Results Immunol, 2015, 5, 23-32

Expression and regulation of Schlafen (SLFN) family members in primary human monocytes, monocyte-derived dendritic cells and T cells

Alexander Puck[a], Regina Aigner[a], Madhura Modak[a], Petra Cejka[a], Dieter Blaas[b] and Johannes Stöckl[a].

[a] Institute of Immunology, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria
[b] Department of Medical Biochemistry, Max F. Perutz Laboratories, Vienna Biocenter, Medical University of Vienna, Vienna, Austria

Schlafen (SLFN/Slfn) family members have been investigated for their involvement in fundamental cellular processes including growth regulation, differentiation and control of viral replication. However, most research has been focused on the characterization of Slfns within the murine system or in human cell lines. Since little is known about SLFNs in primary human immune cells, we set out to analyze the expression and regulation of the six human *SLFN* genes in monocytes, monocyte-derived dendritic cells (moDCs) and T cells. Comparison of *SLFN* gene expression across these three cell types showed high mRNA expression of *SLFN11* in monocytes and moDCs and high *SLFN5* expression in T cells, indicating functional importance within these cell types. Differentiation of monocytes to moDCs leads to the gradual upregulation of *SLFN12L* and *SLFN13* while *SLFN12* levels were decreased by differentiation stimuli. Stimulation of moDCs via human rhinovirus, lipopolysaccharide, or IFN-α lead to strong upregulation of *SLFN* gene expression, while peptidoglycan poorly stimulated regulation of both *SLFNs* and the classical interferon-stimulated gene *MxA*. T cell activation was found to downregulate the expression of *SLFN5*, *SLFN12* and *SLFN12L*, which was reversible upon addition of exogenous IFN-α. In conclusion, we demonstrate, that *SLFN* gene upregulation is mainly dependent on autocrine type I interferon signaling in primary human immune cells. Rapid decrease of *SLFN* expression levels following T cell receptor stimulation indicates a role of SLFNs in the regulation of human T cell quiescence.

Paper in Revision

Rhinovirus induces an anabolic reprogramming in host cell metabolism essential for viral replication

Guido A. Gualdoni[1,2,*], Katharina A. Mayer[1], Anna-Maria Kapsch[1,4], Katharina Kreuzberg[1], Alexander Puck[1], Felicitas Oberndorfer[5], Karin Frühwirth[2], Dieter Blaas[6], Gerhard J. Zlabinger[1], Johannes Stöckl[1]

[1]Institute of Immunology, Center of Pathophysiology, Immunology & Infectiology, Medical University of Vienna, Austria
[2]Division of Nephrology and Dialysis, Department of Medicine 3, Medical University of Vienna, Austria
[3] Division of Infetious Diseases and Tropical Medicine, Department of Medicine 1, Medical University of Vienna, Austria
[4]Global Pathogen Safety, Shire, Vienna, Austria
[5]Department of Pathology, Medical University of Vienna, Austria
[6]Department of Medical Biochemistry, Max F. Perutz Laboratories, Vienna Biocenter, Medical University of Vienna, Vienna, Austria

Rhinoviruses (RVs) are responsible for the majority of upper airway infections; despite their high prevalence and the resulting economic burden, effective treatment is lacking. We report herein that RV induces metabolic alterations in host cells, which offer an efficient target for antiviral intervention. We show that RV-infected cells rapidly upregulate glucose uptake in a PI3-Kinase dependent manner. In parallel, infected cells enhance the expression of the PI3-Kinase regulated glucose transporter GLUT1. In depth metabolomic analysis of RV infected cells revealed a critical role of glucose-mobilization from extracellular and intracellular pools

-via glycogenolysis- for viral replication. Glucose was primarily required to attain a highly anabolic state in the infected cells including enhanced nucleotide synthesis and lipogenesis. Consistently, we observed that glucose-deprivation both from medium and via glycolysis inhibition by 2-deoxyglucose (2-DG) potently impairs viral replication. Metabolomic analysis showed that 2-DG specifically reverts the RV-induced anabolic reprogramming. In addition, treatment with 2-DG inhibited RV infection and inflammation in a murine model. Thus, we demonstrate that the specific metabolic fingerprint of RV infection can be used to identify new targets for therapeutic intervention.