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INFLAMMATION

Inflammatory pathology of Fanconi anaemia

> pathology might be explained by the potentiation of inflammatory signalling pathways as a result of impaired selective autophagy

The Fanconi anaemia pathway has a well-characterized role in maintaining genomic stability through the repair of nuclear DNA damage. Patients with mutations in any of the ~19 genes of this pathway have a range of clinical symptoms, most commonly involving bone marrow failure and increased cancer risk. New evidence now indicates that the pathology might be explained by the potentiation of inflammatory signalling pathways as a result of impaired selective autophagy, in addition to defective DNA repair.

Mouse embryonic fibroblasts lacking the Fanconi anaemia gene *Fancc* had a defective virophagic response to two neuronotropic viruses — the single-stranded RNA virus Sindbis virus and the double-stranded DNA virus herpes simplex virus type 1. FANCC was shown to target viral capsid proteins to autophagosomes. As a result, $Fancc^{-/-}$ mice infected with either virus had impaired viral antigen clearance from the central nervous system, increased neuronal cell death and increased mortality. Thus, FANCC is required for antiviral host defence through an autophagic response.

Similarly, FANCC was shown to have an essential role in Parkin-mediated mitophagy *in vitro*, and FANCC co-localized with Parkin on the surface of dysfunctional mitochondria. $Fancc^{-/-}$ mice had marked accumulation of abnormal mitochondria in brain and heart tissue, and fibroblasts from patients with a null *FANCC* mutation accumulated damaged mitochondria and increased levels of mitochondrial reactive oxygen species (mtROS) in response to mitochondrial damage. In $Fancc^{-/-}$ bone marrow-derived mouse macrophages, the inflammasome aberrantly increased production of interleukin-1β (IL-1β) in response to the inflammasome agonists lipopolysaccharide and ATP. This effect was partially reversed by a mitochondria-localized oxygen scavenger, which indicates that increased mtROS generation in the absence of FANCC-mediated mitophagy enhances inflammasome activation. The mitophagy function of FANCC was independent of its role in DNA damage repair, as a naturally occurring amino-terminal deletion mutant of FANCC (FANCC c.67delG) rescued Parkin-mediated mitochondrial clearance and hypersensitivity to inflammatory cytokine-induced cell death of *FANCC*-knockout HeLa cells but did not rescue nuclear DNA repair.

These previously unappreciated cytoplasmic roles of the Fanconi anaemia pathway in virophagy and mitophagy may both protect organisms against the accumulation of unwanted cytoplasmic constituents and also modulate inflammatory pathways induced by virus infection or mitochondrial damage. These new functions may coordinate with the well-known nuclear functions of Fanconi anaemia genes to maintain cellular homeostasis, thereby protecting bone marrow function and preventing tumorigenesis.

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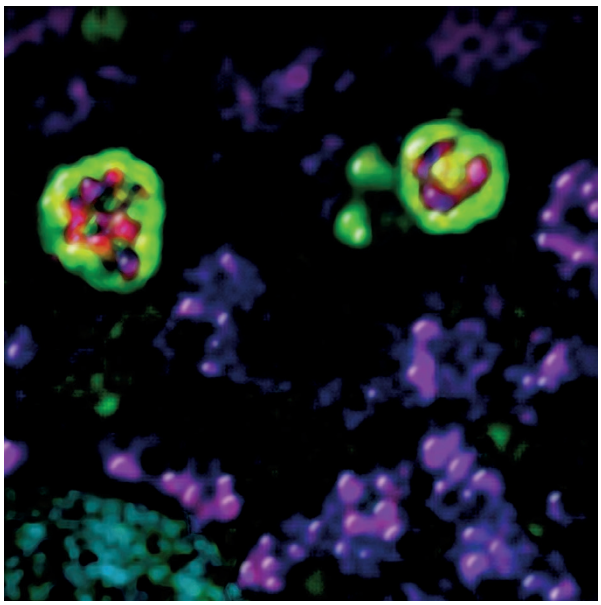

Structured illumination micrograph of HeLa cells depicting mitophagy: the envelopment of damaged mitochondria (red/magenta) by autophagosomes (green). Image courtesy of B. Levine and R. Sumpter.

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