SKIN CANCER

Benevolent viruses in skin cancer

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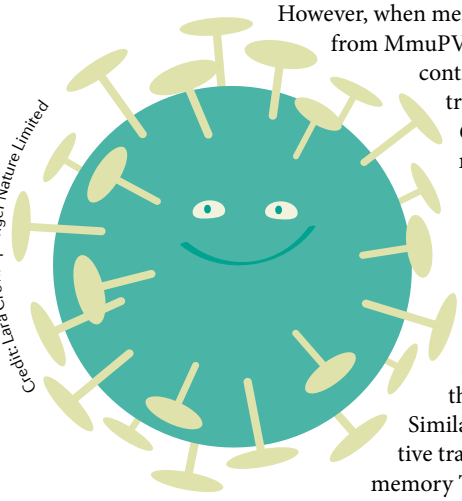
The risk of cutaneous squamous cell carcinoma (SCC) is increased in patients with immunosuppression and associated with beta human papilloma virus (β-HPV). Strickley, Messerschmidt et al. now show that β-HPV infection itself is not causal in SCC development in the context of immunosuppression, but instead it is the loss of β-HPV-mediated T cell immunity that promotes SCC in this context.

β-HPV infection has been hypothesized to facilitate the initiation of carcinogen-driven skin cancer. The authors used back-skin infection of mouse papillomavirus type 1 (MmuPV1) in mice to model carcinogen-driven SCC. C57BL/6J mice infected with MmuPV1 or sham infected were exposed to a chemical carcinogen protocol 2 months after infection, for 30 weeks. MmuPV1-infected mice developed skin tumours, although onset was delayed and the tumour burden was lower than in sham-infected mice. When immunodeficient *Cd4*$^{-/-}$*Cd8*$^{-/-}$ mice were infected with MmuPV1, they developed confluent warts, in contrast to immunocompetent MmuPV1-infected control mice.



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However, when memory T cells from MmuPV1-infected control mice were transferred to *Cd4*$^{-/-}$*Cd8*$^{-/-}$ mice, MmuPV1 infection led to fewer skin warts than in those *Cd4*$^{-/-}$*Cd8*$^{-/-}$ mice that did not receive these T cells. Similarly, the adoptive transfer of memory T cells from MmuPV1-immune mice led to regression of persistent warts in MmuPV1-colonized FVB mice. These mice were also protected from chemical carcinogenesis, suggesting that T cells from MmuPV1-immune mice confer antiviral adaptive immunity that can protect from carcinogenesis.

Moving on to explore ultraviolet (UV) radiation-induced SCC, the authors used the MmuPV1–back-skin infection system in SKH-1 hairless mice. MmuPV1- or sham-infected mice underwent UVB radiation three times a week for 25 weeks, which led to tumour development in both conditions, although MmuPV1-infected mice had fewer tumours and a lower tumour burden than sham-infected mice. Of note, when UVB treatment cycles were completed, the skin of MmuPV1-colonized mice as well as their skin tumours had an increased number of CD8$^+$ T cells compared with sham-infected control mice. When SKH-1 mice underwent antibody-mediated CD8$^+$ T cell depletion after infection with MmuPV1 or sham infection, control MmuPV1-colonized mice developed fewer UVB-induced tumours than the CD8$^+$ T cell-depleted MmuPV1-colonized mice, and fewer tumours than sham(VLP)-infected mice in either treatment group.

Moving on to patients, the authors analysed β-HPV infection in SCC lesions from patients with or without immunosuppression, using RNA in situ hybridization to detect E6 transcripts of 25 types of β-HPV. SCC lesions from patients with immunosuppression had higher levels of β-HPV RNA expression than SCC lesions from immunocompetent patients. Also, β-HPV RNA expression was reduced in cancer cells compared with adjacent normal skin cells in both groups. These results were reflected in a higher viral load in SCC lesions in patients with immunosuppression compared with immunocompetent patients, and also correlated with fewer tumour- and skin-infiltrating CD8$^+$ T cells in patients with immunosuppression. In line with antiviral adaptive immunity in immunocompetent patients, β-HPV E7 peptides were able to activate CD8$^+$ T cells isolated from the normal facial skin of these patients. Returning to their animal model, the authors performed RNA sequencing of skin warts, MmuPV1-infected UVB-treated skin and tumours, and sham-infected tumours of SKH-1 mice. Among the genes that were upregulated in MmuPV1-induced warts and UVB-induced tumours from MmuPV1-infected compared with sham-infected mice, immune-related genes including damage-associated molecular pattern (DAMP) genes were detected.

This study highlights the role of commensal HPVs in priming adaptive immunity in immunocompetent hosts and presents an opportunity for developing antiviral T cell-based vaccines to prevent skin carcinogenesis.

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ORIGINAL ARTICLE Strickley, J. D. et al. Immunity to commensal papillomaviruses protects against skin cancer. *Nature* https://doi.org/10.1038/s41586-019-1719-9 (2019)
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