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Control of Lymphatic Remodelling by miR-132

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Abstract : Metastasis is the lethal aspect of cancer for most patients. Remodelling of lymphatic vessels associated with a tumour is a key initial step in metastasis because it facilitates the entry of cancer cells into the lymphatic vasculature and their spread to lymph nodes and distant organs. Although it is clear that vascular endothelial growth factors (VEGFs), such as VEGF-C and VEGF-D, are key drivers of lymphatic remodelling, the means by which many signaling pathways in endothelial cells are coordinately regulated to drive growth and remodelling of lymphatics in cancer is not understood. We seek to understand the broader molecular mechanisms that control cancer metastasis, and are focusing on microRNAs, which coordinately regulate signaling pathways involved in complex biological responses in health and disease. Here, using small RNA sequencing, we found that a specific microRNA, miR-132, is upregulated in expression in lymphatic endothelial cells (LECs) in response to the lymphangiogenic growth factors. Interestingly, ectopic expression of miR-132 in LECs in vitro stimulated proliferation and tube formation of these cells. Moreover, miR-132 is expressed in lymphatic vessels of a subset of human breast tumours which were previously found to express high levels of VEGF-D by immunohistochemical analysis on tumour tissue microarrays. In order to dissect the complexity of regulation by miR-132 in lymphatic biology, we performed Argonaute HITS-CLIP, which led us to identify the miR-132-mRNA interactome in LECs. We found that this microRNA in LECs is involved in the control of many different pathways mainly involved in cell proliferation and regulation of the extracellular matrix and cell-cell junctions. We are now exploring the functional significance of miR-132 targets in the biology of LECs using biochemical techniques, functional in vitro cell assays and in vivo lymphangiogenesis assays. This project will ultimately define the molecular regulation of lymphatic remodelling by miR-132, and thereby identify potential therapeutic targets for drugs designed to restrict the growth and remodelling of tumour lymphatics resulting in metastatic spread.

Keywords : argonaute HITS-CLIP, cancer, lymphatic remodelling, miR-132, VEGF
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