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Indirubine-3-Monoxime Inhibits PDGF-Mediated Vascular Smooth Muscle Cell Migration

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During the pathology of atherosclerosis and restenosis, hyperproliferation and migration of vascular smooth muscle cells (VSMC) contribute to lumen loss of the vessel and neointima formation [1]. Drugs interfering with both, proliferation and migration of VSMC are therefore promising candidates for the treatment of vasculoproliferative diseases.

In one of our previous studies Indirubin-3-monoxime (I3MO) has been identified to inhibit VSMC proliferation *in vitro* as well as neointima formation *in vivo* [2]. I3MO specifically interfered with PDGF-BB-induced STAT3 phosphorylation without affecting other common early growth factor signalling pathways.

In this work we now investigated the influence of I3MO on VSMC migration. In order to trigger migration we used PDGF-BB (10 ng/ ml), the major migratory stimulus for VSMC, and assessed migration by employing transwell- as well as wounding assays. With both methods we consistently observed significant and dose-dependent inhibition of migration by I3MO with complete abrogation at 5 µM. Employing phalloidin staining in order to visualise the actin cytoskeleton we show that I3MO already impairs early cytoskeletal rearrangements upon PDGF stimulation, such as formation of stress fibres, membrane ruffles or filopodia. We were able to exclude an inhibitory activity of I3MO on the activation of the small GTPase Rac-1, one of the key regulators of cell migration. However, in consistency with the inhibitory activity of I3MO on STAT3 phosphorylation we found that I3MO inhibits expression of cytosolic phospholipase A2 (cPLA2), a STAT3 target gene and mediator of VSMC migration [3].

To summarize, we demonstrate that next to its antiproliferative activity against VSMC I3MO inhibits VSMC migration. Interference with the STAT3 – cPLA2 pathway is likely to contribute to the anti-migratory action of I3MO, but further studies are needed to elucidate the precise mechanism of action.

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