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Commentary

CD5L:p40, A Third Wheel To IL-12 and IL-23 Biology ?

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DESCRIPTION

IL-12 and IL-23 are disulfide-linked heterodimeric cytokines that share a common subunit IL-12p40. Both cytokines are predominantly secreted by myeloid cells with polarizing functions best studied on T cells, NK cells, and Innate lymphoid cells, driving type 1 and 17 responses. IL-12 was first discovered in 1989 [1] and was thought to be critical in driving autoimmune pathology, a function later attributed to IL-23 [2] leading to successful treatment of immune-mediated inflammatory conditions such as psoriasis and inflammatory bowel disease [3,4]. Despite the clinical successes, analysis of IL-12 and IL-23 biology continues to present paradoxical findings especially in different types of cancer and disease of the Central Nervous System (CNS) [5]. For example, IL-12 is protective against an experimental model of multiple sclerosis [6] but is pathological in models of Alzheimer's disease where no apparent IL-23 was present [7,8]. Although some of this phenomenon can be explained by regulatory function on diverse immune and non-immune cells such as regulatory T cells, neurons and keratinocyte [6,9-11], the possibility of a third p40 binding partner is tantalizing.

CD5L (previously referred to as CD5 like or Apoptosis Inhibitor of Macrophage [AIM]) was first discovered by Miyazaki and colleagues [12] in 1999 as a soluble factor secreted by macrophage and plays a critical role for inhibiting apoptosis of thymocytes. Wang and colleagues subsequently reported a role of CD5L in antagonizing IL-23 and protecting against T cell mediated neuroinflammation [13]. In an unbiased proteomics screen for IL-12p40 binding partner, CD5L emerged as the top binder of p40 in response to lipopolysaccharides in the absence of IL-12p35, with the resulting CD5L:p40 heterodimer presenting distinct but unknown biological function [14]. This interaction is independently validated by Wang and colleagues in a recent publication [15], in which they developed a neutralizing antibody and presented evidence supporting CD5L:p40 as a driver of type 2 immune responses in airway inflammation. At the cellular level, CD5L:p40 antagonizes the effect of IL-23 and instead induces IL-13 from T cells in a dual phosphatase dependent manner.

Similarly to IL-12 and IL-23, CD5L:p40 is predominantly secreted by myeloid cells, inducible by Toll-like receptor 9 ligand, alluding to its potential role in infection and autoimmunity. Expression or functional relevance of CD5L:p40 in human disease is not understood. High CD5L expression is associated with poor prognosis of human papillary lung adenocarcinoma [16] and bevacizumab-resistance and worse survival in ovarian cancer patients, [17] consistent with a pathogenic role in preclinical models. Conversely, CD5L is emerging as a promising protective agent against ischemic stroke [18], sepsis [19], and kidney disease [20]. Future studies aimed at differentiating the function of CD5L:p40 from that of CD5L monomer, IL-12 or IL-23 will be illuminating to the complex underlying biology.

CONCLUSION

The author remains cautiously optimistic about the discovery of CD5L:p40 and its unique function. Structurally distinct from IL-23p19 or IL-12p35, *CD5L* is a member of the scavenger receptor superfamily and how it interacts with p40 remains unresolved. A high-resolution crystal structure and identification of CD5L:p40 receptor(s) will be crucial for interrogating the relevance of this new heterodimer to human disease..

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