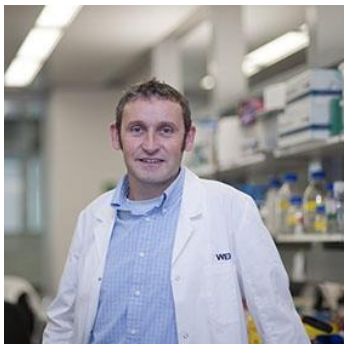
Cologne Cell Death Club Seminar

SFB 1403 CELL DEATH IN IMMUNITY, INFLAMMATION AND DISEASE

University of Cologne



Speaker: John Silke

The Walter and Eliza Hall Institute (WEHI), Victoria, Australia
Information about the Silke Laboratory

Title: "Tankyrase-1-mediated ADP-ribosylation is a novel regulator of TNF-induced death"

Tuesday 04.05.2021 at 1 pm

Please register here to receive the Zoom login data:
https://uni-koeln.zoom.us/meeting/register/tJUtfu6grj0qGdxOlcDQOjxksmJyfISuvmtW

Abstract:
Tumor necrosis factor (TNF) is an inflammatory cytokine that, upon binding to its receptor TNFR1, can drive cytokine production, cell survival, or cell death and is a major component of an organism's anti-pathogen repetoire1,2. TNF stimulation leads to the formation of two distinct signalling complexes, a well-defined membrane bound complex (complex 1), and a less well characterized cytosolic death inducing complex (complex 2). Using mass spectrometry, we identified the ADP-ribosyltransferase, tankyrase-1 (TNKS1/TNKS/ARTD5/PARP5a) as a novel native complex 2 component. Following a TNF-induced death stimulus TNKS1 is recruited to complex 2, resulting in complex 2 poly(ADP-ribosyl)ation (PARylation). Tankyrase inhibitors sensitize cells to TNF-induced death, which is correlated with increased complex 2 assembly. TNKS1-mediated PARylation promotes recruitment of the E3 ligase RNF146 and RNF146 deficiency or proteasome inhibition results in increased levels of complex 2, suggesting RNF146 causes proteasomal degradation of complex 2. Several viruses express ADP-ribose binding MacroD proteins, and expression of the SARS-CoV-2 or VEEV MacroD domain markedly sensitizes cells to TNF-induced death. This suggests that ADP-ribosylation serves as yet another mechanism to detect pathogenic interference of TNF signalling and retaliate with an inflammatory cell death.

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