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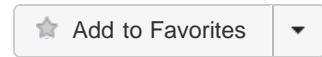
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J Invest Dermatol. 2015 Feb 10. doi: 10.1038/jid.2015.45. [Epub ahead of print]**Exploiting Cannabinoid-Induced Cytotoxic Autophagy to Drive Melanoma Cell Death.**Armstrong JL¹, Hill DS², McKee CS², Hernandez-Tiedra S³, Lorente M³, Lopez-Valero I⁴, Eleni Anagnostou M², Babatunde F², Corazzari M⁵, Redfern CP⁶, Velasco G⁴, Lovat PE².**Author information**¹1] Dermatological Sciences, Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK [2] Faculty of Applied Sciences, University of Sunderland, Sunderland, UK.²Dermatological Sciences, Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK.³Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain.⁴1] Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Madrid, Spain [2] Instituto de Investigaciones Sanitarias San Carlos (IdISSC), Madrid, Spain.⁵Department of Biology, University of Rome 'Tor Vergata', Rome, Italy.⁶Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, UK.**Abstract**

While the global incidence of cutaneous melanoma is increasing, survival rates for patients with metastatic disease remain less than 10%. Novel treatment strategies are therefore urgently required, particularly for patients bearing BRAF/NRAS wildtype tumours. Targeting autophagy is a novel means to promote cancer cell death in chemotherapy-resistant tumours and the aim of the present study was to test the hypothesis that cannabinoids promote autophagy-dependent apoptosis in melanoma. Treatment with Δ⁹-Tetrahydrocannabinol (THC) resulted in the activation of autophagy, loss of cell viability and activation of apoptosis, while co-treatment with chloroquine or knockdown of Atg7, but not Beclin-1 or Ambra1, prevented THC-induced autophagy and cell death in vitro. Administration of Sativex-like (a laboratory preparation comprising equal amounts of THC and cannabidiol (CBD)) to mice bearing BRAF wildtype melanoma xenografts substantially inhibited melanoma viability, proliferation and tumour growth paralleled by an increase in autophagy and apoptosis compared to standard single agent temozolomide. Collectively our findings suggest THC activates non-canonical autophagy-mediated apoptosis of melanoma cells, suggesting cytotoxic autophagy induction with Sativex warrants clinical evaluation for metastatic disease. *Journal of Investigative Dermatology* accepted article preview online, 10 February 2015. doi:10.1038/jid.2015.45.

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