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The FOXO3-FOXM1 Axis: a key Cancer Drug Target and a Modulator of Cancer Drug Resistance

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Abstract

The FOXO3 and FOXM1 forkhead box transcription factors, functioning downstream of the essential PI3K-Akt, Ras-ERK and JNK/p38MAPK signalling cascades, are crucial for cell proliferation, differentiation, cell survival, senescence, DNA damage repair and cell cycle control. The development of resistance to both conventional and newly emerged molecularly targeted therapies is a major challenge confronting current cancer treatment in the clinic. Intriguingly, the mechanisms of resistance to 'classical' cytotoxic chemotherapeutics and to molecularly targeted therapies are invariably linked to deregulated signalling through the FOXO3 and FOXM1 transcription factors. This is owing to the involvement of FOXO3 and FOXM1 in the regulation of genes linked to crucial drug action-related cellular processes, including stem cell renewal, DNA repair, cell survival, drug efflux, and deregulated mitosis. A better understanding of the mechanisms regulating the FOXO3-FOXM1 axis, as well as their downstream transcriptional targets and functions, may render these proteins reliable and early diagnostic/prognostic factors as well as crucial therapeutic targets for cancer treatment and importantly, for overcoming chemotherapeutic drug resistance.