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ORIGINAL ARTICLE

Impact of histamine H4 receptor deficiency on the modulation of T cells in a murine breast cancer model

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Abstract

Background The histamine H4 receptor (H4R) is preferentially expressed in immune cells and is a potential therapeutic target for inflammatory and autoimmune diseases. This study aimed at further exploring the role of H4R in the immunobiology of breast cancer.

Methods We used wild type (WT) and H4R deficient mice (KO) to evaluate whether H4R genotypes show a different distribution of T cell subsets in spleens, tumours and tumour draining lymph nodes (TDLN) in a syngeneic ErbB2-positive breast cancer model developed orthotopically with LM3 cells and its impact on tumour growth.

Results The presence of tumours had a differential impact on the distribution of T cells in TDLN from KO mice compared to WT ones. At day 21 post-inoculation (p.i.) of cells, despite no significant changes in the tumour weight, TDLN from KO mice showed a significantly increased proportion of $CD8^+$ T cells compared to WT mice. At day 38 p.i. of cells a reduced tumour weight was evident in KO mice. This was accompanied by a decreased proportion of $CD4^+CD25^+FoxP3^+$ regulatory T cells in TDLN of KO compared to WT mice. Tumour-bearing KO mice showed a better survival compared to WT mice.

Conclusions H4R-mediated mechanisms may modulate the immune tumour microenvironment, promoting an immunosuppressive milieu. Results suggest that H4R could be explored as an immunotherapeutic target with potential benefit in combination with immunotherapy. Further preclinical and clinical studies are necessary to confirm this hypothesis.

Keywords Histamine H4 receptor · Breast cancer · Antitumour immunity · T regulatory cells

Introduction

Histamine [2-(1H-imidazol-4-yl)ethanamine] was the first inflammatory biogenic amine characterized and has been one of the most studied biological molecules in biomedicine with several pathophysiological functions. Histamine pleiotropic actions are exerted through the four subtypes of histamine receptors (HR) that have been identified: H1R, H2R, H3R, and H4R, all of them belonging to the family of G-protein coupled receptors [1, 2]. Histamine is a major mediator responsible for multiple regulatory responses of innate and adaptive immune systems [3, 4]. Since the discovery of the H4R at the beginning of the twenty-first century with preferential expression in immune cells, it has been described as a potential drug target for the treatment of inflammatory and autoimmune diseases [5, 6]. Most of the previous studies performed in H4R deficient mice show a key role of H4R in inflammatory responses [4, 7]. Although H4R antagonists have shown efficacy in reducing inflammation in different

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