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Metformin targets the GTPase Rac1 to inhibit prostate cancer cell migration

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Background

The anti-diabetic drug metformin has been shown to affect cancer cell metabolism [1,2] and to display anti-tumoral properties in numerous cancers [3,4], however, its role in the formation of metastases remains poorly documented. Cell migration is a critical step in the progression of prostate cancer to the metastatic state, the lethal form of the disease.

Results

We show here that metformin reduces the occurrence of metastases in an orthotopic metastatic prostate cancer cell model established in nude mice. As predicted, metformin hampers cell motility in PC3 and DU145 prostate cancer cells and triggers a radical reorganization of the cell cytoskeleton. The small GTPase Rac1 is a master regulator of cytoskeleton organization and cell migration. We report that metformin inhibits Rac1 GTPase activity by interfering with some of its multiple upstream signaling pathways, namely P-Rex1 (a Guanine nucleotide exchange factor and activator of Rac1), cyclic AMP and CXCL12/CXCR4, resulting in decreased migration of prostate cancer cells. Importantly, overexpression of a constitutively active form of Rac1 (Rac1-Q61L or Rac1-V12), or P-Rex1 as well as the inhibition of the adenylate cyclase were able to reverse the anti-migratory effects of metformin.

Conclusion

Our results establish a novel mechanism of action for metformin through Rac1 and highlight its potential anti-metastatic properties in prostate cancer.

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