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Psoriasis and papillomaviruses

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ORIGINAL ARTICLE, p 771

For many years, a search for a viral trigger or cofactor for psoriasis has failed to give any clear pathogenetic lead. Among the candidates for disease-influencing infectious agents are the cutaneous papillomaviruses, especially the betapapillomaviruses, the genotypes originally described in epidermodysplasia verruciformis. They are found commonly in the skin and skin cancers of the immunosuppressed and are not uncommon in normal individuals. With the ability to remain latent or as subclinical commensals on the skin, but with known epidermal proliferative effects, this virus group fulfils some of the possible requirements to influence development of psoriasis lesions on the skin.

It is over a decade since the first report suggested a possible link between psoriasis and papillomavirus infection, when both anti-papillomavirus antibodies and human papillomavirus (HPV) detection in patients with psoriasis were found to be higher than in normal individuals and patients with atopic dermatitis.[1] de Koning *et al.*,[2] in this issue, compare patients with psoriasis and with atopic dermatitis, using both the detection of betapapillomavirus DNA in eyebrow hair bulbs and the level of antibodies to the viral capsid coat protein, the L1 protein, in 15 β-HPVs.

The authors report β-HPV detection in 100% of 27 patients with psoriasis compared with 81% in 17 patients with atopic dermatitis. These viruses can be detected in up to 90% of normal individuals, so the atopics would be within the normal range. Antibodies to the β-HPVs, however, were more common in patients with atopic dermatitis (88%) compared with patients with psoriasis (56%). Some larger, more detailed studies have suggested that antibodies to β-HPVs may increase with age in the general population,[3,4] but the prevalence of a large range of antibodies in a group of relatively young patients with atopic dermatitis (mean age 40 years) is higher than expected. It could be speculated that the immune response is helping to control the virus carriage or the effects of its presence, but as antibodies to HPV are not known to clear infection it is unlikely that they could play an active role in removal of established HPV presence.

This study does not confirm a pathogenetic role for HPV in psoriasis, but it does add further support to the published data suggesting that β-HPVs are readily detectable in psoriasis and that this may not just be due to inflammation and poor barrier function of the skin. There is no universal agreement that patients with psoriasis harbour a larger number of HPV types than normals,[5] but the results here corroborate this previously reported finding.[6] There is quite some way to go before we will really know if and how psoriasis is influenced by these papillomaviruses.

Cambridge University Hospitals J.C. STERLING
NHS Foundation Trust, Cambridge CB2 0QQ, U.K.
E-mail: jcs12@cam.ac.uk

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Conflicts of interest
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Stratum corneum RNA levels are diagnostic for melanoma

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The stratum corneum (SC) is continually shed from the skin surface and renewed from underlying keratinocytes that terminate growth and digest their DNA. While it would be reasonable to assume that most DNA and RNA would be broken down into nucleotides and returned to the body, an adequate amount of RNA molecules remains in the SC to allow for molecular characterization.[1] The article by Wachsman *et al.*[2]

reveals that RNA isolated from the SC overlying skin lesions includes sufficient information to diagnose melanoma. In their study, the SC was isolated by removing adhesive tape affixed over skin lesions. The RNA isolated from the SC was studied on gene expression arrays to determine relative gene expression levels. Wachsman *et al.* showed that 312 genes were differentially expressed between melanomas, naevi and normal skin specimens. Hierarchical clustering revealed two major branches: one including melanomas and the other including normal skin. The RNA expression patterns from the naevi studied were split, with 13 lesions segregating with melanoma and 55 lesions with normal skin. Genes segregating with the melanomas included melanocytic differentiation genes such as tyrosinase, tyrosinase-related protein 1 and dopachrome tautomerase. Further to optimize segregation of the lesions, melanomas were compared directly with naevi to develop a classifier containing 168 genes with a sensitivity of 100% and a specificity of 88% on a test set of 39 melanomas and 89 naevi.

The classifier was further reduced to a set of 17 genes that maintained the 100% sensitivity and 88% specificity. The melanocytic differentiation markers noted above were not included. Upregulated genes in this 17-gene set included: *KIT* and *EDNRB*, genes associated with melanocytic development and proliferation; *PRAME*, a gene preferentially expressed in melanoma, breast cancer and ovarian cancer; *TRIB2*, a gene that promotes melanoma growth and survival;[3] and *NAMPT*, a gene overexpressed and implicated in the survival of prostate cancer cells.[4] This reduced classifier includes genes more likely to be associated with malignancy and appears to give better segregation of melanomas from benign naevi.

How the RNA markers get into the SC is not known but it seems likely that the source is pagetoid cells extruded into the SC. Pagetoid cells are common over melanoma but they may also be present over benign naevi.[5] It is likely that this represents a normal melanocytic elimination pathway. The difference between the moles that segregated with normal skin vs. melanoma with the first 312-gene cluster including melanocytic differentiation markers may have been due to differences in growth phase and elimination of excess melanocytic cells into the SC. The problem with overcalling the benign naevi was reduced in the 17-gene classifier presumably due to selection of genes more likely to be associated with malignant melanocytic cells.

The findings of Wachsman *et al.* open a new area for the molecular diagnosis of melanoma. It is clear that larger prospective studies with higher naevus to melanoma ratios are needed, but the technology holds significant promise. The ability to use SC RNA for diagnostic purposes may also have utility in a vast number of other dermatological conditions. While this technology may hold great utility in the clinic, it also lends itself to self diagnostics. It is possible that at some point in the future, a worried patient will be able to place the tape over a skin lesion, draw around the lesion location, and send the tape to a central laboratory for diagnosis. The patient might even have the result faster than the appointment with the dermatologist.

Miller School of Medicine, University of Miami, Miami, FL 33136, U.S.A.
E-mail: *grichnik@miami.edu*
J.M. GRICHNIK

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Spatial variation in incidence of nonmelanoma skin cancers

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This paper by Carsin *et al.*[1] in the current issue of *BJD* is the first to look at the important issues of geographical, urban/rural and socioeconomic variations in incidence of nonmelanoma skin cancers (NMSCs). As the authors note, NMSCs are the commonest cancers in white populations yet few cancer registries comprehensively record data on them. This has significantly hampered epidemiological study of these cancers which are rarely fatal, but because of their great number, impose a significant burden on both primary and secondary care services. Moreover, a clinically important proportion of patients will need extensive and cosmetically challenging surgery. The setting is ideal: a fairly homogeneous fair-skinned population with a cancer registry which registers all NMSCs. The study is an ecological study which cannot provide definitive aetiological answers. However, it makes some interesting discoveries. A key finding is of a significant inverse association between deprivation and incidence which is stronger for basal cell carcinoma (BCC) than squamous cell carcinoma (SCC).