Impedance-based Characterization of pH-dependent Cell Behavior

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Changes in cellular behavior, caused by alterations of the extracellular pH, are of fundamental interest. Cells exhibit a characteristic pH gradient across their plasma membrane, which is different for different cell types and reveals differences in cell metabolism. It is known that certain cell behaviors are strongly dependent on a physiological extracellular microenvironment. Therefore acidification can lead to crucial changes regarding membrane-associated enzyme activities, ion transport activity, protein and DNA synthesis, and intracellular calcium levels [1]. Several phenotypic key features like proliferation, migration, respiration or wound healing efficiency have also been found to be pH-sensitive. It is noteworthy that differences in migration are closely linked to enhanced invasive and metastatic properties. Monitoring the speed of migration serves as an important experimental parameter to describe metastatic potential as well as to for screen drugs and toxins with respect to their impact on cell dissemination.

In our studies we used ECIS® to search for potential impacts of extracellular pH on (i) cell migration, (ii) proliferation and (iii) adhesion of normal rat kidney epithelial (NRK) cells as a model cell line.

(i + ii) NRK cells were grown to confluence, before they were incubated with buffers of varying pH value. The cells on the electrode were then killed by invasive voltage pulses. As the cells in the electrode periphery are not compromised, the electrode is repopulated in time by migration and proliferation of neighboring cells.

(iii) To study the pH-dependency of cell spreading, cells were suspended in buffers with the respective pH value, seeded on the electrodes and the time course of cell spreading was monitored.

We observed that healing as well as proliferation rates were strongly pH-dependent: with increasing pH value of the applied buffer, wound closure was observed to be faster. Lower pH values, in contrast, resulted in a drastically decreased healing and proliferation velocity, ultimately resulting in cell death. In contrast, cell spreading is only affected under severe extracellular acidification.

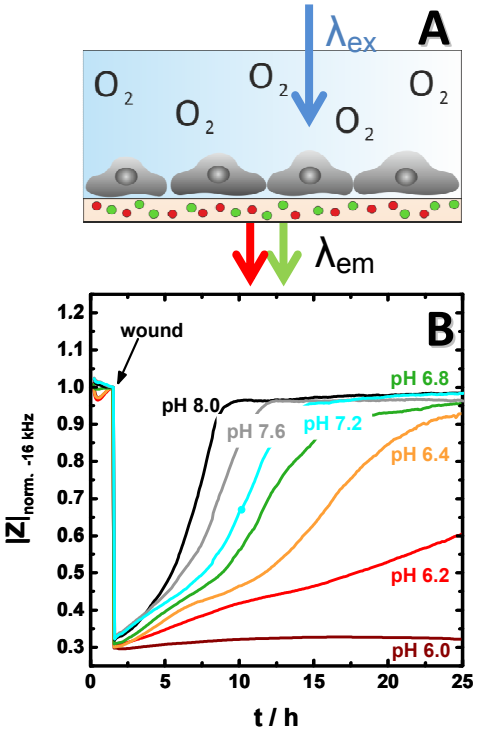

Fig. 1**A** Scheme of the ratiometric oxygen measurement setup, **B** Normalized impedance signal of wound healing process of NRK cells as a function of time

In addition to these impedimetric studies, we investigated the respiratory activity under varying extracellular pH values by monitoring the oxygen concentration beneath the cells using oxygen sensitive sensor foils and an imaging system provided by PreSens®. Cellular respiration is reduced by lowering the extracellular pH value in accordance with the functional ECIS assays. The combination of various ECIS modes to characterize cell phenotypes with studies on their metabolism may help to analyze specific aspects of tumorigenesis.

References:

[1] A. Lardner, *J. Leukocyte Biol.*, 69 (2001) 522-530.