Mammalian target of rapamycin in inflammatory skin conditions (Article)

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Abstract

The conserved serine/threonine kinase mammalian target of rapamycin (mTOR) is a major regulator of survival growth, proliferation and motility, in response to mitogens, energy and nutrient levels. Dysregulation of mTOR pathway has been observed in various inflammatory or neoplastic human diseases. To assess the potential involvement of mTOR in some of the most common inflammatory skin diseases, and its interaction with other inflammatory mediators, we investigated mTOR expression in psoriasis, allergic contact dermatitis (ACD) and atopic dermatitis (AD). mTOR gene expression was assessed in the following conditions: i) skin biopsies from 15 patients affected by psoriasis, 5 patients with ACD, 5 patients with AD and 3 patients with EGFR-inhibitor-induced skin rash; ii) in immortalized keratinocytes HaCaT, primary human keratinocytes (KCs) and full thickness skin organ cultures, incubated with tumor necrosis factor (TNF)-α, interleukin (IL) 17A or their combination; iii) in HaCaT cells stimulated with ultraviolet (UV)B; iv) in skin biopsies from 5 psoriatic patients before and after 16 weeks of anti-TNF-α therapy; mTOR expression was also evaluated through immunohistochemistry in lesional and non-lesional skin samples from 5 psoriatic patients. Moreover, mTOR major up-stream and down-stream regulator gene expression was assessed in skin biopsies from 15 patients affected by psoriasis, 5 patients with ACD, 5 patients with AD and 3 patients with EGFR-inhibitor-induced skin rash. All analyzed skin diseases showed an increase of mTOR gene expression whereas mTOR up-stream negative regulators were reduced or not enhanced in all of them. mTOR was strongly expressed in all epidermal layers of lesional and non-lesional psoriatic skin. Conversely, pro-inflammatory conditions, in vitro, were not able to increase mTOR levels, except for UVB. Similarly, anti-TNF-α therapy was not able to reduce mTOR gene expression in patients with psoriasis. Our study provides evidence that mTOR is involved in cutaneous inflammatory process, but through a signalling not directly dependent from Th1-Th17 pathway.