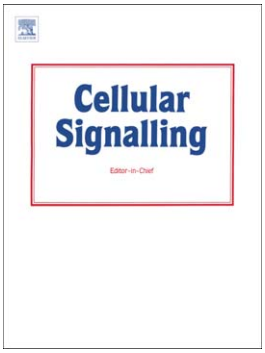

Negative regulation of the FOXO3a transcription factor by mTORC2 induces a pro-survival response following exposure to ultraviolet-B irradiation

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Negative regulation of the FOXO3a transcription factor by mTORC2 induces a pro-survival response following exposure to ultraviolet-B irradiation

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Highlights:

- Regulation of FOXO3a protein is dependent on mTOR signaling in response to UVB.
- Inhibition of mTORC2 signaling increases nuclear localization of FOXO3a
- Disruption of mTORC2 sensitizes cells to FOXO3a-dependent, UVB-induced apoptosis.
- FOXO3a activation by mTORC2 inhibitors may assist in skin cancer chemoprevention.

ABSTRACT

Exposure to ultraviolet-B (UVB) irradiation, the principal cause of non-melanoma skin cancer (NMSC), activates both the rapamycin-sensitive mammalian target of rapamycin complex 1 (mTORC1) and the rapamycin-resistant mTORC2. We have previously reported that UVB-induced keratinocyte survival is dependent on mTORC2, though the specific mechanism is not well understood. FOXO3a is an important transcription factor involved in regulating cell survival. The activity of FOXO3a is reduced as a result of protein kinase B (AKT/PKB) activation, which is downstream of mTORC2; however, the specific function of FOXO3a during UVB-induced apoptosis is unclear. In this study, we establish that in cells with wild-type mTORC2 activity, FOXO3a is quickly phosphorylated in response to UVB and sequestered in the cytoplasm. In contrast, loss of mTORC2 causes FOXO3a to be localized to the nucleus and sensitizes cells to UVB-induced apoptosis. Furthermore, this sensitization is rescued by knockdown of FOXO3a. Taken together, these studies provide strong evidence that inhibition of mTORC2 enhances UVB-induced apoptosis in a FOXO3a-dependent manner, and suggest that FOXO3a activation by mTORC2 inhibitors may be a valuable chemopreventive target in NMSC.

Key Words: Keratinocyte, UVB, apoptosis, FOXO, mammalian target of rapamycin (mTOR), cancer chemoprevention

Footnotes

Abbreviations: mTOR, mammalian target of rapamycin; UVB, ultraviolet-B; NMSC, non-melanoma skin cancer; mTORC1, mTOR complex 1; mTOC2, mTOR complex 2; AKT/PKB, protein kinase B; SCC, squamous cell carcinoma; ERK, extracellular-signal-regulated kinases; MEK, Mitogen-activated protein kinase/ERK kinase; PP2A, protein phosphatase 2A; MST1, mammalian sterile 20–like kinase-1; IKK, IκB kinase; JNK1, c-Jun N-terminal kinases 1; SIRT1, silent mating type information regulation 2 homolog 1; MDM2, mouse double minute 2 homolog; MEF, mouse embryonic fibroblasts; 4OHT, 4-hydroxytamoxifen; 7-AAD, 7-aminoactinomycin D; ANOVA, analysis of variance; PI3K, PI3-kinase; PDK1, phosphoinositide-dependent protein kinase-1; S6K1, ribosomal protein S6 kinase beta-1; FOX, forkhead box.