ability to test ST2 functions via IL-33-mediated activation, others had reported that neutralization of the putative ST2 ligand by soluble ST2 markedly reduced joint inflammation, synovial hyperplasia, and joint erosion when given in the therapeutic phase of collagen-induced arthritis in mice (Leung et al., 2004). Moreover, it appears that organs with high numbers of mast cells appear to undergo dramatic changes upon injection of IL-33 into mice. Consistent with a role in allergic diseases, IL-33 induces the cytokines IL-5 and IL-13 in vivo, known contributors of allergic diseases. Mice deficient in ST2 do not develop a T_H2 response to Schistosoma egg antigen (Townsend et al., 2000).

It remains unclear how IL-33 favors the T_H2 response. As shown in the Figure, following engagement of ST2, IL-33 initiates signal transduction such as activation of NF-κB typical of those of IL-1α, IL-1β, and IL-18 (Schmitz et al., 2005), but other studies have shown that antibody crosslinking of ST2 does not result in activation of NF-κB but rather AP-1 (Brint et al., 2002). However, IL-33 gains considerable legitimacy as a member of the IL-1 ligand family, since processing of the IL-33 precursor is accomplished by caspase-1 (Schmitz et al., 2005), similar to IL-1β and IL-18. Caspase-1, formerly termed the IL-1β converting enzyme, cleaves the inactive IL-1β and IL-18 precursors into active cytokines. Indeed, caspase-1-deficient mice fail to develop colitis, arthritis, acute renal failure, T cell-mediated hepatitis, and metastatic melanoma. In some of these disease models, capsase-1 deficiency is due to reduced IL-1β processing and secretion, but in others, it is due to reduced IL-18. Since the IL-33 precursor is also cleaved by caspase-1 into an active cytokine, it remains possible that lack of processing IL-33 into an active cytokine may contribute to the protection afforded caspase-1-deficient mice.

In humans, there are several severe systemic inflammatory diseases in which an increase in functional caspase-1 activity appears to play an important role. Increased release of processed IL-1β has been demonstrated in monocytes of patients with these diseases (Agostini et al., 2004; Hoffman et al., 2004), and treatment of affected subjects with IL-1 receptor blockade, neutralizing antibodies to IL-1β or the IL-1 Trap, returns affected patients to normalcy (Dinarello, 2005). Some of these diseases are inherited and the genetic defect results in a reduced capacity to control of activation of

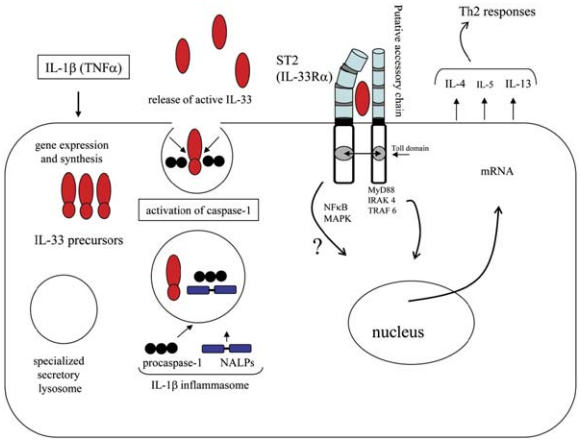

Figure 1. Production and Activity of IL-33 in the Generation of T_H2 Responses

Cytokines such as IL-1β (but also TNFα) stimulate responsive cells to synthesize IL-33. The initial translation product is the IL-33 precursor. Assuming that IL-33 is similar to the other two members of the IL-1 ligand family, IL-1β and IL-18, the IL-33 precursor enters the specialized secretory lysosome together with components of the IL-1β inflammasome (procaspase-1 and a member of the NALP family [Tschopp et al., 2003]). Following activation of caspase-1 via a potassium channel and calcium-dependent mechanism (Andrei et al., 2004), the IL-33 precursor is cleaved, the membrane of the secretory lysosome fuses with the cell membrane, and IL-33 is released as an active cytokine. Mature IL-33 binds to ligand binding ST2 (which may also be termed IL-33 receptor α chain, IL-33Rα). Again, assuming that IL-33R is similar to that of IL-1 and IL-18 receptors, a heterodimeric signalling complex is formed with a second accessory chain, the latter of which can be hypothesized to also be a member of the IL-1 receptor family. Alternatively, the IL-33 receptor may share such an accessory chain with those of IL-1 or IL-18. The cytoplasmic domain of ST2 contains the Toll-IL-1 receptor sequence, essential for signalling in members of the IL-1 receptor family. As described in the report (Schmitz et al., 2005), IL-33 binding to ST2 results in activation of MyD88, IRAK4, and TRAF6 as well as activation of NF-κB and MAPK (mitogen-activated protein kinases). The question mark in the figure indicates unknown signaling pathways that preferentially induce gene expression for T_H2 cytokines or alternatively suppress genes of Th1 cytokines. Transcription and translation of IL-4, IL-5, and IL-13 dominate in cells triggered by activation of ST2 and IL-33. These cytokines stimulate other cells that execute the immunological mandate for T_H2 responses to antigen. Structurally, IL-33 is related to IL-18, and IL-18 also evokes T_H2 responses (Nakanishi et al., 2001).

caspase-1 (Agostini et al., 2004). Regardless of the mechanism by which there is increased release of active IL-1β, it is now clear that IL-33 processing and secretion by caspase-1 must now be considered to contribute to these diseases.

Why? From the first report of the existence of ST2 (Bergers et al., 1994), a high level of expression of this receptor on mast cells has been a prominent finding. The T_H2 response favors antibody production, including IgE and IgG. Mast cell activation is associated with IgE and the clinical manifestations of skin rashes including urticaria (itchy hives). In fact, the clinical syndromes of the diseases due to increased caspase-1 activity often include skin rashes and/or urticaria. Most notably are the known inherited forms of these diseases such as familial cold-induced autoinflammatory syndrome (Hoffman et al., 2004) and Muckle-Wells syndrome (Hawkins et al., 2004). Patients with Schnitzler's syndrome have a gammopathy and chronic pruritic urticaria (de Koning et al., 2005); hyper IgD syndrome is also likely associated with poor control of caspase-1. In systemic onset juvenile idiopathic arthritis and adult onset Still's disease, for which the mechanism for increased release of IL-1β is not known, rashes characterize their clinical descriptions. Although each of these diseases respond to reducing the activity of IL-1β, IL-1β may drive IL-33 production (both being caspase-1 dependent), and it is IL-33 that likely mediates the T_H2 responses of these diseases (Figure 1).

Charles A. Dinarello
University of Colorado Health Sciences Center
Denver, Colorado 80262

Selected Reading

Agostini, L., Martinon, F., Burns, K., McDermott, M.F., Hawkins, P.N., and Tschopp, J. (2004). Immunity *20*, 319–325.

Andrei, C., Margiocco, P., Poggi, A., Lotti, L.V., Torrisi, M.R., and Rubartelli, A. (2004). Proc. Natl. Acad. Sci. USA *101*, 9745–9750.

Bergers, G., Reikerstorfer, A., Braselmann, S., Graninger, P., and Busslinger, M. (1994). EMBO J. *13*, 1176–1188.

Brint, E.K., Fitzgerald, K.A., Smith, P., Coyle, A.J., Gutierrez-Ramos, J.C., Fallon, P.G., and O'Neill, L.A. (2002). J. Biol. Chem. *277*, 49205–49211.

de Koning, H.D., Bodar, E.J., Simon, A., van der Hilst, J.C.H., Netea, M.G., and van der Meer, J.W.M. (2005). Ann. Rheum. Dis., in press.

Dinarello, C.A. (2005). J. Exp. Med. *201*, 1355–1359.

Hawkins, P.N., Lachmann, H.J., Aganna, E., and McDermott, M.F. (2004). Arthritis Rheum. *50*, 607–612.

Hoffman, H.M., Rosengren, S., Boyle, D.L., Cho, J.Y., Nayar, J., Mueller, J.L., Anderson, J.P., Wanderer, A.A., and Firestein, G.S. (2004). Lancet *364*, 1779–1785.

Leung, B.P., Xu, D., Culshaw, S., McInnes, I.B., and Liew, F.Y. (2004). J. Immunol. *173*, 145–150.

Nakanishi, K., Yoshimoto, T., Tsutsui, H., and Okamura, H. (2001). Annu. Rev. Immunol. *19*, 423–474.

Schmitz, J., Owyang, A., Oldham, E., Song, Y., Murphy, E., McClanahan, T.K., Zurawski, G., Moshrefi, M., Qin, J., Li, X., et al. (2005). Immunity *23*, this issue, 479–490.

Townsend, M.J., Fallon, P.G., Matthews, D.J., Jolin, H.E., and McKenzie, A.N. (2000). J. Exp. Med. *191*, 1069–1076.

Tschopp, J., Martinon, F., and Burns, K. (2003). Nat. Rev. Mol. Cell Biol. *4*, 95–104.