Göteborg, 2019

Energy metabolism and angiogenesis in atherosclerosis and cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Karl Isaksson, Medicinaregatan 16A, Göteborg, den 8 november, klockan 09:00

av Matias Ekstrand

Fakultetsopponent:
Docent Harry Björkbacka
Lunds universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. **Depletion of ATP and glucose in advanced human atherosclerotic plaques**
Ekstrand M, Widell E, Hammar A, Akyürek LM, Johansson M, Fagerberg B, Bergström G, Levin MC, Fogelstrand P, Borén J, Levin M.
PLoS One. 2017 Jun 1;12(6):e0178877. PMID: 28570702

II. **Imaging of Intracellular and Extracellular ROS Levels in Atherosclerotic Mouse Aortas Ex Vivo: Effects of Lipid Lowering by Diet or Atorvastatin.**
Ekstrand M, Gustafsson Trajkovska M, Perman-Sundelin J, Fogelstrand P, Adiels M, Johansson M, Mattsson-Hultén L, Borén J, Levin M.
PLoS One. 2015 Jun 22;10(6):e0130898. PMID: 26098110

III. **Intussusceptive angiogenesis in malignant melanoma**
Ekstrand M, Pandita A, Bjursten S, Ekelund E, Fogelstrand P, Le Gal K, Nilsson J, Ny L, Johansson I, Bergö M, Akyurek LM, Levin MC, Boren J, Ewald AJ, Mostov K, Levin M.
Manuscript

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Energy metabolism and angiogenesis in atherosclerosis and cancer

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Abstract

Energy metabolism requires supply of glucose and oxygen. In atherosclerotic plaques and cancer tumors, there are local areas with mismatch in demand and supply of oxygen and nutrients. The resulting cellular energy imbalance may promote energy failure and stimulation of angiogenesis.

In the first paper, energy metabolites were analyzed in human atherosclerotic plaques using high-resolution bioluminescence imaging. Advanced plaques were deficient in ATP and glucose, whereas lactate accumulated. ATP and glucose deficiency was most pronounced in macrophage-rich areas adjacent to the necrotic core. ATP depletion may promote necrotic core expansion and progression from stable to unstable plaques.

In the second paper, reactive oxygen species (ROS) production was studied during the development of atherosclerosis in mice. Intracellular ROS levels increased before lesions were visible, suggesting that intracellular ROS promote initiation of atherosclerosis. In advanced atherosclerotic plaques, atorvastatin decreased ROS production in a lipid-lowering independent manner. The decrease in ROS may promote stabilization of plaques.

In the third paper, intussusceptive angiogenesis (IA) was demonstrated in human, but not mouse, melanoma metastases. IA may contribute to the growth of human melanoma metastases and help explain the poor effect of current anti-angiogenic drugs targeted to classic sprouting angiogenesis. We further demonstrated that MMP inhibition blocks IA *in vitro*.

In summary, this thesis provides evidence of energy deficiency in human atherosclerotic plaques, new insights into ROS distribution during atherosclerosis development, and finally, evidence of intussusceptive angiogenesis in human malignant melanoma metastases. These data may be used to further the research into better treatments of atherosclerosis and cancer.

Keywords: Energy metabolism, Hypoxia, Reactive oxygen species, Intussusceptive angiogenesis

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