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Shabaana A. Khader and Shyamala Thirunavukkarasu

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# The Tale of IL-12 and IL-23: A Paradigm Shift

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Interleukin-12 was considered to be the driving force behind pathological conditions associated with several autoimmune disease models, including experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis, as well as models of ocular inflammation (1–4). However, the pioneering study by Cua et al. (5) in 2003 challenged this deep-rooted paradigm of the deleterious role of IL-12 and instead established that IL-23 was the main culprit mediating the pathological effects associated with autoimmune disease models in mice, a finding that has had a tremendous downstream impact on the field (this article is available at https://www.nature.com/articles/nature01355).

The enigmatic IL-12 family of cytokines comprises four members, IL-12, IL-23, IL-27, and IL-35, and displays both positive and negative regulatory roles in health and disease (6, 7). IL-12 was identified in 1989 as an NK cell growth factor and activator and, therefore, serves as a regulatory link between innate and adaptive immune responses (8). IL-12 is produced by innate cells, including macrophages and dendritic cells, and drives the differentiation of naive T cells into T helper type 1 cells producing IFN-γ (9). Although the function of IL-12 in driving Th1 responses is a protective feature in several intracellular microbial infection models (10–12), IL-12 gained notoriety as the cytokine promoting a wide variety of inflammatory responses associated with autoimmune diseases (13). In mice and humans, IL-12 is composed of the IL-12p40 subunit linked to the IL-12p35 subunit, and signals through the IL-12 receptor made up of IL-12Rβ1 and IL-12Rβ2 subunits (8, 14). Experimental studies demonstrated mice lacking IL-12p40 or the IL-12β1 receptor were more resistant in autoimmune models, including collagen-induced arthritis and EAE (15–18). Studies using neutralizing Abs to IL-12p40 in mouse models of inflammation further established that targeting IL-12 may be an attractive therapy for reducing the pathological conditions associated with autoimmune diseases (19).

In 2000, the status quo was challenged when IL-23 was discovered. This new cytokine, produced by dendritic cells and macrophages, is composed of IL-12p40, which pairs with a novel IL-23p19 subunit and signals through the IL-23R and the shared subunit IL-12Rβ1 (20). The pioneering study by Cua et al. generated mice lacking the IL-23p19 subunit, which would correspond to a lack of IL-23 only, although IL-12 function would be retained. Using the IL-23p19–deficient mice (IL-23p19$^{-/-}$) and comparing them with IL-12p35–deficient (IL-12p35$^{-/-}$) and IL-12p40–deficient (IL-12p40$^{-/-}$) mice, the authors specifically addressed the relative contribution of IL-12 and IL-23 in autoimmune inflammation. Although IL-23p19$^{-/-}$ mice exhibited normal Th1 differentiation and IFN-γ production, they did not develop EAE. In contrast, the IL-12p35$^{-/-}$ mice, which lack only IL-12, exhibited reduced Th1 generation and IFN-γ production but retained susceptibility to EAE. Consistent with an IL-23–specific role in driving inflammation associated with EAE, the IL-12p40$^{-/-}$ mice also exhibited resistance to EAE. Additionally, the authors demonstrated that IL-23 expression locally in the CNS reversed resistance to EAE in the IL-23p19$^{-/-}$ and IL-12p40$^{-/-}$ mice, confirming that downstream effects on induction of inflammation were indeed IL-23–dependent. These experiments, for the first time, provided experimental evidence that therapeutically targeting IL-23 rather than IL-12 would limit inflammation associated with autoimmune models.

Based on this landmark paper, the function of IL-23 was thought to be due to direct effects on myeloid cells, as microglial cells and inflammatory macrophages in the CNS expressed IL-23R during EAE but not at baseline. In turn, it was proposed that IL-23 induced proinflammatory cytokines, including TNF-α and IL-1β. Park et al. (21) further demonstrated that the IL-17–producing subset of Th cells mediated inflammation during EAE because IL-17–deficient (IL-17$^{-/-}$) mice recapitulated the EAE-resistant phenotype seen in the IL-23p19$^{-/-}$ mice. Following this, Harrington et al. (22) reported that IL-23 could induce naive CD4$^{+}$ precursors to differentiate into Th17 effector cells, especially in the absence of IFN-γ and IL-4. Subsequent studies have gone on to demonstrate that, in mouse models, IL-23 may not robustly promote Th differentiation, likely because IL-23R is not expressed on naive precursors (23–25), but TGF-β, IL-1, and IL-6 induce the expression of retinoic acid–related orphan receptor γ T in Th17 cells, which then promotes the expression of IL-23R and IL-17 (26). Thus, it is possible that IL-23 impacts the progression of autoimmune inflammation through both its effects on myeloid cell activation, as described in this innovative study, as well as by driving downstream Th17 responses.

The study by Cua et al. for the first time defined a specific role for IL-23, which challenged the long-held belief that IL-12 was key in driving pathologies associated with autoimmune

Department of Molecular Microbiology, Washington University School of Medicine in St. Louis, St. Louis, MO 63110

ORCID: 0000-0002-9545-4982 (S.A.K.).

Address correspondence and reprint requests to Dr. Shabaana A. Khader, Department of Molecular Microbiology, Washington University School of Medicine in St. Louis, Campus Box 8230, 660 South Euclid Avenue, St. Louis, MO, 63110-1093. E-mail address: sakhader@wustl.edu

Abbreviation used in this article: EAE, experimental autoimmune encephalomyelitis.



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diseases. Generation of the IL-23p19$^{-/-}$ mouse model and the results reported in this exemplary study spurred the intense interest that IL-23 has received as a therapeutic target for a number of autoimmune conditions in recent clinical trials. Indeed, at least 10 therapeutic agents targeting IL-23 and/or IL-12 (IL-23p19 or IL-12p40) or IL-17 are being tested in the clinic for immune-mediated pathologies. The importance of selective IL-23 targeting was one of the take-away messages from this seminal work by Cua et al. The recent clinical approval of mAbs against IL-23p19 for the treatment of plaque psoriasis, guselkumab and tildrakizumab, is a paragon for the importance of this therapeutic differentiation (27–29). Furthermore, discovery of the pathogenic effects of IL-23p19 subunit by Cua et al. initiated research into identifying other proinflammatory members of the IL-12 family that use the p19 subunit, such as IL-39, which also signals via IL-23R (30). In summary, the early discovery by Cua et al. propelled the evolution of this field over the past 15 y, including recent insights into the structural modifications of the p19 and p40 subunits that contribute to IL-23R activation (31).

## Disclosures

The authors have no financial conflicts of interest.

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