Investigating the role of ribosome hibernation and activation during cancer cell dormancy and relapse

Bertram Daum, Steffen Scholpp, Ke Li

Cancer relapse often arises from a small population of tumour cells that enter a dormant, non-proliferative state and evade therapy for years or even decades. Despite the clinical importance of cancer dormancy, the molecular mechanisms that allow tumour cells to suppress growth while remaining viable are poorly understood. One potential mechanism is the regulation of protein synthesis through structural changes in the ribosome. In many organisms, ribosomes can enter inactive “hibernating” states during stress or dormancy, yet whether similar structural mechanisms operate in dormant cancer cells remains unknown. This PhD project will investigate the structural basis of translational shutdown in dormant tumour cells using cryo electron microscopy.

The project will employ two complementary and well-established experimental systems that capture key aspects of tumour dormancy. First, the T-HEp3/D-HEp3 carcinoma model provides one of the best-characterised mechanistic systems for studying true tumour dormancy. In this model, closely related cell lines display either aggressive tumour growth (T-HEp3) or stable dormancy (D-HEp3), allowing direct comparison of proliferative and dormant cellular states within the same genetic background. Second, the D2.OR breast cancer system models the clinically relevant balance between metastatic dormancy and outgrowth. In this system, cells can be experimentally switched between proliferative and dormant states depending on culture conditions: standard 2D culture promotes proliferation, whereas 3D culture induces a dormant phenotype. These states can be distinguished by growth behaviour and established dormancy markers.

Using these models, the PhD candidate will compare proliferating and dormant cancer cells at the structural level. Cells will first be characterised using growth assays and molecular dormancy markers to confirm their physiological state. Ribosomes will then be isolated from proliferating and dormant populations and analysed using state-of-the-art cryo-electron microscopy. High-resolution structures will be determined and interpreted with in-house developed AI-guided modelling approaches to identify structural changes, as well as novel hibernation factors associated with translational shutdown.

This work will reveal whether dormant cancer cells reorganise ribosomes or form inactive ribosomal assemblies consistent with translational hibernation. By identifying structural mechanisms that regulate protein synthesis in dormant tumour cells, the project aims to uncover a new layer of translational control in cancer biology and provide a potential route towards preventing tumour relapse.