Inhibition of ALDH2 activity impairs angiogenesis

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Background

Maintenance of endothelial function is essential for the prevention and control of many diseases associated with deregulation of angiogenesis.

Like most cells, endothelial cells contain mitochondria, despite their having relatively little dependence on oxidative phosphorylation for ATP production. However, endothelial mitochondria are centrally involved in maintaining the fine regulatory balance between mitochondrial calcium concentration, reactive oxygen species (ROS) production, and NO. Recent findings have shown a prominent role of mitochondria in angiogenesis (Wilhelm et al., 2016). However, how mitochondria affect the angiogenic function of endotheial cells is unknown (De Bock et al., 2013).

Aldehyde dehydrogenases (ALDHs) are a family of NADP-dependent enzymes with common structural and functional features that catalyze the oxidation of a broad spectrum of aldehydes.

Experimental data from literature demonstrate that mitochondrial ALDH2 plays a role in tubulogenesis (Solito et al., 2010).

Aim

During the first 6 months of my PhD, I evaluate the role of mitochondrial ALDH2 activity on HUVEC pro-angiogenic functions.

Materials and methods

To investigate the role of ALDH2 activity on HUVEC pro-angiogenic functions, the contribution of ALDH2 activity on HUVEC sprouting and proliferation were investigated. Cells were pretreated with Daidzin, ALDH2 selective inhibitor, in the presence or absence of a branching mediator, and they were tested for their ability to migrate and growth using scratch assay and cell proliferation assay.

Results

First, I investigated the effect of ALDH inhibition on cell survival of HUVECs. In particular, I evaluated cell proliferation of HUVEC treated with Daidzin. The results show that Daidzin reduces cell proliferation. Similarly, Daidzin impairs cell ability to migrate. Together these data support my hypothesis that ALDH2 inhibition causes angiogenic dysfunction.

Future works

To measure the oxidative stress associated with ALDH2 activity, I will determine whether the lipid peroxidation-generated aldehyde, 4-HNE, accumulates following ALDH2 inhibition. In addition, the direct contribution of 4-HNE, in degradation of angiogenic growth factors by forming 4-HNE-adducts will be investigated. The HNE-protein adduct content will be measured using ELISA, and, specifically, the proangiogenic protein-adducts will be investigated by immunprecipitation and western blotting.

To insight into the molecular mechanism associated with ALDH2 activity, I will investigate the role of ALDH2 inhibition on the major pathways governing vessel branching. In particular the angiogenic growth factors, such as VEGF, FGF-2 and inhibitors expression and activity in presence/absence of Daidzin will be investigated using western blotting analysis and QPCR.

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