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Promoting intolerance: learning from warts

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The current issue of the *BJD* includes an article by Xie *et al.*,¹ demonstrating that condyloma, a common manifestation of human papillomavirus (HPV) infection, expresses high levels of an enzyme, indoleamine-2,3-dioxygenase (IDO), that mediates immunosuppression. In this study, Xie *et al.* found that IDO is more highly expressed in the keratinocytes of HPV-infected skin than in surrounding control keratinocytes. In addition, they showed that levels of IDO were not systemically elevated in these patients, thus demonstrating that the immunosuppression in patients with condyloma is not systemic but localized. Finally, in culture experiments, they demonstrated that wart cells can suppress the proliferation of autologous T cells, and this can be blocked by an IDO inhibitor.

Why should dermatologists care about this mouthful of words? Because warts are among the top 10 diagnoses in dermatology. They are a source of frustration for patients, and have additional significance because of the premalignant potential of genital and oral warts. Warts are caused by HPV, and in addition to being bothersome, they have been implicated in head and neck cancer, and cervical and anal carcinomas.²

HPV involves several genes that could potentially elicit an immune response, including E6 and E7, which bind to the tumour suppressors p53 and Rb, respectively.³ In addition, they have viral capsid genes for packaging of mature virions. Despite the presence of multiple foreign proteins, warts are difficult to eliminate. In fact, most dermatologists would testify that it is often easier to eliminate a 1-cm-diameter basal or squamous cell carcinoma than a similar-sized wart. Thus, warts have potent local immunosuppressive mechanisms.

We have previously studied condyloma acuminata, and have demonstrated that these lesions have elevated interleukin-10 and interferon (IFN)- γ compared with uninvolved skin, and decreased transporter associated with antigen processing (TAP) 1 expression.⁴ The elevated IFN- γ indicates that the lesion is being recognized by the immune system, but the response is ineffective.

Xie *et al.* have identified elevated levels of the immunomodulatory enzyme IDO, an enzyme that depletes tryptophan into immunosuppressive metabolites. These immunosuppressive

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Conflicts of interest

None declared.

Supporting Information

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metabolites stimulate the production of T regulatory cells (Tregs), which impair the beneficial CD8 cytotoxic response required to clear the wart (Fig. 1).⁵ An unexpected finding in this study is that HPV-infected keratinocytes were the major site of IDO expression, while in a K14-E7 transgenic mouse the primary site of IDO expression is dendritic cells.⁶ Given that condylomata express both E6 and E7, and that E6 degrades p53 and E7 degrades Rb, it is likely that the inhibition of p53 in itself results in increased expression of IDO.

We now have enough of an understanding of the immunology of warts to translate to the clinic. HPV infection causes an appropriate stimulation of IFN- γ in humans. However, IFN- γ may be a double-edged sword. HPV oncogenes E6 and E7 inactivate p53 and Rb, leading to a situation where IFN- γ promotes the production of IDO and interleukin-10.⁷ Activation of the antioxidant enzyme haem oxygenase 1 blocks IDO expression, and can be induced by compounds like brilliant green, related to gentian violet.^{8,9} Finally, the expression of the antigen-expressing protein TAP1 is controlled by the master regulator NLRC5 (NOD-like receptor family CARD domain containing 5), which also controls the expression of major histocompatibility complex (MHC) class 1.¹⁰ As TAP1 is downregulated, it is likely that MHC class 1 is downregulated, so the wart does not present the HPV antigen, while it promotes Treg production through the activity of IDO.

How can we translate this to the clinic? Currently, imiquimod is widely used in the treatment of warts, in combination with destructive modalities. Given that IFN- γ can promote the activity of IDO, and that warts already have elevated levels of IFN- γ , one would predict that imiquimod alone will not cure warts. Additional steps are necessary. Recent findings have shown that nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived reactive oxygen promotes the development of Tregs, and that decreased NADPH oxidase decreases Treg function.¹¹ Thus, we propose the addition of topical NADPH oxidase inhibitors to imiquimod; as dermatologists, we have access to a topical NADPH oxidase inhibitor, gentian violet. We currently use the combination of gentian violet and imiquimod for plantar warts after paring, and have found it to be successful (unpublished data).

Finally, these findings have implications far beyond warts. Currently, immunotherapy, including checkpoint inhibitors, is becoming widely used, but for most malignancies these novel inhibitors are effective only one-third of the time. It is highly likely that the resistant tumours have poor antigen presentation due to loss of MHC class 1/TAP1 activation and produce IDO to stimulate Tregs. The principles that guide the treatment of warts, namely destructive modalities, combined with blockade of immunosuppressive modalities (i.e. IDO) and enhanced antigen presentation, will likely lead to enhanced success in the treatment of malignancies. The paper by Xie *et al.*¹ demonstrates that even benign lesions have multiple mechanisms of immunosuppression, and that blocking multiple local immunosuppressive factors may be required to convert a neoplastic cell into an effective antigen-presenting cell.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Human papillomavirus (HPV) E6 and E7 coordinately upregulate indoleamine-2,3-dioxygenase (IDO) expression in condyloma tissue while downregulating antigen-presenting proteins, allowing tolerance of lesions expressing viral proteins. MHC, major histocompatibility complex; TAP1, transporter associated with antigen processing 1; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.