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Targeting the DNA damage response pathways in the repair of acute thermal and ultraviolet light injury

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Abstract

Damage to the DNA resulting in double stranded breaks in the DNA (DSB) triggers the DNA damage response or DDR. This results in cell cycle arrest, associated with DNA Damage Response (DDR) pathways channeling repair enzymes to the damaged DNA histones. The presence of the DSBs is sensed by a multifunctional sensor complex (MRN). MRN complexes can bind to the exposed DNA ends directly and unwind the DNA ends in an ATP-dependent manner. This is important for nucleotide excision of the damaged segments of DNA, and later replication of the nucleotides during DNA repair. The DDR pathway involves recruitment of multiple proteins to the damaged DNA sites, including checkpoint proteins 1 and 2, and ubiquitin kinases. All activities within the cell are put on hold (cell cycle arrest), while nucleotide excision and repair pathways are initiated. When the cell is too badly damaged, apoptosis is induced but this only occurs after many attempts at repair, and apoptosis is only induced by replication stress when repair fails to occur. Cell cycle arrest is inhibitory to rapid healing of tissues. Moreover, the intrinsic repair processes are slow and laborious, and do not return the tissues to pre-injury levels. When large segments of the DNA are damaged, or if the damage involves both strands of the DNA, replication errors occur, producing a potentially premalignant cell. Curcumin is a phytochemical with anti-inflammatory, anti-photodamage and anti-carcinogenic properties. Curcumin induces apoptosis through inhibition of DDR pathways, with rescue of the damaged cells from cell cycle arrest. In this paper, we describe curcumin signaling targets in the DDR pathways as a basis for the rapid repair with no residual scarring in acute injury such as burns and sun-burn.

Biography

Madalene C. Y. Heng MD, FRACP, FACD, FAAD is clinical professor of Medicine/Dermatology UCLA School of Medicine. She was chief, Division of Dermatology at the UCLA San Fernando Valley Program from 1979 to 2003. Dr Heng is a reviewer of multiple journals including the Journal of the American Academy of Dermatology, International Journal of Dermatology, British Journal of Dermatology, Lancet (London), Molecular Pharmaceutics, among others. With more than 130 publications including 76 publications in peer-reviewed journals on topics such as phosphorylase kinase activity in psoriasis and photodamaged skin, Dr Heng is able to link treatment of disease to their pathophysiology. Dr Heng is the developer of curcumin gel.