S1PR1 drives a feedforward signalling loop to regulate BATF3 and the transcriptional programme of Hodgkin lymphoma cells

ABSTRACT

The Hodgkin/Reed–Sternberg cells of classical Hodgkin lymphoma (HL) are characterised by the aberrant activation of multiple signalling pathways. Here we show that a subset of HL displays altered expression of sphingosine-1-phosphate (S1P) receptors (S1PR)s. S1P activates phosphatidylinositide 3-kinase (PI3-K) in these cells that is mediated by the increased expression of S1PR1 and the decreased expression of S1PR2. We also showed that genes regulated by the PI3-K signalling pathway in HL cell lines significantly overlap with the transcriptional programme of primary HRS cells. Genes upregulated by the PI3-K pathway included the basic leucine zipper transcription factor, ATF-like 3 (BATF3), which is normally associated with the development of dendritic cells. Immunohistochemistry confirmed that BATF3 was expressed in HRS cells of most HL cases. In contrast, in normal lymphoid tissues, BATF3 expression was confined to a small fraction of CD30-positive immunoblasts. Knockdown of BATF3 in HL cell lines revealed that BATF3 contributed to the transcriptional programme of primary HRS cells, including the upregulation of S1PR1. Our data suggest that disruption of this potentially oncogenic feedforward S1P signalling loop could provide novel therapeutic opportunities for patients with HL.

Keyword: Hodgkin lymphoma; Lymphoid; Sphingosine-1-phosphate (S1P); Sphingosine kinase 1 (SPHK1)