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The Role of Gadd45a in the Survival of Melanocytes and Melanoma Cells

Vidya Rajpara,[1] Shasa Hu[1] and Robert S. Kirsner[1]

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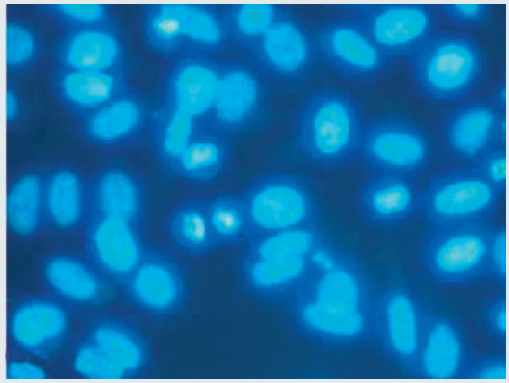

Despite improvements in prevention and screening, mortality from advanced melanoma has not improved (Geller *et al*., 2007) and ultraviolet radiation (UV) is a major risk factor for melanoma development (Fears *et al*., 2002). Greater understanding of the mechanisms of melanoma development may lead to novel treatment options. As opposed to keratinocytes, which routinely undergo apoptosis after UVB irradiation, melanocytes resist apoptosis. In previous work, melanocytes and melanoma cells responded to UVB by activating an original pathway involving Gadd45a, one of the several growth-arrest and DNA damage–inducible genes (Lefort *et al*., 2001).

Fayolle *et al*. (2008, this issue) describe in greater detail the relationship between melanoma cells and UVB-induced apoptosis mediated by Gadd45a, an apoptosis regulator gene. After production of Gadd45a was inhibited, the authors found that melanoma cells reduced colony formation and underwent cell death after UV irradiation, unlike cells with uninhibited Gadd45a (Fayolle *et al*. 2008). To better understand these findings, the investigators explored the mechanisms of this UVB-induced cell death and determined that it was due to apoptosis rather than mitotic catastrophe. They demonstrated that inhibition of Gadd45a led to increased levels of pro-apoptotic proteins (caspase-3) and decreased levels of anti-apoptotic proteins (Bcl-x_L) after UVB exposure, leading to melanoma cell death.

Through the following questions, we will examine this paper in greater detail. For brief answers, refer to http://network.nature.com/group/jidclub.

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QUESTIONS

1. What are the known functions of Gadd45a, and how was it hypothesized to be important in melanoma pathogenesis?
2. What is shRNA, and why was it important for this study?
3. Why was it important for the authors to differentiate apoptosis from mitotic catastrophe as a response to UVB in melanoma cell lines? What surrogate markers of apoptosis did the authors use in their experiments?
4. What can be concluded about the role of Gadd45a in melanoma survival based on this article?
5. What may be the clinical implications of this article?

[1]*Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA*