Endothelial cell metabolism in health and disease: impact of hypoxia

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Abstract:(600words)

In contrast to the general belief, endothelial cell (EC) metabolism has recently been identified as a driver rather than a bystander effect of angiogenesis in health and disease. Indeed, different EC subtypes present with distinct metabolic properties, which determine their function in angiogenesis upon growth factor stimulation. One of the main stimulators of angiogenesis is hypoxia, frequently observed in disease settings such as cancer and atherosclerosis. It has long been established that hypoxic signalling and metabolism changes are highly interlinked. In this review, we will provide an overview of the literature and recent findings on hypoxia-driven EC function and metabolism in health and disease. We summarize evidence on metabolic crosstalk between different hypoxic cell types with ECs and suggest new metabolic targets.Endothelial cells (ECs) line the vessels of the (cardio)-vascular systems and play a major role in maintaining oxygen and nutrient supply to all tissues in the body. Normal adult ECs remain largely quiescent in health, but can become rapidly activated in response to injury or pathological conditions, where angiogenesis (the formation of new blood vessels) is required to facilitate delivery of oxygen and nutrients to (hypoxic) tissues. Angiogenesis is governed by three main EC subtypes, which carry out specialized tasks in angiogenesis and EC function (Potente et al, 2011): migratory tip cells, which guide the growing vascular sprout in response to growth factors; stalk cells, which proliferate and elongate the sprout; and quiescent phalanx cells, identified by their cobblestone-like shape, which are present in established vessels and function to regulate vascular homeostasis and endothelial barrier function.

Biography: (200 words)

Brian W Wong was in Laboratory of Angiogenesis and Vascular Metabolism, Department of Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium, and the Laboratory of Angiogenesis and Vascular Metabolism, VIB Center for Cancer Biology, VIB, Leuven, Belgium, and he also published more than 10 articlesHer dissertation was “Seeking and Obtaining Help for Alcohol Dependence by Women who have Posttraumatic Stress Disorder and aHistory of Intimate Partner Violence.

About Research Topic: (200 words)

The most well-characterized activator of angiogenesis is the vascular endothelial growth factor (VEGF). VEGF receptor (VEGFR) 2 is the primary receptor mediating angiogenic signalling, whereas VEGFR1 has primarily been characterized as a decoy receptor (Meyer et al, 2006). VEGF

contains a hypoxia-responsive element (HRE), which is activated in situations of reduced oxygen availability, allowing hypoxic tissues to stimulate angiogenesis to restore oxygen and nutrient supply to hypoxic areas. In the resultant growth factor gradient, VEGF binds to VEGF receptor 2 (VEGFR2) on ECs and induces tip cell formation. Tip cells express delta-like ligand 4 (DLL4), which binds Notch receptors on neighbouring cells, inducing stalk cell formation. DLL4 signalling induces Notch-intracellular domain (NICD) to be cleaved in stalk cells, which then reprogramed the cell to produce VEGFR1 instead of VEGFR2. VEGFR1 has greatly reduced sensitivity to VEGF, thus ensuring stalk cell behaviour (Phng & Gerhardt, 2009). This interaction between tip and stalk cells is dynamic, and continuous cell shuffling from tip to stalk position ensures the most competitive cell, with the highest levels of VEGFR2, to be located at the tip of the sprout (Jakobsson et al, 2010). When two adjacent tip cells come in contact, they can fuse and a lumenized, perfused vessel is formed.

About Institution:(200 words)

Our focus is angiogenesis, the growth of new blood vessels, in health and disease. Abnormal blood vessel growth contributes to multiple disorders, including cardiovascular disease and cancer. Our ambition is to develop new therapeutic concepts and treatments given the urgent medical need to improve clinical anti-angiogenic therapy. To this end, we use a fundamentally distinct approach and pioneered the study of endothelial cell (EC) metabolism during angiogenesis, hypothesizing that targeting the metabolic "engine" of ECs would paralyze blood vessel growth and normalize tumour vessels. In addition, we are interested in unravelling the molecular basis of EC dysfunction and EC regeneration.

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