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Current state of development of human polymerase α inhibitors as innovative tumour therapeutics

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Actinic Keratosis (AK) is considered to be the most frequent carcinoma in situ today. AK lesions commonly occur on sun-exposed areas of the skin and organ transplant recipients with AK have the highest risk to develop invasive squamous cell carcinoma (SCC)[1]. Current AK therapy is limited either due to adverse drug reactions and/or limited efficacy. Hyperkeratosis, frequently associated with AK, reduces drug penetration to the target site.

Human polymerase-α inhibitors, identified by molecular modelling[2,3], outperformed the current standard for AK therapy, 5-fluoruracil, when tested in the tumour cell line SCC25, while not or at least less affecting normal human keratinocytes[4]. In order to achieve satisfactory penetration into skin of the most selective human polymerase-α inhibitor OxBu, the agent was loaded to solid lipid nanoparticles (SLN) with glyceryl behenate as lipid phase. The dispersion containing DMSO as penetration enhancer was embedded in a hydroxyethyl-cellulose gel matrix. In vitro release studies indicated prolonged OxBu release.

Based on the 3D SCC construct developed by Hoeller Obrigkeit and co-workers [5] an AK-like construct was grown in our laboratories and characterised. SCC12 cells forming nests were detectable in particular in the epidermis. OxBu induced a reduction in Ki-67 (proliferation marker), cytokeratin-10, AxL (SCC markers), MMP2 (invasion marker), while caspase-7 was activated (apoptosis marker). Aiming to substantiate the mode of cell death, the secretion of total cytokeratin-18 (marker for necrosis and apoptosis) and its caspase cleaved product (marker for apoptosis) were investigated by ELISA following OxBu exposure for up to 7 days. OxBu 0.05% solution appeared to be at least equipotent compared to solutions of both 5-fluorouracil 0.1% and aphidicolin 0.025%. The former being the gold standard of current AK therapy, the latter being frequently used as standard inhibitor of human polymerase alpha and delta for in vitro testing, however, failed to be introduced into clinical use. Taken together, OxBu may offer a novel approach for actinic keratosis therapy.

References

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