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Raf Kinase Inhibitor Protein (RKIP) expression and function in human myometrium and leiomyoma

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Many growth factors been identified in human myometrium and leiomyoma and activate multiple signaling pathways in order to regulate major cellular processes, including proliferation and fibrosis which are linked to uterine leiomyoma development and growth. The Raf kinase inhibitor protein (RKIP) has emerging roles as regulator of multiple signaling networks including mitogen activated protein (MAP) kinase cascade, as well as interaction with glycogen synthase kinase 3 (GSK3). In our study, we aimed to investigate the presence of RKIP in human myometrium and leiomyoma as well as to determine the effect of locostatin (RKIP inhibitor) on extracellular matrix (ECM) production, proliferation and migration in human myometrial and leiomyoma cells. Myometrial and leiomyoma tissues were used to investigate the localization and the expression level of RKIP through immunohistochemistry and western blotting. Myometrial and leiomyoma cells were treated with locostatin to measure ECM expression by real time PCR, GSK3b expression by western blotting, cell migration by wound-healing assay and cell proliferation by MTT assay. We found that RKIP is expressed in human myometrial and leiomyoma tissue. Locostatin treatment resulted in the activation of the MAPK signal pathway (ERK phosphorylation), providing a powerful validation of our targeting protocol. Further, RKIP inhibition by locostatin reduces ECM components. Moreover, the inhibition of RKIP by locostatin impaired cell proliferation and migration in both leiomyoma and myometrial cells. Finally, locostatin treatment reduced GSK3β expression. Therefore, even if the activation of MAPK pathway should increase proliferation and migration, the destabilization of GSK3β leads to the reduction of proliferation and migration of myometrial and leiomyoma cells.

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Keywords

Myometrium; uterine leiomyoma; RKIP; locostatin; extracellular matrix; cell migration.