IMMUNE EVASION

Orthopoxviruses cut to the chase

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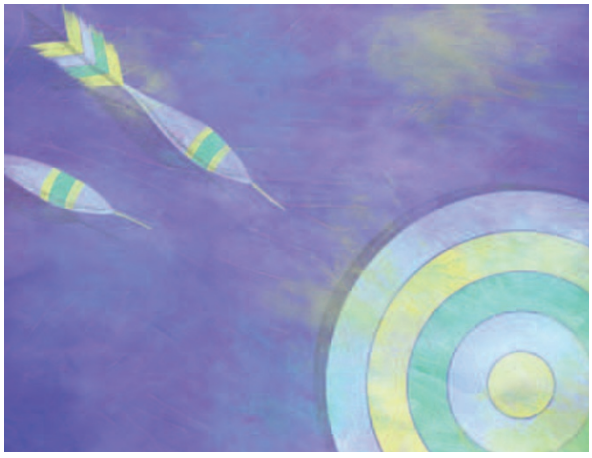
A recent paper in *The Journal of Experimental Medicine* shows that zoonotic orthopoxviruses encode a competitive antagonist of the stimulatory natural killer (NK)-cell receptor NKG2D (natural-killer group 2, member D).

NKG2D is among the most fully characterized of the stimulatory NK-cell receptors and recognizes ligands belonging to the MHC class I superfamily. The expression of these ligands can be upregulated in response to virus infection, thus tagging virus-infected cells for NK-cell-mediated killing. Both human and mouse cytomegaloviruses are known to interfere with the NKG2D signalling pathway by encoding MHC-class-I-like proteins that block the expression of NKG2D ligands on the surface of cytomegalovirus-infected cells.



In this work, the authors were interested in determining whether orthopoxviruses also interfere with NKG2D signalling. Campbell *et al.* reasoned that sequences encoding MHC-class-I-like proteins might be difficult to detect using a BLAST search because of low sequence conservation, and instead used a Hidden Markov Model, which can better detect remote homologies. An orthopoxvirus MHC-class I-like protein (OMCP) was identified in cowpox and monkeypox viruses. Analysis of the predicted protein sequence revealed the presence of a MHC-class-I-like fold and no transmembrane-spanning regions or glycosylphosphatidylinositol transamidation sites, suggesting that OMCP is a secreted MHC-class-I-like protein, and this was confirmed by immunoblotting.

Campbell *et al.* speculated that as a secreted protein with an MHC-class-I-like fold, OMCP might bind NKG2D and act as a competitive antagonist. Using a combination of *in vitro* binding assays, tetramer analysis and surface plasmon resonance, the authors demonstrated that OMCP binds with high affinity to human and mouse NKG2D and blocks the interaction between NKG2D and its host-encoded ligands. Further experiments showed that OMCP inhibits NKG2D-dependent killing by NK cells.

Virus modulation of NKG2D signalling has been reported previously, but OMCP is the first example of a virus-encoded effector protein that targets the NKG2D receptor directly, rather than targeting the ligands. The authors conclude by stating that the discovery of OMCP highlights the importance of NKG2D in the interaction between zoonotic orthopoxviruses and their hosts.

Sheilagh Molloy
Senior Editor,
Nature Reviews Microbiology

ORIGINAL RESEARCH PAPER
Campbell, J. A. *et al.* Zoonotic orthopoxviruses encode a high-affinity antagonist of NKG2D. *J. Exp. Med.* 4 June 2007 (doi:10.1084/jem.20062026)