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The mitochondrial connection: Why blood vessels in wounds and tumors start sprouting

New Kashkar study shows: With high energy demand and under challenging nutrient conditions during tissue repair or tumor growth, mitochondrial respiration is crucial for the formation of new blood vessels

A team of scientists from the University of Cologne's CECAD Cluster of Excellence (Cellular Stress Responses in Aging-Associated Diseases) led by Hamid Kashkar has found that new sprouts of blood vessels during development, wound healing or tumor growth are controlled by cellular energy metabolism involving mitochondrial respiration. Mitochondria, also known as the cell's powerhouse, provide the organism with vital energy. The endothelial cells that build up a thin layer within the vessels utilize mitochondrial energy production, as shown in this study. Immunologist Kashkar and his team provide genetic evidence of the requirement for mitochondrial respiration during angiogenesis – the forming of new sprouts of vessels – and shed new light on the metabolic control of vascular formation during development, tissue repair and cancer.

The decline of mitochondrial activity in endothelial cells could play an important role in aging and aging-related diseases – but also in tumor growth – and could therefore become a focus for therapeutic treatments in future. The study 'Mitochondrial respiration controls neoangiogenesis during wound healing and tumor growth' was published in Nature Communication.

Blood vessels remain mostly quiescent throughout adult life, yet they possess the capacity to rapidly form new sprouts (neoangiogenesis) in response to injury or under pathological conditions, such as tumor growth, where additional blood supply is required. The inner surface of blood vessels is lined by a thin layer of endothelial cells with remarkable functional plasticity that can rapidly switch from a quiescent to a highly angiogenic state. This angiogenic switch has long been considered to be mainly controlled by vascular growth factors.

The Cologne research team studied the physiological role of mitochondrial respiration in blood vessels in cell cultures and mice. Kashkar's group showed that mitochondrial respiration is required for neoangiogenesis.

'We found that a blood vessel-specific blocking of mitochondrial function in mice results in embryonic lethality. In contrast, we could not detect any obvious change in adult mice without endothelial mitochondrial respiration. These mice, however, revealed slowed wound vascularization and healing and reduced tumor growth and angiogenesis,' explain Lars Schiffmann and Paul Werthenbach, the first authors of the study.

'The lack of mitochondrial activity in endothelial cells under normal conditions with low energy consumption does not primarily cause vascular alteration. In contrast, endothelial cells sprouting with high energy demand and under challenging nutrient conditions during tissue repair or tumor growth are highly dependent on mitochondrial function,' adds Hamid Kashkar .

The current study hypothesizes that the progressive decline of mitochondrial activity in aging and aging-associated diseases reduces angiogenesis and thereby the regenerative capacity of aging tissues. Independently thereof, the specific targeting of tumor blood vessels with mitochondrial agents could represent a valuable cancer therapy and should be explored in future.

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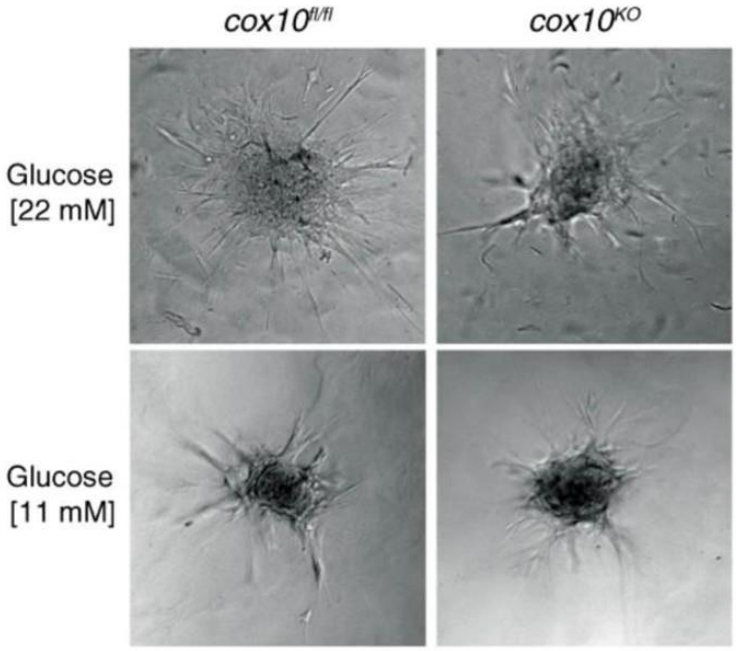

Representative bright field images of sprouting spheroids.