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HIF-1 α molecular stress pathway associates with the development of cervical carcinoma

Abstract:

To understand the mechanism of cellular stress in different cell types of normal cervical epithelium and during different stages of cervical carcinoma, we analyzed the expression/methylation/copy number variation/mutation of HIF-1 α and its associated genes LIMD1, VHL and VEGF in disease-free normal cervix, adjacent normal cervix of tumors, cervical intraepithelial neoplasia, cancer of uterine cervix samples and CACX cell lines. Interestingly, in basal-parabasal layers of normal cervical epithelium, LIMD1 showed high protein expression, while low protein expression of VHL was concordant with high expression of HIF-1 α and VEGF irrespective of HPV-16 infection. Furthermore, there was significant concordance with the low promoter methylation of LIMD1 and high in VHL in the basal-parabasal layers of normal cervix. LIMD1 expression was significantly reduced while VHL expression was unchanged during different stages of cervical carcinoma. In different stages of cervical carcinoma, the expression pattern of HIF-1 α and VEGF was high as seen in basal-parabasal layers and inversely correlated with the expression of LIMD1 and VHL. Additional deletion of LIMD1 and VHL in CIN/CACX provided an additional growth advantage during cervical carcinogenesis through reduced expression of genes. We found that overexpression of HIF-1 α and its target gene VEGF in the basal-parabasal layers of normal cervix was due to frequent inactivation of VHL by its promoter methylation. Thus, it was evident that molecular signature of key regulatory genes of the HIF1- α molecular stress pathway affecting cell fate and cell survival in the proliferating basal-parabasal layers of normal cervical epithelium is maintained during the development of cervical carcinoma through additional methylation/deletion/sequence variation leading to poor prognosis of CACX patients.

Biography

Chandraditya Chakraborty has completed his PhD from Calcutta University in 2017 followed by postdoctoral studies from Dana-Farber/ Harvard Cancer Center and is presently a scientist at Dana-Farber Cancer Institute, Harvard Medical School. He is a recipient of NCI SPORE Career Enhancement Award and IMW Young Investigator Award and published several papers in impactful journals like Blood, gastroenterology etc.