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### **Skin colonisation with beta papilloma virus drives tissue immunity and resistance to squamous cell cancer**

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Strapline

Local immunity to papilloma virus persisting in skin cross-protects against development of squamous skin carcinoma.

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Running title: Epidermal immunity against virus infection and cancer

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Vast numbers of highly diverse bacterial, fungal and viral microorganisms inhabit our body's barrier tissues where they constantly interact with the immune system. Critically, exposure to commensal microbes or low-level infection with persisting pathogens can promote tissue homeostasis and enhance resistance to unrelated pathogens <sup>1, 2</sup>. However, whether this also extends to protection against the carcinogenic effects of environmental factors such as UV irradiation or toxic agents, has remained unclear. In a recent study published in Nature, Strickley and colleagues provide an intriguing example of how constitutive immune activation by a persisting but controlled skin virus, beta papillomavirus, can drive efficient immunity against the development of squamous cell carcinoma (SCC) <sup>3</sup>. As such, their results provide a fresh view on the clinical association between beta human papilloma virus infection (HPV) and SCC in human patients.

SCC is a form of epithelial skin cancer linked to UV irradiation. Immunocompromised individuals are at higher risk of developing SCC and insufficient immunity translates to heightened morbidity, with advanced cutaneous SCC posing a significant risk to organ transplant recipients <sup>4</sup>. Of note, SCC lesions commonly harbour beta HPV <sup>5</sup>, which has led to the proposal that beta HPV infection was a co-factor in SCC development. In contrast to the well-established role for high-risk alpha strains of HPV in promoting cervical cancer however, evidence for a causal link between beta HPV and skin cancer has been missing. To address this question, Strickley *et al.* started off by colonising mouse skin with the murine beta papilloma virus strain, MmuPV1. While genetically immune-deficient mice developed large numbers of MmuPV1-induced warts, most wild-type mice completely resisted wart development or developed immunity over longer periods of time which ultimately resulted in wart regression despite virus persistence in the skin epidermis<sup>3</sup> (Figure 1).

Virus control was T cell-dependent and immunity could be boosted by transfer of CD8<sup>+</sup> T cells from immune mice to recipient mice that previously failed to mount sufficient immunity. It further coincided with the generation of epidermal CD8<sup>+</sup> T cells displaying a CD103<sup>+</sup> phenotype consistent with tissue-resident memory T (T<sub>RM</sub>) cells. Intriguingly, immunosuppressive UV-irradiation triggered wart development in previously immune mice,

emphasising that suppression of warts relied on ongoing immune control, most likely mediated by  $T_{RM}$  cells. The authors went on to show that immune competent wild-type mice that successfully suppressed wart development were protected from chemically or UV-induced carcinogenesis. This was reflected in a lower tumour burden and incidence, and overall slower kinetics in virus-immune compared to non-immune mice. This remarkable finding held true across various genetically distinct strains of MmuPV1-immune mice<sup>3</sup>. Thus, their results paint a picture where  $T_{RM}$  cell-driven virus control in the form of a dynamic host-pathogen equilibrium promotes broader tissue immunity, extending to the suppression of skin cancer (Figure 1).

Consistent with their preclinical data, Strickley *et al.* found that normal human skin harboured high numbers of beta human papilloma (HPV)-reactive  $T_{RM}$  cells. Those cells were significantly reduced in immunosuppressed individuals such as organ transplant recipients, which at the same time presented with increased beta HPV load in skin. Interestingly, beta HPV-DNA and transcripts were significantly reduced in SCC tumours compared to surrounding skin and similar observations were made in a proportion of MmuPV1-immune mice that eventually developed warts<sup>3</sup>. Together, these results imply selection against virus-infected keratinocytes and thus provide a novel link between antiviral immune surveillance by  $T_{RM}$  cells and localised protection from cancer development (Figure 1).

The mode of  $T_{RM}$  control in driving protection from both persisting virus infection and skin carcinogenesis remains to be defined. Malignant transformation and increased division of cancerous keratinocytes may result in stronger or altered presentation of papilloma virus antigens and thus T cell receptor dependent  $T_{RM}$  activation. At the same time,  $T_{RM}$  cells may recognise a broad array of stress molecules which are likely to be expressed at elevated levels by virus-infected SCC cells, including the NKG2D ligands MICA (human) and Rae-1 (mouse). Therefore,  $T_{RM}$  cell-mediated protection may at least in part be due to direct recognition of virus-infected cancer cells, explaining the apparent selection of virus-negative escape variants during eventual SCC development. In addition, intermittent or continuous low level  $T_{RM}$  stimulation by virus persisting in normal keratinocytes may promote innate immune mechanisms that suppress SCC development in an antigen non-specific manner. Consistent with this idea, strong  $T_{RM}$  cell activation by cognate antigens can elicit potent non-specific antiviral immunity<sup>6,7</sup>. Likewise,  $T_{RM}$  cells induced by colonisation of mouse skin with *Staphylococcus epidermidis* has been shown to enhance immunity towards infection with *Candida albicans*<sup>1</sup>. Finally, while  $T_{RM}$  cell-mediated immunity may

result in rapid elimination of malignant keratinocytes during transformation, T<sub>RM</sub> cells may also act to control microscopic and clinically occult SCC lesions in a cancer-immune equilibrium, as recently shown in a mouse model of melanoma<sup>8</sup>.

Overall, the study by Strickley *et al.* provides an intriguing alternative explanation for the association of beta HPV with SCC by demonstrating that virus colonisation of skin facilitates immune control of cancer. This type of cross-protective tissue immunity is orchestrated by a localised pool of T<sub>RM</sub> cells, which echoes the well-documented functions of T<sub>RM</sub> cells in other types of infections and cancers, as well as overall tissue homeostasis<sup>9</sup>. It is therefore tempting to speculate that skin colonisation with other commensal microorganisms may similarly promote T<sub>RM</sub>-mediated immunity to SCC and potentially other cancers. Future studies will have to address these questions and will thereby open new avenues for cancer immunotherapies by harnessing tissue immunity to commensal microflora. Importantly in this respect, Masopust and colleagues recently demonstrated that viral peptide stimulation of tumour-associated T<sub>RM</sub> cells can elicit highly effective cancer immunity<sup>10</sup>. Finally, although mechanistically somewhat different, these strategies are related to recent attempts at exploiting the intriguing link between gut microbiota and improved responses to checkpoint blockade cancer immunotherapy. These are fascinating examples of how we derive a major benefit from our intimate co-existence with the myriad of microorganisms that inhabit our body, and of how future therapies may successfully harness these interactions to fight cancer.

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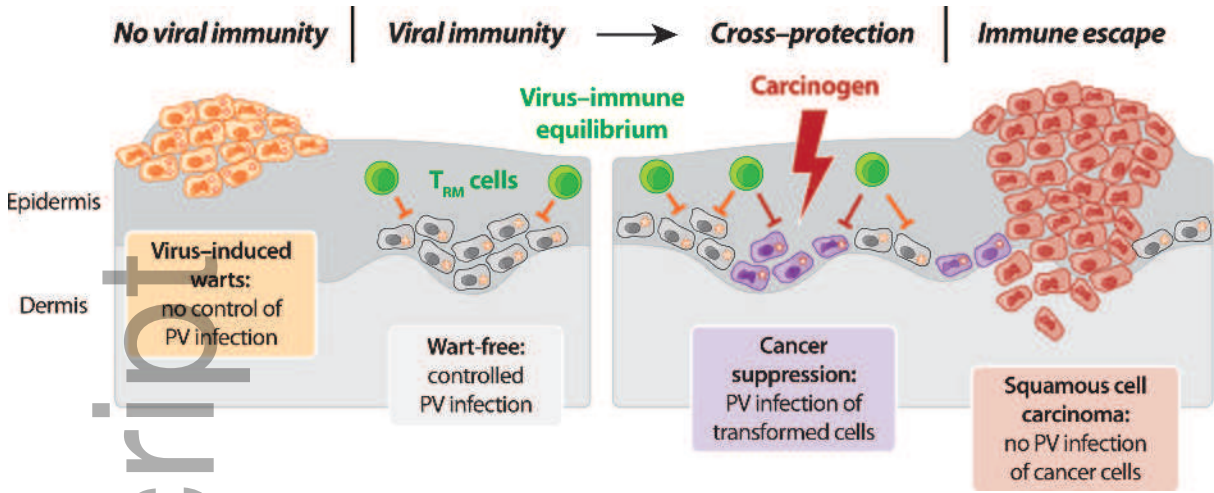
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Figure 1 CAPTION

**Figure 1. T<sub>RM</sub>-mediated immunity to persisting papilloma virus drives protection from squamous skin cell cancer.** In the absence of adaptive immunity, infection of skin cells with beta papilloma virus (PV) induces wart development (orange cells). Efficient local immunity mediated by CD103<sup>+</sup> CD8<sup>+</sup> epidermal T<sub>RM</sub> cells (green) can contain persisting PV infection of skin cells (grey) and suppress wart development in a form of virus-immune equilibrium. T<sub>RM</sub> cell-mediated control extends to PV-infected skin cells that have undergone chemically or UV-induced transformation (purple cells) and thereby suppresses tumour formation. Loss of this cross-protection and development of squamous cell carcinoma may be driven by selection of uninfected cancer cells (red).



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