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Histamine pivotal role in regulating mammary carcinogenesis

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We have previously reported that HA modulates proliferation of MDA-MB-231 breast cancer cells in a dose-dependent manner. The effect of 10 mM HA was associated with an induction of cell cycle arrest, differentiation and apoptosis. In the present work we analyzed the gene expression profiles using expression macroarray analysis and identified several genes in the angiogenic and survival pathways that are modulated by 10 mM HA in MDA-MB-231 cells.

HA markedly up-regulated expression of genes related to growth inhibition and apoptosis as INFβ; CDKN1C (p57); casein β; IL-4; WISP1 (25, 40, 29, 65, 83-fold, respectively). INFα,γ, BCL-XS, IL-4R, TNFSF10, PPARγ, seemed to increase but to a minor extent. Conversely, HA increased expression of genes linked to migration and angiogenesis like ADAMTS1,8; RNASE4; EDG1; ETS-1; FGF1,2,7; ITGB3; PDGFRB; THBS2; TGFA; COL1A1 (41, 84, 31, 42, 265, 9, 33, 40, 9, 24, 14, 30, 52-fold) while decreased the expression of TGFB3; TGFR1,2; TIMP-1; VEGFB. In addition, we investigated whether H_3R and H_4R were implicated in biological responses triggered by HA. Employing specific HA receptor agonists and antagonists we demonstrated that the positive effect on proliferation was exerted via the H_3R while the decrease in proliferation was mediated via the H_1R, H_2R, and H_4R. By using Transwell system we determined that HA induced MDA-MB-231 cell migration. This effect was mimicked by Imetit while was inhibited by Clobenpropit, suggesting that HA could stimulate cell migration via H_3R playing an important role in invasion and metastasis.

Present study, describes a dual role for histamine in tumorigenesis acting not only anti-oncogenically by reducing proliferation and increasing apoptosis and differentiation but also pro-oncogenically by stimulating proliferation and cell migration. It also suggests that H_3R may be involved in the regulation of breast carcinogenesis representing a novel molecular target for new therapeutic approach.