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Role of TGFβ-1 Signaling in Epithelial Mesenchymal Transition Events Induced by Histamine H4 Receptor Agonists in Breast Cancer Cells †

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Abstract: In recent years, GPCR transactivation of serine-threonine kinase receptors like Transforming Growth Factor β Type I receptor (TβR1) has been reported. Several authors have described TGFβ-1 as a strong inducer of epithelial-mesenchymal transition (EMT) in various tumor cell lines. In this work, we proposed to study the relationship between histamine H4 receptor (H4R) activation and TβR1 signaling evaluating EMT traits (nuclear Slug, cell migration, stem cell enrichment) in breast carcinoma cells. MDA-MB231 and MCF7 cell lines were treated with H4 agonists and the selective inhibitor of TβR1 (A83-01) for 5 days. In both cell lines, H4 agonists (VUF 8430; JNJ28610244) produced a significant increase in pSMAD2/3 (canonical TβR1 efector) and Slug positive nuclei, determined by indirect immunofluorescence. There was also an increment in p-ERK1/2 levels (non-SMAD TβR1 signaling) and in both intra and extracellular TGFβ-1 levels assessed by immunoblot, as well as in cell migration and mammospheres number (stem cells surrogate assay). These increments were blocked when cells were pretreated with A83-01. Results indicate a possible interaction between TβR1 and H4R. Autocrine TGFβ-1 could play an important role in the EMT changes induced by H4 agonists in mammary tumor cells.

Keywords: H4 receptor agonist; Transforming Growth Factor β Type I receptor; epithelial-mesenchymal transition; breast cancer.

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Conflicts of Interest

The authors declare no conflict of interest.