Aryl-hydrocarbon receptor-dependent alteration of FAK/RhoA in the inhibition of HUVEC motility by 3-methylcholanthrene

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摘要

Abstract

We previously demonstrated the antiproliferative and antiangiogenic effects of 3-methylcholanthrene (3MC), an aryl-hydrocarbon receptor (AhR) agonist, in human umbilical vascular endothelial cells (HUVECs). Herein, we unraveled its molecular mechanisms in inhibiting HUVEC motility. 3MC down-regulated FAK, but up-regulated RhoA, which was rescued by AhR knockdown. It led us to identify novel AhR binding sites in the FAK/RhoA promoters. Additionally, 3MC increased RhoA activity via suppression of a negative feedback pathway of FAK/p190RhoGAP. With an increase in membrane-bound RhoA, subsequent stress fiber and focal adhesion complex formation was observed in 3MC-treated cells, and this was reversed by a RhoA inhibitor and AhR antagonists. Notably, these compounds significantly reversed 3MC-mediated anti-migration in a transwell assay. The in vitro findings were further confirmed using an animal model of Matrigel formation in Balb/c mice. Collectively, AhR's genomic regulation of FAK/RhoA, together with RhoA activation, is ascribable to the anti-migration effect of 3MC in HUVECs.