TUMOUR IMMUNOLOGY

Early exposure is inflammatory

Sunburn during childhood has been associated with an increased risk of melanoma development, and in a recent *Nature* paper, M. Raza Zaidi, Glenn Merlino and colleagues have shown that changes in the immune response in the skin of young mice after exposure to ultraviolet B (UVB) light could help to promote melanoma development and progression.

Melanocytes (pigment-producing cells) constitute approximately 1% of skin cells, making their biology and behaviour difficult to study *in vivo*. To overcome this, the authors generated a transgenic mouse model in which the expression of green fluorescent protein (GFP) in melanocytes could be switched on and off. These mice were then exposed to either UVB or UVA wavelengths at postnatal day 1,

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and skin samples were examined. UVB but not UVA triggered melanocyte activation (increased proliferation and migration to the epidermis), and this response lasted for at least 10 days. To further understand this, the authors isolated GFP⁺ melanocytes 1 day and 6 days after exposure to UVB and carried out an expression microarray. Although stress response genes showed increased expression 1 day after UVB exposure as expected, a subset of genes indicative of a response to interferon- γ (IFN γ) showed a delayed response to UVB at 6 days.

To verify the involvement of IFN γ , the authors blocked both type I (IFN α and IFN β) and type II (IFN γ) responses in young mice ahead of UVB exposure, and found that inhibition of the IFN γ response blocked melanocyte activation. So, which cells in the skin produce IFN γ after exposure to UVB? Immunohistochemical analyses of the skin from young mice 6 days after UVB exposure showed that the majority of immune cells in the skin were CD11b⁺F4/80⁺GR1⁻ macrophages, and approximately 28% of these cells expressed IFN γ . The microarray data showed that the UVB-exposed melanocytes expressed ligands that bind the CC-chemokine receptors CCR2 and CCR5, and both of these receptors were expressed by the infiltrating macrophages. However, only CCR2-deficient mice showed a defect in the recruitment of F4/80⁺ macrophages after exposure to UVB. Moreover, the expression of CCL8, a CCR2 ligand, was substantially increased in

activated melanocytes at a time that corresponded to the arrival of the CCR2-expressing macrophages.

So, are CCR2 and CCL8 important to melanoma development? Ectopic expression of CCL8 in mouse UV-induced melanoma cells promoted macrophage recruitment, and activated macrophages increased the growth rate of UV-melanoma cells in syngeneic mice, primarily by inhibiting apoptosis of the melanoma cells. Mice treated with IFN γ -specific antibodies showed reduced melanoma growth and, importantly, immunohistochemical analyses of 27 human melanoma samples indicated that 19 contained substantial numbers of macrophages that expressed IFN γ .

On the basis of these findings, and the fact that the activated melanocytes showed an increased expression of genes that are involved in evasion of the immune response, the authors propose that sunburn in young skin enables melanocytes to evade immune-mediated elimination. Thus, these cells may survive in a state of equilibrium with the immune system prior to the development of a clinically apparent melanoma (an example of the immunoediting paradigm of tumour development). Whether patients with malignant melanoma might benefit from anti-IFN γ therapies needs to be addressed.

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ORIGINAL RESEARCH PAPER Zaidi, M. R. et al.
Interferon- γ links ultraviolet radiation to melanomagenesis in mice. *Nature* **469**, 548–553 (2011)