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A helping hand against autoimmunity

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Abstract

The TH17 helper cells of the immune system have a dark side: they mediate autoimmune disorders. Two drugs that prevent the differentiation and activity of these cells might be of therapeutic value.

Immune cells called T-helper cells are the subject of intense research. In particular, one type, the TH17 cell, which produces a cytokine called IL-17, not only participates in host defence against pathogens, but is also implicated in the pathology of several autoimmune diseases, including multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease. The cells are therefore potential drug targets for treating such disorders. Research published in this issue[1,2] describes two compounds that inhibit the differentiation of TH17 cells and the production of IL-17. This delays the onset and reduces the severity of experimental autoimmune encephalomyelitis, a disease in mice that is mediated by TH17 cells and acts as a model for multiple sclerosis.

T-helper cells carry the CD4 molecule on their surface (CD4+ cells) and become active by interacting with antigen-presenting cells, which induce them to differentiate into effector CD4+ cells of various lineages. This differentiation of 'naive' cells is mediated by a lineage-specific set of cytokines and involves specific transcription factors. For TH17 cells, differentiation is promoted by the cytokines IL-6 and TGF-β, and the transcription factors involved include two nuclear receptors called RORα and RORγt (a subtype of RORγ)[3–5]. Loss of RORγt expression abrogates this differentiation and inhibits the production of IL-17 and other cytokines secreted by TH17 cells.

Given their role in TH17-cell differentiation, RORs are attractive targets for treating autoimmune diseases and other disorders with which they are linked, including allergen-induced airway inflammation (RORγ) and metabolic syndrome (RORα). Indeed, Huh *et al.* (page 486) and Solt *et al.* (page 491) now report that antagonist molecules that block the activity of these receptors have therapeutic potential (Fig. 1).

Huh and colleagues[1] used a chemical screen for ligands that could act as RORγ antagonists and identified digoxin, a member of a group of drugs called cardiac glycosides that are used to treat heart conditions. This chemical seems to be a RORγ-specific antagonist, as it did not affect the transcriptional activity of RORα or that of other nuclear receptors, including the liver X receptor (LXR). Of the other cardiac glycosides investigated by the authors, β-acetyldigoxin and dihydrodigoxin also significantly inhibited RORγ activity. This selectivity indicates that digoxin inhibition of RORγt is independent of the ligand's glycoside activity and of its binding affinity for a membrane ion pump involved in this activity[1].

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Using a different approach, Solt *et al.*[2] developed a synthetic ROR ligand called SR1001, a derivative of the benzenesulphonamide drug T0901317, which acts as an agonist of LXR and an antagonist6 of RORα and RORγ. SR1001 inhibited the activity of both RORα and RORγ, but did not affect the activity of other nuclear receptors, including LXR and RORβ.

The interaction between RORγt and either digoxin or SR1001 is probably direct. The transcription-factor activity of RORα and RORγ seems to be ligand dependent, and both digoxin and SR1001 compete for RORγt binding with 25-hydroxycholesterol — a molecule that binds to the ligand-binding domain of RORγ. Also, digoxin increased the thermal stability of the RORγ ligand-binding domain. Furthermore, when various amino acids in the ligand-binding pocket of RORγt were mutated, digoxin's ability to inhibit the activity of this receptor was reduced. Solt *et al.*[2] found that SR1001 binding induced a conformational change in the ligand-binding domain of RORα and RORγ that involved a repositioning of helix 12. This change resulted in a reduced affinity of the receptors for co-activator molecules and an increased affinity for co-repressors.

The investigators[1,2] also examined the effects of digoxin and SR1001 on naive T-cell differentiation into TH17 cells induced by IL-6 and TGF-β. Both compounds inhibited TH17-cell differentiation and the expression of genes encoding IL-17 and the IL-23 receptor (IL23R). The digoxin-induced changes in gene-expression profiles are similar to those observed in RORγ-deficient cells1, a finding consistent with the notion that digoxin exerts its effects by inhibiting RORγt activity. Previous studies[3,5] demonstrated that expression of either RORα or RORγ in T cells induces the expression of IL-17a. Huh *et al.* show that digoxin inhibits RORγ-dependent, but not RORα-dependent, induction of IL-17a. This result is consistent with the RORγ specificity of digoxin.

Treatment with digoxin or SR1001 greatly inhibited the expression of messenger RNAs for IL23R, IL-17a, IL-17f and IL-22, and markedly reduced production of the IL-17a protein[1,2]. RORγt regulates IL-17a and IL23R expression directly by binding to promoter sequences of the genes encoding these proteins[1,5] (Fig. 1). Treatment with digoxin or SR1001 significantly reduced the binding of RORγt to these sequences. These observations are consistent with the idea that the antagonists' binding causes a conformational change in the ligand-binding domain of the receptors that negatively influences their interaction with co-activators and promotes co-repressor recruitment.

SR1001 showed no obvious toxicity at the doses tested. Digoxin, however, was toxic for human cells at concentrations lower than those needed to inhibit RORγt. Huh *et al.*[1] therefore synthesized digoxin derivatives that retained the RORγt-antagonistic effects but were much less toxic in human cells. Intriguingly, in addition to inhibiting TH17-cell differentiation, these derivatives increased the expression of IFN-γ and FOXP3 in human CD4+ T cells; these are markers of two other T-cell types, TH1 and Treg cells, respectively. This finding suggests that inhibiting RORγt activity also promotes the differentiation of human naive T cells into other effector-cell lineages. By contrast, neither digoxin nor SR1001 affected the differentiation of mouse naive T cells into other lineages[1,2].

In mice, loss of RORγ greatly reduces the development of experimental autoimmune encephalomyelitis[3,5]. Both teams[1,2] demonstrated that treatment with either digoxin or SR1001 delays the onset of this disorder in mice and reduces its severity. This was associated with a reduction in the number of TH17 cells entering the animals' spinal cord. The investigators therefore propose that RORγt antagonists might be effective for treating autoimmune diseases. But first a number of caveats must be considered.

Apart from its expression in TH17 cells, RORγ is expressed in several other cell types and tissues, in which its function is unknown. It is therefore unclear what side effects long-term

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treatment might induce in these tissues. Moreover, as recently outlined[7], the role of TH17 cells and their associated cytokines is complex. So, although inhibiting RORγt may have therapeutic merit for autoimmune disease, it might adversely affect the beneficial functions of these cells in fighting pathogens. Despite these concerns, however, generating more-potent and more-selective derivatives of digoxin and SR1001 could offer attractive strategies for treating autoimmune disorders.

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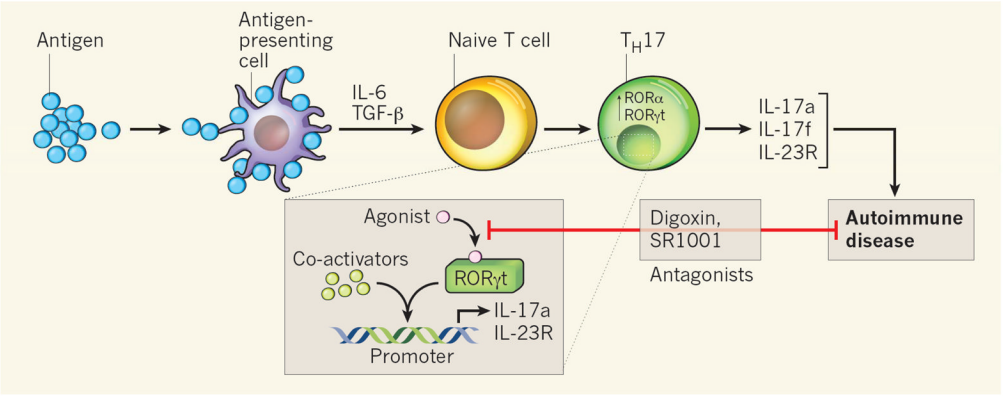

Figure 1. Effects of digoxin and SR1001 on TH17 cells

On encountering an antigen on the surface of antigen-presenting cells (and in the presence of IL-6 and TGF-β), naive T cells differentiate into TH17 cells. This event is associated with expression of the nuclear receptors RORγt and RORα. These receptors, particularly RORγt, are required for TH17-cell differentiation and for the expression of IL-23R and IL-17a, among other cytokines. Two studies[1,2] show that digoxin and SR1001 bind RORγt, possibly by competing with the natural agonists of these receptors. By inhibiting the recruitment of co-activators and promoting the recruitment of co-repressors, these antagonists reduce RORγt transcriptional activity, TH17-cell differentiation and IL-17 production, and delay the onset and reduce the severity of autoimmune disease in mice.