S100A4 is a target of relaxin-like peptide signaling and mediates some of the tumor promoting effects of relaxin and INSL3 in human carcinoma cells

Yvonne Radestock\textsuperscript{a}, Cuong Hoang-Vu\textsuperscript{a}, Sabine Hombach-Klonisch\textsuperscript{b}

\textsuperscript{a}Clinics of General, Visceral and Vascular Surgery, Magdeburger Str. 18, Martin-Luther-University Halle Wittenberg, 06097 Halle, Germany; \textsuperscript{b}Department of Human Anatomy and Cell Science, University of Manitoba, Faculty of Medicine, 130 Basic Medical Sciences, Winnipeg, MB, R3E 0W3, Canada. E-mail: hombach@cc.umanitoba.ca

The heterodimeric peptide hormones relaxin (RLN) and INSL3 and their cognate receptors RXFP1 and RXFP2 (relaxin-family-peptide receptors 1 and 2) are expressed in carcinoma tissues of the human thyroid. We have established RLN and INSL3 expressing transfectant cell clones of the human follicular thyroid carcinoma cell line FTC-133 (FTC-133/RLN and FTC-133/INSL3) and investigated their ability for migration and in-vivo tumor growth. Relaxin and INSL3 transfectants showed an increased cellular motility and in-vitro invasiveness compared to vector controls. This was associated with increased S100A4 protein levels and S100A4 secretion. Relaxin and INSL3 failed to increase cell motility after S100A4 siRNA knock-down suggesting S100A4 to be a downstream target of relaxin/relexin receptor (RXFP1) signaling and INSL3/RXFP2 signaling in thyroid carcinoma cells. In addition, the in-vivo tumor growth of FTC-133/RLN and FTC-133/INSL3 was increased and correlated with S100A4 protein expression. Microvessel density in RLN- and INSL3-expressing xenograft tumors was higher than in control tumors. We show that S100A4 initiates capillary tube formation in a Matrigel tube formation assay using human umbilical vein endothelial cells and suggest that extracellular S100A4 contributes to the increased vascularization of RLN- and INSL3 expressing tumors.

S100A4 is considered a molecular marker for the metastatic potential for thyroid and breast cancer with high prognostic significance. We show here that the relaxin/RXFP1 and INSL3/RXFP2 ligand-receptor signaling is a novel transcriptional regulator of S100A4 expression in human thyroid carcinoma cells and suggest that S100A4 mediates, in part, the relaxin- and INSL3-induced increase in cancer cell invasiveness, neovascularization and tumor growth.