Medical University of Graz

Live-Cell Fluorescence Imaging of Cell Signaling and Metabolism on Cell-Mg-Implant Interfaces and in Cancer Cells

Summary

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Supervisors:	Prof. Dr. Roland Malli PD Dr. Rainer Schindl
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich)

Description

Background:

The corrosion of Mg-based implants1 is associated with complex chemical alterations on cellular interfaces, that may be similar to those observed in tumor microenvironments. Particularly extracellular changes in pH, ions, and reactive oxygen species can have both, detrimental and beneficial effects, on cells by influencing cell signaling and metabolic activities significantly. Yet little is known how biodegradable Mg implants and respective environmental signals locally impact the biochemistry of cells including endothelial cells, osteoblasts, and osteoclasts.

Genetically encoded fluorescent biosensors allow investigating cell signaling and metabolism with high spatial and temporal resolution2,3 and have thus revolutionized our understanding of cell biology. Combinations of biosensors in multiparametric imaging settings are currently developed to decipher the interrelations and dynamics of complex signaling networks.

Using live-cell fluorescence imaging in combination with structural, genetic, and pharmacological manipulations, we will particularly focus on stress sensors including the microphthalmia-associated transcription factor (MITF), an important Ca2+- and Mg2+-sensitive signaling molecule, which might play multiple roles in the physiology and pathology of osteoclasts as well as cancer cells4.

Hypothesis and Objectives:

In this project, state-of-the-art multiparametric live-cell imaging approaches based on fluorescent biosensors will be developed to scrutinize how extrinsic stresses and stimuli impact molecular pathways and thereby control cell decisions, functions, and fate. The project aims to investigate signaling and metabolic signatures of individual cells in vitro in response to tractable, defined stresses and stimuli that mimic the corrosion of Mg-based implants and might be similarly found in tumor microenvironments. We eventually hypothesize that smart combinations of fluorescent biosensors in designed experimental live-cell imaging setups will allow deciphering cell stress responses in vitro to predict key biological consequences in more complex in vivo settings.

Methodology:

The candidate will start establishing high-resolution fluorescent imaging experiments that aim to characterize signaling dynamics and their interrelations to metabolic activities on the level of individual cells in vitro. Genetically encoded probes and imaging protocols that allow visualizing and quantifying subcellular signaling and metabolic activities with high temporal and spatial resolution will be expanded and established in course of this project. Moreover, these probes and techniques in combination with pharmacological tools, protein knock-down, knock-out, and/or overexpression offer an opportunity to independently characterize cell signaling and metabolism under physiological and pathological conditions.

References:

[1] In vivo and in vitro degradation comparison of pure Mg, Mg-10Gd and Mg-2Ag: a short term study. Marco, I; Myrissa, A; Martinelli, E; Feyerabend, F; Willumeit-Römer, R; Weinberg, AM; Van der Biest, O Eur Cell Mater. 2017; 33(2):90-104

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[2] Immobilization of Recombinant Fluorescent Biosensors Permits Imaging of Extracellular Ion Signals. Burgstaller S, Bischof H, Rauter T, Schmidt T, Schindl R, Patz S, Groschup B, Filser S, van den Boom L, Sasse P, Lukowski R, Plesnila N, Graier WF, Malli R. ACS Sens. 2021 Nov 26;6(11):3994-4000. doi: 10.1021/acssensors.1c01369.

[3] Live cell imaging of signaling and metabolic activities. Depaoli, MR; Bischof, H; Eroglu, E; Burgstaller, S; Ramadani-Muja, J; Rauter, T; Schinagl, M; Waldeck-Weiermair, M; Hay, JC; Graier, WF; Malli, R Pharmacol Ther. 2019; 202:98-119

[4] Mechanism of conditional partner selectivity in MITF/TFE family transcription factors with a conserved coiled coil stammer motif. Pogenberg V, Ballesteros-Álvarez J, Schober R, Sigvaldadóttir I, Obarska-Kosinska A, Milewski M, Schindl R, Ögmundsdóttir MH, Steingrímsson E, Wilmanns M. Nucleic Acids Res. 2020 Jan 24;48(2):934-948. doi: 10.1093/nar/gkz1104.