

Steps in unraveling the mystery of chronic inflammation: TL1A

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What are the initiating factors in chronic inflammation? Are these factors also part of maintaining inflammation? After the introduction of biological treatment of rheumatoid arthritis (RA) and other chronic inflammatory diseases, these questions have become even more vital. The use of monoclonal antibodies directed against mediators of inflammation has revolutionized treatment strategies of several autoimmune diseases, but the diseases respond differently to each of the biologics used. In psoriasis, the IL-12/23-blocking ustekinumab is successfully used, but TNF blockers like adalimumab are only effective for approximately 40% of RA patients treated (adalimumab alone) [1]. When anti-TNF treatment proves unsuccessful, IL-6R blockers like tocilizumab can be applied, but still not all RA patients benefit from treatment. Other strategies involve targeting the cellular response of T cells (blocking CD28 or JAK signaling) or B cells (blocking CD20), and although the effect in some patients is very good, all of these treatments come with the risk of serious infection, because the immune system has been robbed an activation pathway. Our chance of making better drugs for RA treatment could be to address molecules upstream of cytokines like TNF or IL-6.

TL1A as a costimulator

TL1A is a recently described cytokine that is elevated in several autoimmune diseases, particularly in synovial fluid from RA patients [2]. When evaluating possible targets for RA treatment, it is important to consider whether molecules of interest are part of the initiating response, maintenance of inflammation

or both. In our recent study, we have shown that TL1A is able to directly induce IL-6 and TNF- α production in healthy human leukocytes without TCR stimulation [3]. TL1A costimulation further induced growth of several different innate lymphoid cells and although we could not detect the particular cell(s) that produced IL-6 after TL1A costimulation it is likely that these innate cells are involved in the production of IL-6. Our recent studies suggest that TL1A is a potent coactivator of effector CD4 T cells both with respect to specific cytokine production and expression of activating surface molecules [REICHWALD K, JØRGENSEN TZ, SKOV S, UNPUBLISHED DATA]. This indicates that TL1A might be involved in both initiation and maintenance of inflammatory disease.

However, the interesting question from a strictly scientific point of view is: what makes TL1A able to so profoundly change the response of otherwise healthy leukocytes? TL1A seems not to have any dramatic effects on leukocytes when administered alone; the strong inflammatory potential is only observed when TL1A is present together with other inflammatory cytokines (in our studies IL-12, IL-15 and IL-18). On the other hand, the combination of IL-12, IL-15 and IL-18 does not induce IL-6, but instead results in an IL-10 response [REICHWALD K, JØRGENSEN TZ, SKOV S, UNPUBLISHED DATA], clearly demonstrating the potency of TL1A signaling. This leads us to believe that we are looking at an ‘inflammatory fingerprint’ – a collection of stimuli that imprints and possibly overrules other signals, resulting in growth and massive cytokine secretion.



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TL1A as an effector trigger

We believe that TL1A provides a distinct type of stimulation that pushes cells towards an effector phenotype. In our case, IL-12 and IL-18 work in synergy to provide a strong NFκB signal, whereas IL-15 provides the common γ-chain signal, including STAT1/3/5 activation, which is important for lymphocyte activation, including several of the newly described innate lymphocytes. It is interesting to note that our studies suggest that IL-2 cannot replace IL-15 in TL1A-mediated IL-6 production [REICHWALD K, SKOV S, UNPUBLISHED DATA], we believe IL-2 could reprogram the lymphoid cells for other functions, however this scenario needs further investigation. TL1A likely activates AP-1 and p38MAPK through activation of the TRADD/TRAF2 pathway, inducing some of the key transcription factors needed for IL-6 production. Taken together, this collection of stimuli is sufficient to overrule regulatory mechanisms present, and induces a strongly inflammatory response in otherwise healthy leukocytes.

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TL1A may work as a general inflammatory cytokine in a pleiotropic way depending on the costimulatory signals present. In a recent study, Meylan *et al.* thus show that TL1A, overexpressed in transgenic mice, induces IL-13 production from type 2 innate lymphoid cells [4]. TL1A is not present in healthy individuals, and with its apparent innate effector potential we believe that it serves as an instant trigger to rapidly respond to immediate dangers. Moreover, because the effect of TL1A is dependent on the cytokines present, data suggest that a range of different lymphocytes can be regulated.

Delicate STAT balance

In a paper from 2012, Guo *et al.* summarize that a combination of an IL-1 family cytokine and STAT activation could be sufficient to induce cytokine secretion from different innate lymphocytes such as NKT cells, innate CD8 T-cells and γδ T-cells [5]. Although these cell types constitute only a small fraction of lymphocytes, they can produce large amounts of cytokines upon stimulation. All of these subsets of lymphocytes share certain similarities, in that many of them depend on RORγt to produce cytokines. However, Guo *et al.* propose that stimulation with an IL-1 family cytokine triggers a preprogrammed cytokine production, whereas the particular combination of STATs activated determines the actual cytokine profile. We propose that the TNF-homologous TL1A may

in a parallel way regulate innate cytokine expression from innate lymphoid cells depending on the signaling milieu present.

Managing the inflammatory response

This hypothesis leads to an interesting notion: if healthy lymphocytes can be ‘turned’ to become pro-inflammatory by a combined set of cytokine stimuli, should it not be possible to reduce activation or induce tolerance by blocking the activating cytokines or by facilitating suppressive cytokines or stimuli? We know that both pathogenic and nonpathogenic Th17 cells exist, and their development strongly depends on the cytokine environment in which they were activated [6]. STAT3 activation caused by cytokines such as IL-6 is further able to make effector T cells less responsive to Treg suppression [7], but what about the opposite effect? Given the plasticity described in recent years for particular T-cell subsets [8–10], should it not be possible to induce suppressive cytokines or re-establish sensitivity towards Tregs? In their studies from 2009 and 2011, Goodman *et al.* described the effect of IL-6-mediated STAT3 signaling in Treg suppression [7,11]. They showed that STAT3 phosphorylation mediated by IL-6 has profound effects on both Teffs and Tregs. While stimulated effector cells become less susceptible to Treg suppression, Tregs lose their ability to suppress Teff growth. The effect is specific for IL-6 in that other STAT3 activators such as IL-27 do not inhibit Treg suppression. The authors suggest that this difference is because the ratio of STAT3:STAT1 activation is much higher for IL-6 than for IL-27, which fits with the idea that the cytokine-induced STAT profile mediates differentiation/effector programming of the cells.

Conclusion & future perspective

Evolution spent quite some time fine-tuning our immune system, so maybe we should be using it more actively in our search for new treatment. In our pursuit of the next target for RA treatment, we might be too focused on the inflammatory mediators. It could be that other combinations of cytokines are able to reverse the effects of chronic inflammation, inducing a state of tolerance or suppression of inflammation. If we could modulate the immune system using its own mechanisms, we might be able to treat patients without reducing their chance to fight pathogens. A treatment like that would be an absolute game-changer in the treatment of diseases like RA, since the immune system itself would no longer need to be suppressed.

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