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IMMUNE EVASION

Staying undetected

Downregulation of major histocompatibility complex (MHC) molecules is a well-recognized immune evasion mechanism used by several viruses. Cowpox virus (CPXV), for example, encodes the immune evasion protein CPXV203, which inhibits MHC class I trafficking by sequestering it in the endoplasmic reticulum (ER). However, CPXV203-deficient CPXV can still downregulate MHC class I surface expression, indicating that another mechanism must also be involved. Using distinct approaches, Byun *et al.* and Alzhanova *et al.* now show that the previously unknown cowpox protein CPXV12 mediates immune evasion by inhibiting effective MHC class I peptide biosynthesis.

> “CPXV12 mediates immune evasion by inhibiting effective MHC class I peptide biosynthesis.”

Both studies found that CPXV12 efficiently reduced MHC class I levels on the cell surface independently of CPXV203 expression. This was mediated by decreasing MHC class I trafficking to the cell surface, as cells expressing CPXV12 (or infected with CPXV12-expressing virus) showed markedly reduced intracellular trafficking of MHC class I molecules from the ER to the Golgi.

To reach the cell surface, MHC class I molecules need to assemble in a heterotrimeric complex comprising the heavy chain, β2 microglobulin and peptide. Both groups reasoned that the decreased levels of MHC class I expression on the cell surface could be caused by inhibition of complex assembly; indeed, they observed defective peptide loading in the presence of CPXV12. In some cells this was because peptide supply to the ER, which is mediated by transporter associated with antigen processing (TAP), was insufficient. Specifically, some cells transduced with CPXV12 or infected with CPXV12-expressing virus showed decreased TAP-mediated peptide transport compared with wild-type cells and cells infected with virus deficient in both CPXV12 and CPXV203. This suggests that CPXV12 decreases surface MHC class I expression by inhibiting peptide loading and MHC class I assembly.

So what effect does this have on the immune system? $CD8^+$ T cells from mice infected with wild-type CPXV showed an effective immune response (cytokine production and cytotoxicity) when incubated with antigen-presenting cells (APCs) infected with double-knockout virus but not when incubated with APCs infected with wild-type virus.

Furthermore, Byun *et al.* showed that mice infected with the double-knockout virus had a higher rate of survival than those infected with wild-type virus. This was caused not by reduced virus replication but, instead, by a more effective $CD8^+$ T cell-mediated immune response.

These studies reveal that two CPXV proteins interfere with MHC class I antigen presentation through distinct mechanisms, highlighting the importance of this process in host defence. Further work will be required to delineate the mechanism by which CPXV12 prevents peptide translocation by TAP and MHC class I assembly and to understand how CPXV12 and CPXV203 interact to mediate immune evasion.

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ORIGINAL RESEARCH PAPERS Byun, M. *et al.* Two mechanistically distinct immune evasion proteins of cowpox virus combine to avoid antiviral CD8 T cells. *Cell Host Microbe* **6**, 422–432 (2009) | Alzhanova, D. *et al.* Cowpox virus inhibits the transporter associated with antigen processing to evade T cell recognition. *Cell Host Microbe* **6**, 433–445 (2009)