“To be or not to be”

the importance and applications of EmPGI in alveolar echinococcosis

In her PhD thesis (2007-2010), Britta Stadelmann was working on the larval stage of the cestode parasite *Echinococcus multilocularis*, the causative agent of alveolar echinococcosis in humans and also animals. The disease is transmitted through fox faeces, and the incidence of alveolar echinococcosis in this country, and in Europe as a whole, has been steadily increasing. In Switzerland, this has been attributed to the increase in the fox population.
Alveolar echinococcosis represents a serious and fatal disease, if not treated appropriately, and treatment still poses a problem in terms of drugs that are available, treatment duration, and efficacy. The parasite invades the liver, and exhibits tumor-like growth and proliferation, which causes compression of the neighbouring tissue, with possible metastasis formation in other organs at a later stage of the disease. The disease remains often unnoticed until first clinical symptoms occur. Thus, one of the still open questions concerns the mechanisms of the parasite-host interplay, and most notably: how does the parasite ensure its survival as it establishes itself within a relatively unfriendly environment with a potent immune system ready to eliminate potential intruders?

In her thesis project, Britta Stadelmann identified a protein that is incorporated into the laminated layer, and is one of the candidate proteins that could play a key role ensuring parasite survival. This protein is named *E. multilocularis* phosphoglucose isomerase (EmPGI), and it was exploited during her thesis, (i) in terms of its functional relevance and potential importance (“to be”) and (ii) in terms of applications of this protein to combat the parasite using drug screening assays (“not to be”).

(i) Britta Stadelmann identified a classical moonlighting protein in *E. multilocularis* metacestodes **(Stadelmann et al., 2010a)**. Moonlighting proteins are proteins with numerous, non-related functions. EmPGI, classically known as a glycolytic enzyme, was characterized by molecular, immunological and enzymatical means, identified in different fraction of *E. multilocularis* metacestodes, and besides its functional activity in glycolysis, Britta Stadelmann showed that this protein stimulates the proliferation of mammalian endothelial cells, but not of fibroblasts or hepatocytes. Thus, EmPGI could be one of these factors that induces angiogenesis around the developing metacestode. In addition, EmPGI also induces replication of cultured *E. multilocularis* cells, pointing towards an intrinsic function in cellular proliferation/development as well. This mirrors the situation in cancer cells. Vaccination of mice with recombinant EmPGI and challenge-infection with *E. multilocularis* metacestodes resulted in severely reduced parasite growth, underlining the importance of this protein in the host-parasite interplay.

(ii) EmPGI is also a prominent component of the metacestode vesicle fluid, and although exported and incorporated into the laminated layer, this protein is not secreted by intact metacestodes in a soluble form. Britta Stadelmann exploited this property of EmPGI for the development of a novel *in vitro* screening assay, based on the release, or leakage, of EmPGI, into the surroundings of the dying metacestode **(Stadelmann et al., 2010b)**. This standardized assay, which measures EmPGI activity in medium supernatants of

drug-treated *in vitro* cultures now allows to perform high-throughput screening of a larger panel of potentially interesting drugs. Two additional papers report on the application of this assay for the identification of chemotherapeutically interesting drugs. In one study, mefloquine and its anti-echinococcal properties were investigated *in vitro* as well as *in vivo* in the mouse model **(Küster et al., 2011; Stadelmann et al., 2011)**. Another paper **(Stadelmann et al., 2011)**, reported on a series of pentamidine-derivatives with interesting *in vitro* properties. Lastly, two other published research publications dealing with anti-echincoccal chemotherapy (thioureides and artemisinin-derivatives, **(Müller et al., 2009; Spicher et al., 2008)**), and two reviews **(Hemphill et al., 2010, 2007)**, which are co-authored by Britta Stadelmann, illustrate the use of *E. multilocularis in vitro* and *in vivo* models in the assessment of chemotherapeutically interesting components.

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