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Selective protection of healthy human hair follicles and their stem cells from chemotherapy-induced damage by a novel topically effective p53-targeting peptide

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Introduction & Objectives:

Chemotherapy-induced alopecia (CIA) remains one of the most distressing adverse effects of cancer therapy. No pharmacological treatments are available that selectively protect healthy hair follicles (HFs) and their epithelial stem cells (eHFSCs) from acute and permanent chemotherapy-induced damage without awarding survival benefits to cancer cells. Here, we report that human hair matrix keratinocytes and eHFSCs can be protected against two key CIA-inducing drugs (paclitaxel [PTX] and 4-hydroperoxycyclophosphamide [4-HC]) *ex vivo* by transient, p21-dependent cell cycle arrest induced only in healthy proliferating cells by activation of p53 with ALRN-6924. This clinical-stage "stapled peptide" binds to MDM2 and MDMX, the endogenous inhibitors of p53, and thus activates p53 signaling in cells with a wild-type TP53 genotype (note that 50% of cancers are TP53-mutant).

Materials & Methods:

Full-length anagen VI scalp HFs or 4 mm scalp full-thickness skin punches were collected from healthy donors and cultured for 3 days in a serum-free medium. After 3 days of organ culture, the samples were frozen in liquid nitrogen. 6µm of tissue cryosections were performed and processed for quantitative (immuno)-histomorphometry analyses.

Results:

Pretreatment of human scalp HFs with ALRN-6924 significantly inhibits PTX- and 4-HC-induced premature catagen development and hair matrix damage, HF pigmentary abnormalities, apoptosis measured by cleaved-caspase-3, "mitotic catastrophe" and micronucleation. It also reduces DNA damage (g-H2Ax), apoptosis, and pathological epithelial-mesenchymal transition in eHFSCs (co-expression of vimentin/Slug and Keratin 15). Most of these CIA-protective effects were also seen after topical ALRN-6924 application to organ-cultured, chemotherapy-treated human scalp skin.

Conclusion:

We thus introduce a novel principle for the selective protection of rapidly proliferating healthy human epithelial tissues and their stem cells from chemotherapy-induced damage as a highly innovative strategy for protecting patients with TP53-mutant cancers against acute and permanent CIA.