Basic information

Entosis is a form of a non-apoptotic cell death in which one cell invades the neighboring cell, resulting in a cell-in-cell structure and the ultimate death of an internalized cell. This effect is frequent in tumors and its role is elusive. The described entosis-inducing factors include matrix detachment, starvation and mitosis. That last factor suggests that entosis may be a mechanism of removing highly proliferating early-tumor cells from the epithelial layer, and thus, it would have a tumor-suppressing role. Our group obtained new results, showing that anti-apoptotic HAX1 protein, the main object of our studies, has a role in entosis. Thus, in this project, we propose to resolve this role and the molecular mechanisms behind it. This assumption is in line with our previous reports in which we have demonstrated that HAX1 is overexpressed in breast cancer and that it is an independent risk factor for breast cancer metastasis. Concurrently, we aim to elucidate some basic mechanisms of entosis, like the role of cell-cell junctions and the involvement of septins.

Preliminary research

This project is based on the preliminary data pointing to the role of the HAX1 protein and septins (cytoskeletal proteins) in the regulation of entosis in adherent breast cancer cells. As shown by my group, HAX1 status affects cell-cell junctions and actomyosin contractility. We have also reported HAX1 interaction with different septins, which may be important for the regulation of entosis. Septins have been shown to sense the curvature of the membrane, and this ability may be crucial for the elimination of the round, mitotic cells by entosis it the same way as these proteins entrap dividing bacterial cells. Thus, septin participation may provide an explanation of the mechanism of entosis. The rationale behind this mechanism may be the elimination of highly proliferating, round, mitotic cells in early cancerous lesions.

Research proposal

Proposed experiments should resolve several issues: what is the role of cell-cell junctions in entosis, if septins are really involved in the mechanism of entosis and what is the role of HAX1 in the regulation of septins. They should also resolve the question what is the role of entosis in tumor progression (in the mouse model).

Significance of the project

In this project it is proposed how to link all the above mentioned factors and interacting proteins together in one, coherent mechanism of entosis regulation. There is an ongoing discussion if cancer progression is linear (the tumor acquires metastatic potential gradually) or parallel (the dissemination takes place early on and both, primary and secondary lesions evolve independently). In breast cancer accumulated evidence support parallel progression model, which makes everything what happens at early stages particularly important. Entosis, as a factor in eliminating cancerous cells in early, pre-clinical stage could be the key factor in metastasis, therefore, the more we know about its mechanisms the better are our chances to combat cancer metastasis, which is the main cause of cancer death.