Editorial

Viral regulation of cell death

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The cell autonomous immune response is multi-faceted and forms an important first line of defence upon pathogen infection (Randow *et al.* 2013). A major element of this response is the induction of cell suicide pathways, which contribute to the limiting of infection through elimination of a replication niche. Consequently, pathogens have evolved a multitude of strategies to intercept this pathway to promulgate infection. Human Cytomegalovirus (HCMV), a human herpes virus, is no exception and expresses an armoury of gene functions that promote viability (McCormick 2008). However, a key biological characteristic of HCMV is the ability to establish lifelong latent infections which are hallmarked by limited viral gene expression and no viral replication (Dupont & Reeves 2016).

One of the first host cell 'trip wires' is the detection of the pathogen upon entry into the cell. Importantly, we and others have shown that the virus must ameliorate this response for the establishment of non-lytic but functional infections (Chan *et al.* 2010, Reeves *et al.* 2012). Crucially, the absence of many viral anti-apoptotic functions during this phase of infection has rendered the virus dependent on the activation of key cellular functions. The favoured model proposes that HCMV engages with the cell and triggers the activation of cell death pathways but, via concomitant activation of the survival pathways, the outcome is positive for the virus, resulting in long term infection of these cells.

For HCMV, and the establishment of latency in CD34+ cells, the activation of ERK-MAPK signalling appears to be a crucial event (Reeves *et al.* 2012). In the current issue, Kew *et al.* (2017) have investigated this in more detail and demonstrate that ERK activation underpins a multi-faceted survival response encompassing post translational down-regulation of pro-apoptotic Bim and the induction ELK -1 transcriptional activity. Importantly, the activation of ERK is required to prevent the consequence of a concomitant activation of the pro-apoptotic protein, Bak, by viral infection. The challenge now is to fully understand how these multiple events tip the balance in favour of survival in the infected cells. For instance, deletion of ELK-1 was not overly deleterious to CD34+ cells until the cells were subsequently stressed by viral infection, supporting a role in acute survival responses rather than long term homeostasis of viability.

The question remains as to why this is important. Clearly, the immediacy of understanding how pathogens promote cell survival has direct impact on our understanding of the complexity of the host-pathogen interaction. However, the wider implications are driven by a desire to decipher the biology of the cell. Dysregulated cell death underpins the pathogenesis of many infectious and non-infectious diseases and thus, understanding how these pathways are regulated can give new insight and, potentially, new hope for treatment of many complex diseases. For example, a proof of principle study showed that a CMV-encoded RNA that maintained energy production in virally infected cells (Reeves *et al.* 2007) could be used to protect rodents from the symptoms of Parkinson's disease (Kuan *et al.* 2012). Ultimately, viruses are assiduous molecular biologists - experts at hijacking, partitioning or re-directing cellular functions. It is hoped that, as we further unravel and define the complexity of the host-pathogen interaction, we will provide the foundation to interrogate host cell biology and reveal the many secrets still hidden by Mother Nature.

References

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