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COMMENT

Targeting immune checkpoints in juvenile idiopathic arthritis: accumulating evidence

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Chronic inflammatory diseases are characterized by inflammatory attacks in tissues mediated by autoreactive T cells, but their exact properties are still a matter of study. Recently, the role of immune checkpoints (IC) on T lymphocytes is gaining importance, and an article by Sag et al.[1] has explored this subject in patients with juvenile idiopathic arthritis (JIA).

JIA is the most common chronic rheumatic disease of childhood, and T cells are among the major drivers of the disease and are considered one the main potential targets for therapy. In this context, T cells infiltrating the affected joints have been investigated both at cellular and molecular level.[2,3] The T cell infiltrate is predominantly characterized by the presence of IFN-γ-producing Th1 cells or IL-17-producing Th17 cells.[2] For this reason, efforts have been spent to define which T cell subset has the primary pathogenic role in JIA, but the discovery that Th17 cells may convert to Th1 during chronic inflammation suggests that both cell subsets may have a pathogenic role.[4] In line with this, it has been demonstrated that Th1 cells can promote leukocyte retention in inflamed joints,[5] while Th17 cells can induce cartilage degradation by synovial fibroblasts.[6]

IC are part of a family of surface receptors expressed on immune cells with the ability to provide positive or negative signals that ultimately affect T cell activation status. Positive IC such as CD28 are expressed by resting T cells and are engaged by their ligands expressed on antigen-presenting cells at the immune synapse during the antigen recognition process, while inhibitory IC are commonly upregulated following T cell activation and in the course of chronic inflammation, to restrain T cell responses and avoid tissue damage. Inhibitory checkpoints such as CTLA4, PD-1, TIM-3, and LAG-3 represent a powerful tool to down-regulate T cell responses when the antigen has been eliminated. The demonstration of the importance of IC in maintaining the homeostasis of the immune system also comes from the observation that germline inactivating mutations in the CTLA4 gene lead to aberrant immune responses with increased frequency of autoinflammatory events.[7]

In recent years there has been a fine characterization of the biological function of several IC, and this advancement has led to the development of novel therapeutic strategies for cancer treatment based on the neutralization of IC activity with specific monoclonal antibodies. Indeed, blocking IC with inhibitory functions has demonstrated to be a powerful tool to reactivate the suppressed anti-tumor immunity in different types of cancer.[8] Interestingly, a side effect of this type of treatment is loss of self-tolerance and development of autoimmunity. While the role of immune checkpoints has been extensively investigated in the context of chronic infections and cancer, there is paucity of data in the field of chronic inflammation where delivering an inhibitory signal or blocking a stimulatory signal to achieve immune suppression can be fundamental.

The observation that T cells, independently of their cytokine production, express IC following activation may open the way towards new therapeutic approaches. The article by Sag et al. in this issue[1] is a first step in this direction. Previously, an overrepresentation of PD-1^{+}CD8^{+} T cells had already been found in the synovial fluid of JIA patients.[9] In the same study the authors identified PD-1^{+}CD8^{+} T cells as metabolically active effectors, and postulated a targeting strategy against this T cell subset. Sag et al. demonstrated instead that memory CD4+ T cells derived from the synovial fluid of patients with oligoarticular JIA express significantly higher levels of the IC CTLA-4, PD-1, LAG-3, and TIM-3 when compared to T cells in peripheral blood. Moreover, the authors suggested that LAG-3 may be involved in the regulation of cytokine production. Indeed, targeting LAG-3 could modify cytokine production in an in vitro co-culture model. Of note, oligoarticular JIA is different from adult rheumatoid arthritis (RA), and the authors point out some differences between what found in their study and what has been described in patients with RA (where CTLA-4 and PD-1 were reported to be more important than LAG-3 and TIM-3). Even if synovial inflammation is similar in the two diseases, there might be differences that are yet to be studied. The experimental disease model established in this study will likely be useful for the identification of potential therapeutic targets. There are however some points that need to be underlined. First, the number of patients included was quite small; second, only a subset of T cells were analyzed; and third, only MCP-1, IFN-gamma, and IL-2 were measured in the supernatants. Moreover, inhibitory receptor levels did not correlate with clinical and laboratory parameters and, as the authors pointed out, there was great individual variation regarding the expression of specific inhibitory receptors. These preliminary observations need therefore to be confirmed in independent reports by other groups both in animal models and in human samples, but the possibility to target simultaneously all overactive T cell subsets is appealing. Supporting this hypothesis, it has been demonstrated that PD-1 expression is a common feature of two distinct subsets of CD4

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T cells with different effector capacities but both with the potential to promote inflammation in JIA.[3] Ideally, IC could be therapeutically approached using agonist antibodies that may drive inhibitory signals on T cells, thus favoring the suppression of pro-inflammatory cytokines production. Antibody binding on cell surface may also promote pathogenic T cell elimination via antibody-dependent cell cytotoxicity (ADCC). In line with this, an IC-targeting drug, i.e. abatacept, is already approved and available in clinical practice. Abatacept is a chimeric fusion protein composed of CTLA-4 linked to the Fc of IgG. It acts via binding to CD80 and CD86 on antigen-presenting cells, thus preventing T cell costimulation and final activation, but does not induce ADCC.[10] It has been shown that it can improve symptoms and parameters of inflammation in JIA, suppressing IFNγ and TNFα production by T cells and their proliferative response.[11,12] Taking into account all these considerations, T cell suppression by targeting IC seems a promising therapeutic strategy. Additional studies are surely needed to understand the biology of IC in inflammatory diseases, including JIA. It is mandatory to understand the kinetics of IC expression in chronic inflammation, and if different subsets of T helper cells with different pathogenic potential can be identified by the combined expression of different types of IC. This may also lead to define therapeutic strategies simultaneously targeting multiple IC, in order to maximize the suppression of pathogenic T cells at sites of inflammation.

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COMPETING INTERESTS

The authors declare no competing interests.

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