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Global transcriptome and chromatin occupancy analysis reveal the crucial role of p63 and p73 in skin carcinoma development

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Aberrant expression of transcriptional regulators can affect oncogenic gene expression programs in cancer. Mutations in the tumor suppressor TP53 (p53) are commonly found in UV-damaged skin and are thought to protect damaged epidermal cells from senescence and or oncogene-induced apoptosis, favoring cancer formation. In contrast, the other p53 family members TP63 (p63) and TP73 (p73) are rarely mutated in cancer and TP63 is often amplified or overexpressed in squamous cell carcinoma (SCC). Here, we demonstrate that both p63 and p73 are required for cell proliferation in skin SCC and are overexpressed in preneoplastic lesions and in skin SCCs. p63/p73 form heterotetramers and co-occupy thousands of regulatory regions, jointly controlling a transcriptional program that promotes cell proliferation and tumorigenesis. Combining gene targeting with transcriptomic and epigenetic analyses revealed that p63 and p73 control a transcriptional feed-forward circuit that sustains cell proliferation. We find that in skin SCC a key signaling pathway downstream of p63/p73 is the Epidermal Growth Factor Receptor (EGFR)/MAP kinase. p63/p73 directly and positively control transcription of the EGFR ligands, among which amphiregulin (AREG) is the most highly expressed. p63, p73 and AREG are required to maintain skin SCC proliferative potential, anchorage independent growth, and to promote tumorigenesis. Thus, p63 and p73 act as oncogenic drivers in skin SCC, and AREG is a crucial non-cell-autonomous effector downstream of p63 and p73 in skin SCC formation.

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