Area 2: Pathogenetic mechanisms of microbially associated diseases

MODULATION OF GROWTH FACTOR RECEPTOR SIGNALING INDUCED BY THE EXPRESSION OF THE HPV16 E5 VIRAL ONCOPROTEIN.

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The E5 oncoprotein encoded by the human papillomavirus (HPV) type 16 transforms epithelial cells by deregulating cell growth, survival and differentiation through the modulation of growth factor receptors. Out-of-context and deregulated oncogenic signaling of the FGFs and their receptors have been shown to play a role in the pathogenesis of different types of cancer and in tumor progression. Dysregulated expression and activity of TGFβ□TGFβRI/II□and SMADs have been also frequently described in human cancer in association with tumor progression. Therefore, it is possible that, in early infection and in the context of low-grade and high-grade lesions, HPV16 E5 might exert its oncogenic activity through modulation of FGF and TGFβ signaling. At the light of our recent demonstration of a functional crosstalk among 16E5 protein and KGFR/FGFR2b, aim of our research project will be to investigate the effects of 16E5 expression and expression/signaling of growth factor receptors, focusing in particular on FGFR2 epithelial and mesenchymal isoforms and on TGFβRII. We plan also to identify the molecular mechanisms and pathways linking dysregulated growth factor signaling and altered receptor expression to viral infection. Specific aims of the project will be: a) to analyze the modulated expression in vitro of FGFR2b/FGFR2c and TGFβRII in 16E5-expressing cellular models as well as in lesional tissues; b) to identify the molecular mechanisms and signaling pathways linking 16E5 with the altered receptor expression and cellular response; c) to evaluate the possible role of 16E5 in the induction of epithelial-mesenchymal transition through FGFR isoform switching and dysregulated TGFβ signaling.

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