Signal transduction pathways involved in the delayed wound healing of skin injuries induced by sulfur mustard


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Sulfur mustard (SM) is a chemical warfare agent that provokes severe inflammation and blistering upon exposure to the skin accompanied by disturbed wound healing. The potential use of SM in terroristic assaults amplified the interest in understanding the underlying cellular and molecular pathomechanisms in order to improve therapeutical intervention.

The results of our studies demonstrated that the activity of the mitogen activated protein kinase (MAPK) p38 was essentially required for differentiation of normal human epidermal keratinocytes (NHEK) into mature keratinocytes whereas ERK1/2 activity impeded this process. Remarkably, treatment of NHEK to SM prematurely induced differentiation of these cells implicating enhanced activity of p38. Studies on cell function showed that SM-pretreated NHEK exhibited a significantly reduced invasion potential that could be rescued by the application of a p38 inhibitor. These findings suggest that exposure of NHEK to SM triggers a premature p38-dependent differentiation process in epidermal progenitor cells. This may lead to a deprivation of functional progenitor cells required for normal tissue regeneration thus contributing to impaired wound healing of the skin (Popp T. et al., Toxicol Lett., 204:43-51, 2011).

Moreover, we detected that hypoxia-inducible factor 1 alpha (HIF-1α) and its target genes were significantly upregulated during hypoxic conditions in primary skin keratinocytes and fibroblasts with a less pronounced extent of increase upon SM-treatment of the cells. This effect may contribute to the SM-evoked pathophysiology because HIF-1α essentially facilitates normal wound healing by stimulating cell proliferation, migration, autophagy, and angiogenesis in skin.

Thus, our findings suggest the usefulness of specific p38 MAPK inhibitors and modulators of HIF-1α signalling in the therapeutical treatment of skin lesions caused by exposure to SM.

Biography

Tanja Popp was born in Munich in 1979. She studied biology at the Ludwig-Maximilians-University (LMU) of Munich with a focus on cell biology and biochemistry. In 2011 she finished her PhD thesis entitled “Molecular mechanisms in skin cells after the exposure to sulfur mustard” at the Department of Clinical Chemistry and Clinical Biochemistry of the Medical Faculty of the LMU. Currently she works as a postdoc at the Institute for Cardiovascular Prevention (LMU) in a project supported by the German Federal Ministry of Defense investigating the influence of hypoxia in delayed wound healing of the skin after exposure to sulfur mustard.

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