Karolinska Institutet

Institutionen för molekylär medicin och kirurgi

PATHOGENIC MECHANISMS BEHIND DYSREGULATED ANGIOGENESIS WITH FOCUS ON HIF AND IGF-I SIGNALING

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ABSTRACT

Angiogenesis is a complexly regulated process activated to assure cells with normal supplies of nutrients and oxygen. Playing such an essential role in the homeostasis of tissues, it is critical to understand its physiology and pathology to be able to design therapies for several diseases where angiogenesis is dysregulated (either excessive or diminished).
We aim to better characterize the angiogenesis during chronic complications of diabetes and tumors, focusing on the roles of two pathogenic factors common for both diseases: hypoxia inducible factor (HIF) and insulin-like growth factor (IGF).

Chronic complications of diabetes significantly increase the mortality and morbidity in patients with diabetes and lack for the moment efficient therapies. Hypoxia along with hyperglycemia has been relatively newly identified as a pathogenic factor for complications in diabetes. We have therefore investigated in our studies the cross-talk between hyperglycemia and hypoxia and we have demonstrated that cells fail to properly adapt to hypoxia due to repression of HIF's stability and function in the presence of high glucose. Moreover we have shown that hyperglycemia leads to HIF destabilisation through a VHL-mediated mechanism and complexly affects the HIF transactivation. In agreement with the *in vitro* data, we have detected repressed HIF in ulcers of diabetic mice. Local stabilization of HIF, either pharmacologically or by adenovirus mediated transfer, improves wound healing rate in diabetic mice, which indicates the pathogenic relevance of the hyperglycemia-induced HIF repression for diabetes complications. We further studied the consequences of the HIF repression in diabetes and identified that it is also responsible for increased mitochondrial radical oxygen species (ROS), which are essential for the development of chronic complications of diabetes. In consequence the stabilization of HIF is followed by normalization of ROS production, both *in vitro* and *in vivo*, even under the persistence of the high glucose concentrations.

In a third study we investigated the role of IGF-I for diabetic wound healing. IGF-I, a growth factor and regulator of angiogenesis, is secreted into the blood stream by the liver but also produced locally in the tissues. The relative contributions of local vs systemic IGF for wound healing is still unclear. This is even more relevant for diabetic wounds where reduced IGF-I levels were detected. We demonstrated here that liver-derived IGF-I does not affect wound healing in mice with or without diabetes. This indicates that local therapy with IGF-I is sufficient for improving wound healing in diabetes, avoiding the potential side effects of a systemic therapy.

Dysregulated angiogenesis is also essential for tumor development. Kaposi's sarcoma (KS) is a highly vascularized tumor and its biology is dependent on angiogenic stimuli. We demonstrated here that the vascularized phenotype characteristic for KS is highly dependent on the interplay between IGF-I and HIF. We showed that IGF-I induced accumulation of both HIF-1α and HIF-2α paralogues. IGF increased also HIF activity as demonstrated by the HRE reporter gene assay and by induction of VEGF (classic target gene of HIF). We have further described that IGF induces HIF accumulation by increasing the translation of the HIF-α subunits. The biological relevance of the HIF signaling in KS biology was highlighted by its expression through all the characteristic progressive stages of the disease. Moreover, we demonstrated that blocking the IGF-IR signaling decreases HIF accumulation and blunts the VEGF expression, offering a promising therapeutic option in the management of KS.

In conclusion, we identified new mechanisms of dysregulated angiogenesis in diabetes and tumors and proposed new therapeutic strategies based on our findings.

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