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INSIGHTS

IL-22: Immunity's bittersweet symphony

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Epithelial cells play a crucial role in barrier defense. Here, Moniruzzaman et al. (2023. *J. Exp. Med.* https://doi.org/10.1084/jem.20230106) discovered that interleukin-22 (IL-22) represses MHC class II expression by epithelial cells with an opposite impact on chronic inflammatory disease and viral infection.

Mucosal epithelial cells (ECs) act as physical and chemical barriers, separating the host from the environment (Grootjans et al., 2016). Despite being distinct anatomical cavities, intestinal ECs (IECs) and airway ECs (AECs) share many similarities (Wosen et al., 2018). First, they are polarized cells with distinct apical and basolateral membrane surfaces that face and respond to the lumen and engage host immune cells, respectively. Secondly, they are highly secretory cells that require a robust unfolded protein response (UPR) for managing the endoplasmic reticulum (ER) stress that emerges from their tissue-associated responsibilities (Burman et al., 2018; Kaser et al., 2008). Moreover, although not considered to be professional antigen-presenting cells (APCs), they have been long recognized to express major histocompatibility complex class II (MHC II) proteins since the pioneering studies of Bland and Warren (in the rat intestine) and Mayer and Shlien (in the human intestine) in the 1980s, which includes landmark papers in this journal (Bland and Warren, 1986; Mayer and Shlien, 1987). It is now clear that MHC II is constitutively expressed on IECs and AECs but becomes significantly upregulated in inflammatory and infectious diseases, whereupon it allows these barrier-associated cells to present antigens to $CD4^+$ T cells and guide their behaviors, often in a pathologic manner (Heuberger et al., 2021; Wosen et al., 2018). While cytokines such as interferon-γ (IFNγ), interleukin-27 (IL-27), and IL-18 are known to induce MHC II expression under homeostatic as well as pathologic conditions (Thelemann et al., 2014; Wei et al., 2020), the regulatory mechanisms that govern MHC II expression on ECs have been less well studied. In the current *Journal of Experimental Medicine*, Moniruzzaman et al. (2023) linked cytokine-mediated regulation of the UPR to the expression of MHC II on ECs. Here, they employed mouse models and organoids from human and mouse IECs and mouse AECs to show that IL-22 represses MHC II expression through its ability to ameliorate ER stress. Specifically, their studies revealed that IL-22 significantly restricts EC MHC II expression under conditions of homeostasis, inflammation, and infection with disparate consequences for the host depending upon the initiating event.

First, in line with earlier findings, Moniruzzaman et al. (2023) observed increased *Ciita*, a transcriptional master regulator of MHC II genes, and histocompatibility 2, class II antigen A (*H2Aa*) expression in AECs during murine pneumovirus (PVM) infection and IECs during dextran sulfate sodium (DSS)–induced chronic colitis, and primary *Muc2* gene mutation–induced colitis; the latter are so-called Winnie mice that develop spontaneous colitis due to the accumulation of misfolded mutant MUC2 proteins resulting in a pathologic ER stress response (Hasnain et al., 2013; Heuberger et al., 2021). Using germ-free and specific pathogen–free mice and intestinal and respiratory organoids, they further confirmed that microbiota and IFNγ induced MHC II expression in ECs. Secondly, they found lung and IECs in *Il22ra1*^{KO} mice exhibited upregulated MHC II expression compared to *Il22ra1*^{WT} mice under homeostatic conditions, suggesting IL-22 restricts MHC II expression. Thirdly, Moniruzzaman et al. (2023) administered recombinant (r)IL-22 to DSS-treated mice or Winnie mice. This treatment ameliorated body weight loss, EC proliferation, and decreased the diarrhea score; these beneficial changes further correlated with reduced MHC II and *Ciita* expression. Conversely, *Il22ra1*^{KO} mice displayed increased body weight loss and diarrhea scores during DSS treatment in association with upregulated MHC II and *Ciita* expression. These findings suggest that IL-22 could repress MHC II expression and ameliorate chronic colitis. Fourthly, to assess IL-22's function during infection, Moniruzzaman and colleagues treated mice with 20 or 100 ng/g rIL-22 2 d before PVM infection (Sikder et al., 2023). In contrast to the effects of rIL-22 in models

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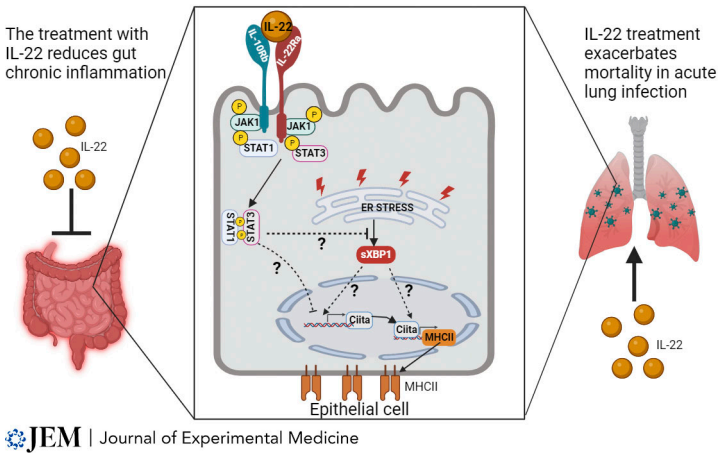

Dual role of IL-22 in immune response modulation. IL-22 exhibits a dual function, acting as both an anti-inflammatory cytokine during chronic gut inflammation and a pro-inflammatory cytokine during acute lung infection. The binding of IL-22 to the heterodimeric receptor complex IL-22Rα/IL-10Rβ initiates JAK-STAT signaling. In this pathway, phosphorylated STAT1 and STAT3 may negatively regulate MHC II expression by suppressing ER stress. Activated ER stress can lead to the upregulation of MHC II or *Ciita*, the critical transcription factor responsible for MHC II expression in ECs. Alternatively, phosphorylated STAT1 and STAT3 might directly inhibit the expression of *Ciita*, consequently downregulating MHC II expression. The question marks within the figure indicate speculative hypotheses, necessitating further direct experimental validation.

of intestinal inflammation, treatment with rIL-22 in the model of pulmonary infection increased the mortality rates and lung pathogenic scores in association with an upregulation of MHC II and *Ciita* expression. Interestingly, rIL-22 treatment on days 7, 8, and 9 after infectious exposure showed no effect on mortality or respiratory tract pathology. Finally, to explore IL-22's mechanism of controlling MHC II expression in ECs, Moniruzzaman et al. (2023) treated primary human bronchial ECs, lung organoids, and intestinal organoids with IFNγ, which increased ER stress marker genes, such as spliced-X-box binding protein 1 (*sXbp1*) and *Citta*. Further, they observed that treatment with rIL-22 could counteract IFNγ-induced upregulation of *sXbp1* and *Citta*. These observations are consistent with their own previous work that rIL-22 could restore IEC integrity by directly ameliorating ER stress (Gulhane et al., 2016). These results together indicate that IL-22 mediates the suppression of epithelial MHC II expression through ER stress inhibition.

The implications of these findings are extensive and critical to the field of mucosal immunity. These studies provide additional and important new insights into the role of IL-22 as a barrier protective factor in the gut. Unabated EC-associated ER stress plays an important role in initiating and propagating small and large intestinal inflammation. The studies here suggest that one mechanism by which ER stress induces inflammation is through the upregulation of MHC II on ECs, which potentially drives a pathologic T cell response that is opposed by IL-22 through down-regulation of an inflammatory cytokine (IFNγ)–induced UPR. It is also interesting to consider that as an ER stress response is quite common, even under homeostatic conditions in ECs, IL-22 may also be an important means to modify the consequences of this physiologic UPR and its consequences for engaging local regulatory or effector T cells. These studies also draw similarities with IL-10, which regulates MHC II on professional APCs and whose absence can be associated with intestinal inflammation (Wei et al., 2020). These studies are also consistent with those by Giacomin et al. (2015), who found that inhibitory κB kinase α EC knock-out mice, which display impaired IL-22 expression, are susceptible to *Citrobacter rodentium* infection–induced pathology and are protected by administration of rIL-22. Although the findings of Moniruzzaman et al. lend additional support to the use of rIL-22 as a promising therapeutic option for treating inflammatory bowel diseases (Mizoguchi et al., 2018; Wei et al., 2020), they also provide a cautionary note. Specifically, the presence of rIL-22 at the time of, but not after, an infectious exposure can significantly increase disease morbidity, possibly by suppressing a barrier-associated antiviral T cell response, as their data imply.

Although Moniruzzaman and colleagues provide compelling evidence and mechanistic insights into IL-22's pro- and anti-inflammatory functions under various conditions, some unresolved questions remain. For instance, Tamoutounour et al. (2019) have reported that IL-22 can promote MHC II expression by keratinocytes, which contrasts with the findings of the current study. These discrepancies may arise from differences in the mouse models used, cell types examined, and context (such as the presence or absence of ER stress) in the experiments performed. Further research to elucidate the underlying mechanisms responsible for these differences would be valuable and could shed light on the complex and context-dependent role of IL-22 in regulating MHC II expression. Direct evidence linking IL-22's impact on colitis and infection to its effects on EC MHC II expression would be valuable. Further investigations are warranted into the mechanisms underlying IL-22's differential effects between chronic inflammation and acute infections. Identifying specific targets to mitigate the adverse effects while harnessing the benefits of rIL-22 treatment could significantly advance future therapeutic strategies with this agent.

In conclusion, the study presented in this paper contributes significantly to our understanding of IL-22's dual role in homeostasis and disease conditions. This research has potential implications for developing targeted therapies in mucosal immunity that address both the pro- and anti-inflammatory aspects of IL-22 to improve disease management and overall patient outcomes.

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