Satellite Session 2: L'Oreal Session

Lectures

L23.1

Stem cells – how to turn them into skeletal muscles

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Stem cells, including pluripotent stem cells – such as ESCs (Embryonic Stem Cells) and iPSCs (induced Pluripotent Stem Cells), are widely considered as the ones that can be used in the regenerative medicine or tissue engineering that aims to repaire or improve function of damaged or degenerated tissues. Both ESCs and iPSCs are easy to maintain and propagate *in vitro*. Importantly, when cultured under defined conditions they remain pluripotent, i.e. potentially able to differentiate into any given cell type. However, derivation of some cell types might be not as easy as described in the textbooks. Among such "difficult" cells are skeletal muscle myoblasts that could be used to treat such pathologies as skeletal muscle dystrophies or massive injuries. During my talk I will summarize currently available methods that can be used to induce and improve stem cells myogenic differentiation.

L23.2

Inflammatory signaling from the endocytic pathway

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Cytokine receptors from the TNFR superfamily signal via the NF-κB pathway which induces a proinflammatory and stress response of the cells. However, endocytic trafficking of the TNFR receptors and its impact on signaling remain poorly investigated. We have recently uncovered a role of ESCRT-dependent sorting of cytokine receptors as an important factor limiting constitutive NF-κB signaling (Mamińska et al (2016) *Science Signaling* **9**: ra8). Depletion of selected ESCRT components potently activates both the canonical and noncanonical NF-κB pathways without cytokine stimulation, inducing proinflammatory transcriptional response in cultured human cells, zebrafish embryos and fly fat bodies. These effects depend on cytokine receptors, such as lymphotoxin β receptor (LTβR) and tumor necrosis factor receptor (TNFRI). ESCRT-dependent defects in their trafficking can induce receptor oligomerization and signaling in a ligand-independent manner. We propose that ESCRTs constitutively control levels and distribution of ligand-free cytokine receptors to restrict their signaling. This may represent a general mechanism to prevent spurious NF-κB activation. Moreover, this study demonstrates that cytokine receptors from the TNFR superfamily can elicit stress signals intracellularly when localized to endosomes.

L23.3

Development and function of distinct populations of cardiac macrophages in healthy and injured heart

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Upon myocardial infarction (MI) immune system becomes activated by extensive necrosis of cardiomyocytes. Overactive and prolonged immune responses can be responsible for heart failure in patients surviving the ischemic episode. Cardioprotective effects of heme oxygenase-1 (HMOX1) were previously demonstrated in experimental models of MI. Nevertheless, its importance in suppression of post-ischemic inflammation remains incompletely understood.
The aim of this study was to investigate the role of HMOX1 in the monocyte/macrophage-mediated late acute and subacute phases of inflammation in a mouse model of MI.
HMOX1 knockout (*Hmox1*$^{-/-}$) and wild type (*Hmox1*$^{+/+}$) mice were subjected to a permanent ligation of the left anterior descending coronary artery. Shortly after MI WT mice responded with a strong up-regulation of cardiac *Hmox1* expression, which decreased in time. A more potent deterioration of heart function during the 3-week follow-up in *Hmox1*$^{-/-}$ mice was accompanied by higher numbers of classical inflammatory Ly6C^{hi} monocytes in the peripheral blood and upregulation of monocyte chemoattractant protein-1 (MCP-1) in the heart. These changes were associated with increased abundance of pro-inflammatory MHCII^{+}Ly6C^{+}CD11c^{+} and MHCII^{++}Ly6C^{+}CD11c^{+} cardiac macrophages. Transplantation of *Hmox1*$^{-/-}$ bone marrow to *Hmox1*$^{+/+}$ recipients revealed that HMOX1 deprivation restricted to bone marrow-derived blood cells does not, *per se*, impair post-ischemic recovery.
HMOX1 provides a timely resolution of inflammation after MI by restricting monocytopoiesis, monocyte/macrophage-mediated adverse cardiac remodeling and infarct expansion in animals surviving the ischemic episode. HMOX1-deficient monocyte-derived cardiac macrophages may not solely be responsible for the more severe in *Hmox1*$^{-/-}$ mice post-MI heart failure and/or their function may depend on the concurrent inflammatory milieu of the heart.

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L23.4

Small virus, big problem: why do we still need a drug for flu?

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Influenza virus is a major human and animal pathogen with the potential to cause staggering mortality rates. The emergence of an extremely aggressive influenza strains has made the likelihood of the human influenza pandemic and its possible socio-economic impact a major worldwide concern. It has also emphasized the need for new therapeutic strategies to combat these pathogens. The heterotrimeric influenza virus polymerase, containing the PA, PB1 and PB2 proteins, carries out numerous essential roles in viral replication and pathogenesis. In particular, the polymerase is responsible for 'cap-snatching': that is the cleavage of the capped leaders from the host cell pre-messenger RNA, which are subsequently used to prime transcription of the viral genome. For such reasons, the viral polymerase complex represents a potential target for the rational design of the new class of antiviral medications.
Determination of the crystal models of the viral endonuclease domain provided a structural framework for the identification of compounds that inhibit the nuclease activity in the viral polymerase complex. To this end, we used the structure-based virtual screening protocol followed by applying the combination of 2D and 3D descriptor clustering techniques. *In vitro* evaluation of selected compounds has been carried out against isolated, purified influenza nuclease domain in the in-house-designed FRET assay and followed by receptor specificity verifications, biophysical studies of protein-small molecule interactions and cytotoxicity tests (HEK293 and human fibroblast cell lines). Candidate leads have been also assessed for antiviral activity in cell culture assays (MDCK cell line) infected with influenza virus (A/H5N2) which proved no detectable cytotoxicity with high virucidal activity. Our lead compounds provide a starting point for the rational development of antiviral drugs.