Epigenetic insights - Resminostat regulates targets associated with the pathogenesis of cutaneous T cell lymphoma (CTCL)

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Introduction

Cutaneous T cell lymphoma (CTCL) is a heterogeneous group of extra-nodal non-Hodgkin lymphomas arising from transformation and clonal expansion of skin-homing T cells. An imbalance between Th1/Th2 cells with a Th2 bias is discussed as a possible immune-related mechanism of pathogenesis. Furthermore, pruritus is one of the major symptoms affecting health-related quality of life (HRQoL) of CTCL patients and is associated with high levels of IL31 expression. Epigenetic alterations have been described in the context of CTCL pathogenesis.

Resminostat is a potent, orally bioavailable histone deacetylase (HDAC) inhibitor targeting class I, IIb, and IV, and is currently in phase II of clinical development. Resminostat showed anti-tumoral in vitro efficacy by inhibiting proliferation of CTCL cell lines. Here, we investigated the molecular mechanism of action of the HDAC inhibitor resminostat in CTCL in vitro using a genome-wide approach.

Epigenetic mode of action of the HDAC inhibitor resminostat in CTCL cell lines

➢ Resminostat increases global lysine acetylation
➢ Resminostat increases histone H3K27 acetylation on a genome-wide level in a dose-dependent manner

Resminostat broadly affects gene expression in CTCL cell lines

➢ HDAC inhibition by resminostat results in up- and down-regulation of gene expression

Conclusions from a genome-wide in vitro study of resminostat in CTCL

➢ Resminostat's effects are translated genome-wide in a dose-dependent manner
- HDACi resminostat increases histone H3K27 acetylation levels
- Significant modulation of gene expression with pleiotropic effects
- Regulation of both gene induction and repression

➢ Resminostat regulates genes associated with CTCL pathogenesis
- Modulation of genes associated with CTCL disease progression
- Switch from unfavorable Th2 to favorable Th1 gene expression
- Reduced expression of skin-homing receptors
- Inhibition of lurching mediator IL31

➢ Data support the clinical development of resminostat in CTCL in a maintenance setting
➢ Current phase II trial RESMAIN (Resminostat for Maintenance Treatment of Patients With Advanced Stage Mycosis Fungoides (MF) or Sézary Syndrome (SS); NCT02953301)


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