Graduate School Event

Thesis Defense: Mechanistic insights into MDA5 selectivity and regulation

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Host: Eva Benková

MDA5 is an antiviral protein that is activated by long dsRNA molecules. This RNA can be of various origins such as viral, bacterial, synthetic or, upon certain stimuli, even cellularsources. Upon sensing immunogenic RNA, MDA5 coats the dsRNA, forming a filament. Filament formation brings CARD domains into close proximity, resulting in CARD oligomerisation. These oligomers are not involved in the RNA recognition but are crucial for activation of downstream signalling. MDA5 activation leads to a type I interferon response and apoptosis. Loss of function mutations are linked to recurrent, life-threatening viral infections whereas gain of function mutations are linked to monogenic and polygenic autoimmune diseases. For these reasons, MDA5 needs to be tightly regulated by various mechanisms including post-translational modifications, post-transcriptional modifications, and protein-protein interactions. In the first chapter, we focused on the characterisation of novel phosphorylation sites in MDA5. Using biochemistry, molecular dynamics simulations, virology, cell biology and mass spectrometry, we characterised two phosphorylation sites that altered MDA5 activity andwere regulated in cells upon EMCV infection or IFN-β treatment. Furthermore, we discovered an additional phosphorylation site in a non-conserved region, which is upregulated under both stimuli.In the second chapter, we focused on biochemical, biophysical, and structural characterisation of various RNAs and MDA5 filaments assembled on them. We discovered that poly I:C, a synthetic RNA used to activate an immune response in cells, has distinct physicochemical characteristics and is not a true mimic of viral RNA, as is often described. Additionally, we used cryogenic electron microscopy to gain structural insights into which RNA features define a strong activator of MDA5. To address this, we compared poly I:C to poly A:U, an RNA that does not activate an MDA5 signalling in cells, and to a virus-derived dsRNA. In the last chapter, we focused on activators of MDA5 signalling. In the first part, we present our efforts to isolate and identify a small molecule agonist of MDA5. In the last part, we described our contribution to a collaborative project during which we characterised the interaction of ANXA2 with MDA5 and activation of MDA5 by a small molecule.

Thursday, July 9, 2026 02:00pm - 03:00pm
Sunstone Bldg / Ground floor / Big Seminar Room B / 63 seats (I23.EG.102)

This invitation is valid as a ticket for the ISTA Shuttle from and to Heiligenstadt Station. Please find a schedule of the ISTA Shuttle on our webpage: https://ista.ac.at/en/campus/how-to-get-here/ The ISTA Shuttle bus is marked ISTA Shuttle (#142) and has the Institute Logo printed on the side.