Original Article

Subject Category: Melanocytes/Melanoma

Journal of Investigative Dermatology (2010) **130**, 2250–2258;
doi:10.1038/jid.2010.146; published online 3 June 2010

Targeting X-Linked Inhibitor of Apoptosis Protein to Increase the Efficacy of Endoplasmic Reticulum Stress-Induced Apoptosis for Melanoma Therapy

Emma L Hiscutt[1,4], David S Hill[1,4], Shaun Martin[1], Ryan Kerr[1], Andrew Harbottle[1], Mark Birch-Machin[1], Christopher P F Redfern[2], Simone Fulda[3], Jane L Armstrong[1,5] and Penny E Lovat[1,5]

1. [1]Dermatological Sciences, Institute of Cellular Medicine, Newcastle upon Tyne, UK
2. [2]Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK
3. [3]Children's Hospital, University of Ulm, Ulm, Germany

Correspondence: Penny E. Lovat, Dermatological Sciences, Institute of Cellular Medicine, Newcastle University, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, UK. E-mail: p.e.lovat@newcastle.ac.uk

[4]ELH and DSH are joint first authors.

[5]JLA and PEL are joint senior authors.

Received 12 February 2010; Revised 9 April 2010; Accepted 14 April 2010; Published online 3 June 2010.

Abstract

Melanoma remains notoriously resistant to current chemotherapeutics, leaving an acute need for novel therapeutic approaches. The aim of this study was to determine the prognostic and therapeutic significance of X-linked inhibitor of apoptosis protein (XIAP) in melanoma through correlation of XIAP expression with disease stage, *RAS/RAF* mutational status, clinical outcome, and susceptibility to endoplasmic reticulum (ER) stress-induced cell death. XIAP expression and *N-RAS/B-RAF* mutational status were retrospectively determined in a cohort of 55 primary cutaneous melanocytic lesions selected and grouped according to the American Joint Committee on Cancer staging system. Short hairpin RNA interference of XIAP was used to analyze the effect of XIAP expression on ER stress-induced apoptosis in response to fenretinide or bortezomib *in vitro*. The results showed that XIAP positivity increased with progressive disease stage, although there was no significant correlation between XIAP positivity and combined *N-RAS/B-RAF* mutational status or clinical outcome. However, XIAP knockdown significantly increased ER stress-induced apoptosis of melanoma cells in a caspase-dependant manner. The correlation of XIAP expression with disease stage, as well as data showing that XIAP knockdown significantly increases fenretinide and bortezomib-induced apoptosis of metastatic melanoma cells, suggests that XIAP may prove to be an effective therapeutic target for melanoma therapy.

Abbreviations:

AJCC, American Joint Committee on Cancer; ER, endoplasmic reticulum; FFPE, formalin-fixed, paraffin-embedded; IAP, inhibitor of apoptosis protein; shRNA, short hairpin RNA; SNP, single-nucleotide polymorphism; XIAP, X-linked inhibitor of apoptosis protein