IJAE Vol. 115, n. 1/2 (Supplement), 2010

Impaired cytokine expression in hydrogen sulphide-treated keratinocytes

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Hydrogen sulfide is a component of several natural compounds known to be effective in many inflammatory pathologies. We have recently demonstrated that: i) exogenous H_2S can delay the onset of apoptosis of granulocytes *in vitro* [Lab Invest 2006;86:391]; ii) H_2S exerts a subset-specific toxicity on peripheral blood lymphocytes in terms of cell survival and cytokine production [J Cell Physiol 2007;213:826]; iii) H_2S impairs adhesion and proliferation of human keratinocytes by preventing the activation of Raf-MEK-ERK signaling pathway. Moreover, performing *in vivo* experiments we have observed that NaHS-treatment reduced pERK levels in the epidermis of patients affected by psoriasis [Lab Invest 2009;89:994].

Psoriasis, a chronic inflammatory skin condition that is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, and also by neutrophil and lymphocyte infiltration of epidermal and dermal layers.

On the basis of the biochemical analyses and in vitro studies, it has become evident that IL-8 greatly contributes to the major pathologic changes seen in psoriasis. Furthermore, others cytokines have an emerging role in the pathogenesis of this disease: in particular, IL-17 and IL-22 activate keratinocytes, interfere with keratinocyte and lymphocyte differentiation and proliferation, promote the secretion of inflammatory cytokines.

The signaling pathway downstream IL-17 receptor appears to involve ERK activation: however additional molecular mediators may be recruited as PI3K and Akt.

On this basis, we have now studied the ability of NaHS to affect IL-8 transcription and secretion in human normal keratinocyte NCTC cell line. IL-8 expression was analyzed both at transcriptional and protein level by RT-PCR and ELISA, respectively. Studies have been performed in resting and IL-17 or IL-22-stimulated cell cultures. The ability of NaHS to suppress IL-8 expression *in vivo* was also studied by immunohistochemistry on biopsies from a patient affected by psoriasis, treated for 1 week with NaHS. Results show that NaHS, blocking ERK activation, interferes with IL-8 production.

Sulfurs are able to penetrate the skin, and a sulfur-rich balneotherapy is known to be effective in the treatment of psoriasis. These data suggest that H_2S might be useful to limit the proliferation of keratinoblasts in skin diseases like psoriasis, dermatitis, skin iperplasia and basaliomas, where a functional modification of keratinocyte behavior plays a major pathogenetic role.

Key words
NaHS, ERK, IL-8, NCTC, Western blot, ELISA