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Altering the balance between immune activation versus regulation in the skin to promote CD8+ T-cell activity within epithelial cancers

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The Human Papilloma Virus (HPV) 16 is a high-risk HPV known to be a causative agent in numerous cancers including cervical cancer. While prophylactic vaccines exist to combat the spread of HPV16, successful therapeutic vaccines to combat established HPV16-associcated disease remain elusive. The expression, in a mouse model ("E7"), of the HPV16 E7 gene in keratinocytes under the control of the K14 promoter, leads to a local immune suppressive environment, as evidenced by the lack of graft rejection when E7 skin grafts are placed on WT recipient mice. Furthermore, well healed (>30 days) E7 skin grafts are not rejected when mice are immunised with E7 peptide in combination with Quil A- or CASAC-based adjuvants. This is despite a substantial increase in E7 peptide/H-2D^{b} pentamer staining in the blood, and marked killing of E7-peptide expressing TC-1 cells when injected i.v., confirming that CD8 T-cells respond to vaccination and differentiate into CTL capable of killing E7-expressing target cells. We hypothesised that the removal of regulatory T-cells (T-reg) might lead to E7 graft rejection in immunised mice. The co-administration of an anti-CD4-depeting antibody at the time of immunisation led to rejection of ~50% of grafts. To confirm a role for T-reg, E7-grafted T-reg-deficient Rag1$^{-/-}$ mice received purified donor CD8 T-cells from E7-vaccinated WT mice. FACS staining of Rag1$^{-/-}$ lymph nodes 30 days post CD8^{+} T-cell transfer confirmed the absence of classical CD4^{+}FoxP3^{+} Treg, however the E7 grafts did not reject. As in the WT mice however, rejection could be induced through the co-administration of an anti-CD4 antibody. The data suggest that the removal of a CD4^{+}, non T-reg cell, leads to CD8^{+} T-cell activity in the skin as evidenced by E7 skin graft destruction.