

Molecular mechanisms of KSHV immune evasion

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The downregulation of MHC-I molecules from the cell surface of infected cells is an important mechanism of immune evasion developed by several viruses. Kaposi's sarcoma associated herpesvirus encodes an E3-ubiquitin ligase, MIR1, which mediates the ubiquitination of MHC-I molecules on their intracytoplasmic domain. Ubiquitinated MHC-I molecules are endocytosed and degraded by the lysosome. Interestingly, MIR1 is a member of a growing family of E3 ubiquitin ligases that share structural homologies such as a RING-CH domain and two transmembrane domains. Members of this family are widely distributed among eukaryotes (human, mouse, plant and fungus) and their functions remain unknown. Some of these members have an expression restricted to lymphoid organs.

So far, the attachment of ubiquitin on substrate molecules was thought to involve an isopeptide bond and to require that either a lysine residue or the N-terminus of the substrate molecules be accessible to the ubiquitination machinery. We recently observed that MIR1 promotes downregulation of MHC-I molecules lacking lysine residues in their intracytoplasmic domain. Unexpectedly, we found that these MHC-I molecules are ubiquitinated in the presence of MIR1 and that their association with ubiquitin is sensitive to β -mercaptoethanol, unlike isopeptide bonds. We uncovered that a cysteine residue in the intracytoplasmic tail of the lysine-less MHC-I molecules is necessary and sufficient for this novel form of ubiquitination. All together, these results indicate that ubiquitination is not only restricted to proteins encoding accessible lysines but may be more permissive than previously thought.

This novel form of ubiquitination could add a level of complexity in the regulation processes mediated by ubiquitination. For example, since the thiol-ester bond (Ub-cysteine) is more labile than the isopeptide bond (Ub-lysine), cysteine-dependent ubiquitination might be involved in pathways requiring transient ubiquitination. Additionally, the existence of this alternative ubiquitination site might extend the number of potential substrates for ubiquitination to molecules that do not contain accessible lysines or an accessible N-terminus.

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