IL-13Rα2 Glycosylation Holds the Dance Card for Partnering with IL-13

IL-13 is no stranger to the asthma field, being an important regulator in type 2 immune responses and subsequent disease pathology (1, 2). It is part of a complex network of cytokines that contribute to a hyperresponse during allergic challenge. Thus, IL-13 is one of several leading molecules being studied to understand the role of cytokines in type 2–high asthma, which has sparked the development of biologics designed to block IL-13 or its effects. A simple PubMed search for "IL-13 and asthma" yields nearly 4,000 results. Although the consequences of IL-13 signaling through the IL-4Rα/IL-13Rα1 receptor complex, to which IL-4 can also bind with similar affinity, is now widely appreciated, little attention has been focused on the lesser-known IL-13Rα2 receptor. Often referred to as the "decoy receptor," IL-13 interestingly has an affinity for IL-13Rα2 that is 50 times greater than its affinity for its primary receptor complex!

Earlier findings that engagement of IL-13 with IL-13Rα2 attenuates IL-13 responses associated with type 2 inflammation have contributed to the reputation of IL-13Rα2 as a decoy receptor (3–5). More recently, however, newly described roles for IL-13Rα2, in which IL-13 signals through IL-13Rα2 to regulate a myriad of other cellular and tissue responses, have come to light. For example, in a bleomycin mouse model of lung injury, fibrosis mediated by TGF-β (transforming growth factor β) was shown to be dependent on IL-13Rα2, demonstrating signaling capacity for membrane-bound IL-13Rα2 (6). Adding another layer of complexity, IL-13Rα2 binds not only to IL-13 but also to another ligand—Chi3l1 (chitinase 3–like-1; YKL-40 in humans) (7). Together, these three components form a complex called the chitosome. Chitinase and chitinase-like proteins are major players in many processes, participating in antimicrobial host defense (8) and regulating MAPK/ERK (mitogen-activated protein kinase/extracellular signal–regulated kinase), PI3K/AKT, and Wnt/β-catenin signaling in the lung (7, 9, 10). These proteins are also involved in immunologic activities, including roles in type 1 versus type 2 inflammation, alternative macrophage differentiation, hyperoxia-induced injury, and apoptosis and pyroptosis (reviewed in Reference 11). Not surprisingly, like IL-13, Chi3l1 has also been shown to positively correlate with indices of inflammatory conditions, including asthma (12).

Although it has been shown that IL-13 and Chi3l1 do not compete for binding to IL-13Rα2 (7), how these binding activities are regulated remains unclear. In this issue of the *Journal*, He and colleagues (pp. 386–395) elegantly present findings that the *N*-linked glycosylation status of IL-13Rα2 is a critical determinant in this process (13). Using a number of *in vitro* approaches to alter the *N*-linked glycosylation status of IL-13Rα2 and a combination of human and mouse cell lines, as well as primary murine cells, they found that although IL-13 binding to IL-13Rα2 was diminished by the loss of *N*-linked glycosylation sites on IL-13Rα2, Chi3l1 binding to IL-13Rα2 was unaffected by this loss. They further provide evidence linking previously implicated cellular responses downstream of ERK and Akt activation, as well as stimulation of β-catenin initiated by Chi3l1 binding to IL-13Rα2 (7), to dependence on the absence of *N*-linked glycosylation of IL-13Rα2.

True to its reputation as a decoy receptor for IL-13, binding of IL-13 to IL-13Rα2, in turn, results in diminished effector responses, and *N*-linked glycosylation of IL-13Rα2 was necessary for this to occur. The next question that arises from this, then, is what factor is modulating the *N*-linked glycosylation pathway itself. Here, the authors show that in settings where the presence of Chi3l1 predominates in comparison with IL-13, catalytic components for the IL-13Rα2/*N*-linked glycosylation pathway are inhibited. Again, in contrast, *N*-linked glycosylation of IL-13Rα2 is increased in settings where IL-13 predominates, resulting in binding of IL-13 to IL-13Rα2 and the subsequent abrogation of type 2 responses. The lack of the availability of *in vivo* models to observe *N*-linked glycosylation limits our ability to extend these findings to clinical contexts. Nevertheless, taken altogether, these studies provide clues as to how the dynamic interplay between individual ligands, IL-13 and Chi3l1, and their cognate receptor, IL-13Rα2, may be regulated in specific disease conditions in which one ligand predominates over the other.

Overall, this builds on previous work showing signaling capabilities acting through IL-13Rα2. Not only does IL-13 have greater affinity for this receptor over IL-13Rα1, the authors here show that *N*-linked glycosylation of IL-13Rα2 determines the downstream signaling events that occur, regulated by the binding of IL-13Rα2 to either IL-13 or Chi3l1, depending on which ligand predominates. This raises the immediate next question of how this finding fits into the paradigm of IL-13 binding to its primary receptor complex, IL-13Rα1/IL-4Rα. Intuitively, one would expect that in a setting where Chi3l1 predominates, binding of Chi3l1 to IL-13Rα2 would augment IL-13 effector responses activated by IL-13 binding to IL-13Rα1/IL-4Rα. It will be interesting to see how this knowledge can be harnessed to establish a therapeutic intervention in which *N*-linked glycosylation can artificially be enhanced on the decoy receptor IL-13Rα2 to disrupt IL-13 binding to IL-13Rα1/IL-4Rα, as well as Chi3l1 binding to IL-13Rα2, to dampen inflammatory responses and enhance apoptosis. ■

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