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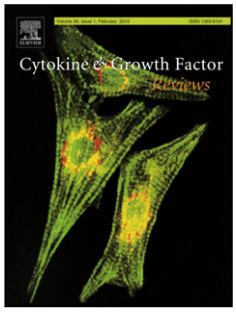

Title: Post-translational regulation of RORγt—A therapeutic target for the modulation of interleukin-17-mediated responses in autoimmune diseases

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<AT>Post-translational regulation of RORγt - a therapeutic target for the modulation of interleukin-17-mediated responses in autoimmune diseases

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<ABS-Head><ABS-HEAD>Graphical abstract
<ABS-P>► Post-translational regulation of RORγt

<ABS-HEAD>Highlights► RORγt is the master transcription factor of IL-17 expression and Th17 cells ► As a nuclear receptor, RORγt activity is also regulated in a ligand-dependent manner ► Multiple post-translational modifications, such as acetylation and ubiquitinylation, as well as interactions with various co-factors, modulate RORγt function

<ABS-HEAD>Abstract
<ABS-P>Retinoic acid-related orphan receptor gamma t (RORγt) is a nuclear receptor, which is selectively expressed by various lymphocytes. RORγt is critical for the development of secondary and tertiary lymphoid organs, and for the thymic development of the T cell lineage. RORγt has been extensively studied as the master transcription factor of IL-17 expression and Th17 cells, which are strongly associated with various inflammatory and autoimmune conditions. Given its essential role in promoting pro-inflammatory responses, it is not surprising that the expression of RORγt is tightly controlled. By its nature as a nuclear receptor, RORγt activity is also regulated in a ligand-dependent manner, which makes it an attractive drug target. In addition, multiple post-translational mechanisms, including post-translational modifications, such as acetylation and ubiquitinylation, as well as interactions with various co-factors, modulate RORγt function. Here we attempt a comprehensive review of the post-translational regulation of RORγt, an area that holds the potential to transform the way we target the RORγt/IL-17 pathway, by enabling the development of safe and highly selective modulators of RORγt activity.

<KWD>Keywords: retinoic acid-related orphan receptor gamma; nuclear receptor; interleukin-17; inverse agonist; ubiquitinylation; posttranslational regulation.