Meeting report on the 12th workshop on 'Cell biology of viral infections' 'Cell Biology of Metabolic Processes'

Claudia Claus[1], Steeve Boulant[2]
[1]Institute of Virology, University of Leipzig
[2]Department of Infectious Diseases, Cellnetworks and DKFZ, University Heidelberg

The 12th Workshop „Cell Biology of Viral Infections" of the Society for Virology (GfV) took place in Deidesheim, December 4th – 6th 2013, and was centered around "Cell Biology of Metabolic Processes". Metabolism is an umbrella term for a complex network of (bio)chemical reactions embedded in various organelles of the cell. Metabolic processes convert molecules in a step-wise manner into metabolic intermediates and finally into metabolic precursors. They are either oxidised into ATP, the energy currency of all cells, or used as building blocks for macromolecules such as amino acids, lipids, and nucleotides. These building blocks are not only required for cellular growth and maintenance, but also for viral replication and assembly of new viral progeny. With the exception of the family Herpesviridae with their rather large coding capacity, viruses lack metabolic enzymes. Hence many viruses have developed various means to manipulate cellular metabolism such that viral replication can be ensured and optimised [1], [2]. This close interconnectivity of cellular and viral metabolism sets the ground for the exploitation of specific metabolites as new and promising drug targets [3]. Metabolic approaches can also be used to visualise distinct parts of the virus life cycle, e. g. through application of fluorescently labelled lipids. Some of these virological aspects parallel other patho-physiological conversions of cellular metabolism such as cancer.

The workshop "Cell Biology of Viral Infections" was originally established by the GfV to promote exchange and lively discussions between virologists and cell biologists. The issue on "Cell Biology of Metabolic Processes" especially bridges virology-centered with cell biology-related research aspects and is in line with the previous topics of this rather informal workshop. The workshop once more took place on the estates of the famous winery Bassermann-Jordan in Deidesheim and was again co-sponsored by the GfV and the DGZ. Four cell biologists gave excellent talks during the keynote sessions and provided insights into their exciting fields of research. These sessions were followed by oral presentations from mostly young scientists undergoing their postgraduate studies covering diverse virological research aspects.
Eric Chevet, INSERM scientific director at the University of Bordeaux, France, is an expert on the role of endoplasmic reticulum in stress signalling and proteostasis. With his talk on "Control of Endoplasmic Reticulum homeostasis in cancer" Dr. Chevet introduced us to the so-called Unfolded Protein Response (UPR), which is triggered upon accumulation of unfolded proteins within the endoplasmic reticulum. This response is mainly mediated by three transmembrane proteins: PERK, ATF6 and IRE1. His talk mostly focused on the protein IRE1, which constitutes a key protein regulating the balance between cytoprotection and induction of apoptosis during proteotoxic stress. Survival is favoured by inducing autophagy.

Nicholas Ktistakis, from the Babraham Institute in Cambridge University, UK, focuses his research on the signalling events and intermediate structures, which eventually end in autophagosome formation. Autophagosomes are the executioners of autophagy, which is triggered during certain developmental stages, stress, starvation, and in response to an infection with viral and bacterial pathogens. They are double-membrane structures and deliver material to lysosomes for degradation. Prof. Ktistakis gave a talk on lipid-based signal transduction entitled "The role of a simple phosphoinositide lipid (PI3P) in the regulation of autophagy and in activation of mTOR". He explained the paradox role of PI3P (phosphatidylinositol 3-phosphate) in nutrient sensing. In the absence of amino acids and growth signals, the protein kinase mTOR (mammalian target of rapamycin), a master regulator of cell growth, is inactive, and PI3P contributes to autophagy induction. Unexpectedly, in the presence of nutrients, PI3P appears as a positive regulator of mTOR and subsequently in the initiation of cell growth. Prof. Ktistakis illustrated how his group contributed to the characterisation of omegasomes, which represent a PI3P-enriched ER-subdomain, where at least some autophagosomes are formed. In this omega-like shape membrane structures, PI3P acts as a key player in autophagosome formation and membrane regulation during the early steps of autophagy.

Jean-Ehrland Ricci, is a young team leader at the French National Institute of Health and Medical Research (INSERM) in Nice, France. His laboratory investigates the role of metabolic processes in apoptosis. His entertaining and illustrative talk on "Metabolic control of cell death: relation to cancer and anti-cancer immune response" gave an impression on how effective the combination of chemotherapy with metabolic inhibitors is in treating cancer. Dr. Ricci gave a general overview on apoptosis induction by extrinsic and intrinsic mechanisms; he especially focused on how much apoptosis and metabolism are intertwined. Furthermore, tumour cell metabolism can be connected with an antitumour immune response. In this context the outcome of chemotherapy can be improved and the problem of chemoresistance in cancer cells could be reduced. He highlighted the importance of cell-induced death pathways (apoptosis vs. necrosis) during

anticancer treatment in the induction of an anti-cancer immune response. However, only a few anticancer agents sufficiently induce immunogenic cell death. A common characteristic of all cancer cells is their reliance on glycolysis, a phenomenon known as the Warburg effect. Dr. Ricci illustrated that the combination of a glycolysis inhibitor with a DNA-damaging agent activated tumour-specific T cells [4]. Moreover, glycolysis inhibition enhances the vaccination potential of chemotherapy. The injection of tumour cells treated with glycolysis inhibitors protects specifically against challenge with these tumour cells.

Christoph Thiele, from the LIMES Institute at the University of Bonn, Germany, focuses on the metabolism of neutral lipids in cells and as such on lipid droplets as their main storage organelle. In the first part of his talk entitled "Lipid metabolism and neutral lipid storage" he gave an overview on lipid droplets, which are mainly composed of triglycerides and sterol esters and are formed between endoplasmic reticulum bilayers, from where they eventually bud off. In the second part of his talk he presented some of his most recent technological developments for lipid detection. Prof. Thiele emphasised the beauty and the high sensitivity of a fluorogenic "click reaction" in tracing fatty acids and in the analysis of their metabolism [5]. The so-called "click reaction" is based on heteroatom links (C-X-C) and was first described by K. B. Sharpless. Click-labelled fatty acids have so far only been used in the study of protein lipidation. Prof. Thiele highlighted in his talk the achievements of his group in establishing clicked lipids as an attractive tool for kinetic pulse-chase analysis experiments of fatty acid metabolism in tissues and cells. They are not only highly suited for metabolic labelling experiments, but also for labelling approaches of viral envelopes during the cell-associated assembly process [6].

In addition to these invited keynote speakers, participants from Germany, France, and the United Kingdom presented their diverse work in the field of virology, which in most cases involved cell biology features. Just to summarize a few, viral entry mechanisms were covered from the involvement of tetraspanin-enriched microdomains in human cytomegalovirus entry and the role played by nectin 1 during uptake of herpes simplex virus in epidermal sheets of murine skin and primary keratinocytes. Nuclear egress processes of cytomegalovirus and herpesviruses were emphasised as well as nuclear envelope breakdown during import of human papillomavirus type 16 and the general role played by nucleoporins during nuclear import. Also metabolic aspects were covered with the participation of the triglyceride synthesising enzyme diacylglycerol acyltransferase 1 and of phosphatidylinositol 4-kinase III alpha in hepatitis C virus replication. Particularly well received and discussed was the talk by

Pascale Schellenberger from the group of Kay Grünewald. She covered the emerging technique of correlative fluorescence and electron cryo microscopy [7].

As usual, the wine tasting event gave the workshop its traditional lively atmosphere favouring exchange between the participants and resulted in fruitful interdisciplinary discussions. Due to organisational considerations last years meeting completed the workshop series in Deidesheim. We, Claudia Claus (Leipzig) and Steeve Boulant (Heidelberg), have been elected as new chairs for the upcoming three years. We will stick to the tradition of the Deidesheim meetings, but change the location from Deidesheim to the Schöntal Monastery (Kloster Schöntal). This former Cistercian abbey is beautifully located on the banks of the Jagst River in the North of Baden-Württemberg. We invite all researchers in the field of cell biology and virology to the 13th workshop that will take place from the 19th to the 21st of November 2014. We are committed to continue this workshop as a place for lively, friendly and stimulating discussions, especially among young scientists.

We are confident that this years topic **"Mimicking Organ Physiology: "Impact of Stem Cells and Tissue Engineering on Virology"**, will cover exciting, promising and expanding aspects of cell biology that will appeal to both virologists and cell biologists. Two outstanding keynote speakers have already confirmed their participation.

Prof. Catherine Verfaillie, KU Leuven, Belgium, will speak about Hematopoietic stem cell proliferation and differentiation and pluripotent stem cells. Prof. Petra Boukamp, DKFZ, Heidelberg, will speak about human epidermal stem cells and 3D organotypic culture. The name of the other keynotes and all necessary information will be provided as soon as possible on the workshop website (www.gfv-cellviro.de).

Finally, we would like to express our gratitude to PD Dr. Susanne Bailer and Dr. Harald Wodrich for organising a very exciting 12th workshop on "Cell Biology of Metabolic Processes" and for their devotion over these past three years in keeping excellence and enthusiasm within the "Cell Biology of Viral Infection" workshop. We also express our thanks to the GfV and DGZ for allowing us to continue this traditional interdisciplinary meeting and to our sponsors without whom this workshop would not be possible: GRIFOLS, aquitaine microsbiology, Fraunhofer Institute, and with a particular thanks to REBLIKON GmbH who has been a continual supporter of this workshop series. We also thank all meeting participants who contributed to the stimulating surrounding of the workshop.

About the organisers

Claudia Claus: Already during my undergraduate studies in Biological Sciences, especially through lectures given by Prof. Louise Cosby and Dr. Paul Duprex at Queen's University of Belfast, I have been fascinated by the viral exploration and manipulation of cellular functions. Last years workshop touched the focus of my current research on the contribution of mitochondrial metabolism to the establishment and progression of viral infections. Mitochondria provide not only most of the ATP, they also participate in calcium homeostasis, in antiviral defence mechanisms (apoptosis and necrosis) and even in innate immune response pathways. With my research I want to explore two main aspects. First, how alterations of mitochondrial metabolism assist cell culture adaptations of viral strains and in this regard establishment of viral persistence. Second, could virus-associated teratogenic alterations involve mitochondrial dysfunctions? This is of special importance in the case of rubella virus, which is a very efficient teratogen and induces perinuclear accumulation of mitochondria and interacts with several important mitochondrial proteins. Notably rubella virus alters mitochondrial functions, including the activity of distinct respiratory chain complexes.

Steeve Boulant: Multidisciplinary research and a broad field of knowledge have always been major driving forces in my scientific career. After a master's degree and Ph.D. in biochemistry studying the capsid protein of the Hepatitis C virus, I learned classical virology during my first post-doctoral position. Following this experience I became interested in understanding the impact of cellular polarity on endocytosis. The research in my laboratory combines biochemistry, virology and cell biology to address how cellular polarity of intestinal epithelium cells can affect viral infection. Specifically, we are investigating how polarized endocytosis and sorting mechanisms can affect the outcome of the infection. Our multidisciplinary approach allows us to determine the direct impact of polarity on the viral pathogen and in the same time determine both the molecular and biochemical mechanisms that the cells have to developed to achieve such polarity and whether this provides an advantage to the host cell. We are looking forward to seeing you this year at the 13th workshop of cell biology of viral infection entitled "Mimicking Organ Physiology: Impact of Stem Cells and Tissue Engineering on Virology".

References

1. Vastag, L., et al., Divergent effects of human cytomegalovirus and herpes simplex virus-1 on cellular metabolism. PLoS pathogens, 2011. 7(7): p. e1002124.
2. Claus, C. and U.G. Liebert, A renewed focus on the interplay between viruses and mitochondrial metabolism. Archives of virology, 2013.
3. Rabinowitz, J.D., et al., Metabolomics in drug target discovery. Cold Spring Harbor symposia on quantitative biology, 2011. 76: p. 235-46.
4. Beneteau, M., et al., Combination of glycolysis inhibition with chemotherapy results in an antitumor immune response. Proceedings of the National Academy of Sciences of the United States of America, 2012. 109(49): p. 20071-6.
5. Thiele, C., et al., Tracing Fatty Acid Metabolism by Click Chemistry. Acs Chemical Biology, 2012. 7(12): p. 2004-2011.
6. Huang, L.L., et al., Enveloped Virus Labeling via Both Intrinsic Biosynthesis and Metabolic Incorporation of Phospholipids in Host Cells. Analytical Chemistry, 2013. 85(10): p. 5263-5270.
7. Schellenberger, P., et al., High-precision correlative fluorescence and electron cryo microscopy using two independent alignment markers. Ultramicroscopy, 2013.