Influence of oncogenic mutations on information transmission in the MAPK signalling pathway

Cell signalling pathways transmit and process extracellular signals, such as cytokine stimulation, and in response regulate internal physiological processes, such as proliferation, apoptosis or motility. We conjecture that pulsatile cytokine stimulation mode is physiologically most ubiquitous due to the local secretion and subsequent endocytosis of receptor-bound cytokines and that this stimulation mode allows to transmit information at the highest rate (measured as bits per hour for a single cell). We also hypothesize that oncogenic mutations diminish the capacity of the regulatory pathways to properly transmit signals. In the project we will focus on pulsatile stimulation and use information theory to analyse the impact of oncogenic mutations on signal transmission.

The main aim of the project is to determine the influence of two frequent oncogenic mutations, specifically G12V in kinase KRAS and H1047R in kinase PI3K on the information transmission rate in ERK and AKT pathways that regulate proliferation, apoptosis and motility. Preliminary data show that in cancer cells information transmission is compromised by the spontaneous onsets of activity of ERK and AKT that may stimulate unwanted proliferation, or protect damaged cells from apoptosis. We will thus analyse these spontaneous onsets of activity and verify whether they are correlated between neighbouring cells, which will indicate for extracellular cause of activation.

Experiments will be based on breast epithelial cell lines (MCF-10A) developed by our Swiss partner, Prof. Oliver Pertz. These lines have light activated growth factor receptors, which allow for application of nearly arbitrary temporal stimulation protocols mimicking *in vivo* stimulation. Additionally, activation of ERK and AKT can be observed in real time under confocal microscope thanks to the presence of fluorescent reporters that translocate between nucleus and cytoplasm in response to either ERK or AKT activation.

I our research we will use mathematical modelling involving partial differential equations, stochastic processes and information theory. We will develop two models. In the first model we will investigate activation of ERK and AKT pathways with subcellular resolutions. We will analyse formation of active membrane clusters of RAS (protein that transmits signals to ERK and AKT). Experimentally local activity of Ras will be measured by the other type of reporters introduced to cells. (2) in the second model we will investigate propagation of ERK activity waves across cell monolayer. These waves play role in the process of wound healing. In this model we will use agent-based modelling in which signalling between cells forming monolayer (agents) modifies their intracellular processes.

We hypothesise that oncogenic mutations, in addition to causing an overall increase in ERK and AKT activity, may render cancer less controllable by external signals. This can be an obstacle for therapies that aim only to reduce ERK and AKT pathway activation.