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Herpesviruses employ amyloid-based mechanisms for sequestration of the host necroptosis machinery

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Abstract

Functional amyloid fibrils display many structural features in common with pathological amyloid but are distinguished by the novel biological activity that is generated by assembly of the fibril. We have investigated viral proteins that contain amyloidogenic RIP homotypic interaction motifs (RHIMs). We find that the proteins from murine cytomegalovirus, Herpes simplex virus-1 and Varicella zoster are capable of forming amyloid fibrils that interfere with host efforts to curtail viral replication. We demonstrate that these viral RHIMs interact directly with host RHIM-containing proteins and sequester a host kinase and a cytosolic viral nucleic acid sensor in host:viral heteromeric fibrils. We have used a suite of biochemical and biophysical approaches to identify the key interactions at the interface between the viral and host proteins in these protein assemblies. The ability of these viral proteins to form competing or “decoy” amyloid fibrils inhibits necroptosis. The effective strategies employed by these viruses shed light on the molecular basis for necroptosis and could identify new therapeutic targets for inhibition of unwanted cell death following ischaemic events or other stress.

Bio

Margie Sunde completed her PhD at the University of Cambridge and then held postdoctoral fellowships at the Universities of Oxford and Cambridge before moving to the Australia in 2001. Her major research focus is the molecular basis for amyloid fibril formation. Her postdoctoral work revealed that all amyloid fibrils share a common underlying beta sheet structure and that amyloid formation associated with disease is caused by protein misfolding. After taking time to focus on family, Margie has built a program investigating functional amyloid structures, in particular amyloids with a biological activity in microbial infection or the evasion of the host response to infection. Margie’s group has elucidated the role of functional amyloids in fungi and viruses, and demonstrated that amyloid-forming viral proteins interfere with host programmed cell death through the formation of host:virus hybrid amyloid complexes.

EVENT DETAILS

DATE:

Tuesday, 21 June 2022

TIME:

11am AEST

ZOOM:

Zoom details to be circulated via email on 21 June 2022

HOST:

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