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Short Communication

Lithium induces Nuclear Translocation of NFAT 1 in Cultured Human Keratinocytes: A Role for NFAT 1 in Mediating Lithium-Exacerbated Psoriasis

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Abstract

Systemic ciclosporin A (CsfA) and tacrolimus are effective treatments for psoriasis. CsA and tacrolimus block T cell activation by inhibiting the phosphatase calcineurin and preventing translocation from the cytoplasm to the nucleus of the transcription factor nuclear factor of activated T cells (NFAT). NFAT compose a family of transcription factors that are turned on during T cell activation. The NFAT family is composed of five members: NFAT 1, NFAT 2, NFAT 3, NFAT 4 and the recently isolated NFAT 5

Keywords: human keratinocytes; lithium; NFAT 1; psoriasis

Introduction

Systemic ciclosporin A (CsfA) and tacrolimus are effective treatments for psoriasis. CsA and tacrolimus block T cell activation by inhibiting the phosphatase calcineurin and preventing translocation from the cytoplasm to the nucleus of the transcription factor nuclear factor of activated T cells (NFAT). NFAT compose a family of transcription factors that are turned on during T cell activation. The NFAT family is composed of five members: NFAT 1, NFAT 2, NFAT 3, NFAT 4 and the recently isolated NFAT 5. Inhibition of T cell activation is thought to account for CsA and tacrolimus therapeutic effects in psoriasis. We have previously shown that treatment of cultured human keratinocytes with agents that induce a sustained rise in intracellular calcium, including elevation of extracellular calcium ([Ca2+]o) leads to nuclear translocation of endogenous NFAT1, which was inhibited by pre-treatment with CsA, tacrolimus(Al-Daraji et al., 2002; Reynolds & Al-Daraji, 2002) and recently with nifedipine(Al-Daraji & Reynolds, 2004).

The export of NFAT from the nucleus back to the cytoplasm has been shown to depend on its rephosphorylation by Glycogen Synthase Kinase-3 beta (GSK-3β) (Beals et al., 1997b). Lithium, a GSK-3β inhibitor, has been shown to increase the duration of NFAT residence in the nucleus (Ohteki et al., 2000). LiCl (2 mmol/ml) resulted in nuclear translocation of NFAT 1 in cultured keratinocytes to the nucleus after 24 h (78.2% nuclear positivity, $P<0.0001$ compared to 10.2% nuclear positivity in cells treated with a vehicle control) and was maximal after 72 h (83.6% nuclear positivity compared to 10.2% nuclear positivity in cells treated with a vehicle control). In addition, cells treated with LiCl for 72 h appeared to be more elongated (Figure 1, Figure 2 and Table 1).

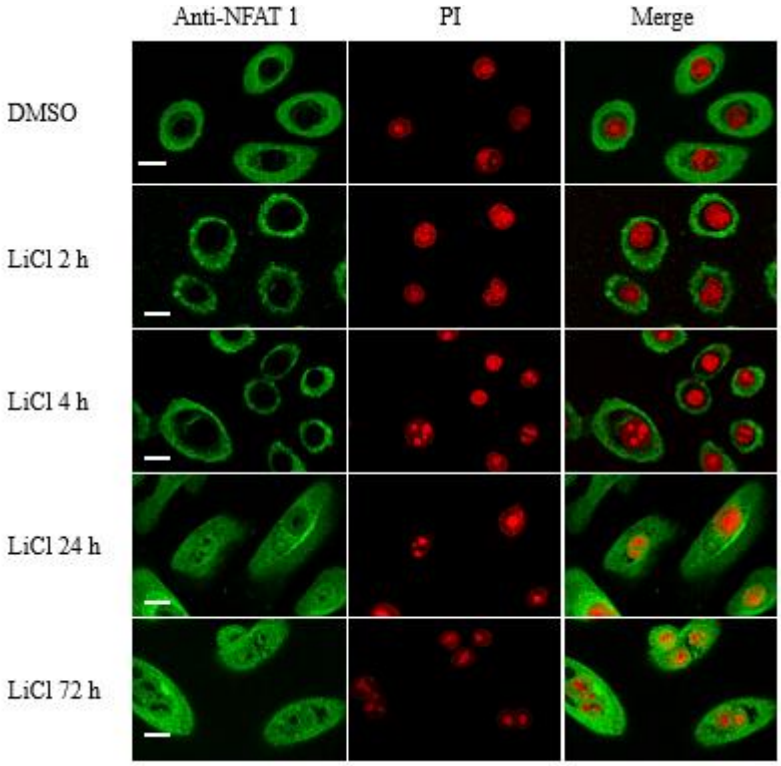

Figure 1: ***Lithium induces nuclear translocation of NFAT 1 in human keratinocytes***. Human keratinocytes were cultured on coverslips in low calcium MCDB 153 medium (control) and then treated with DMSO (vehicle control) or LiCl (2 mmol/l) for 2 h, 4 h, 24 h and 72 h as indicated. Cells were fixed in 4% paraformaldehyde, permeabilised with 0.2% Triton X-100, incubated sequentially with rabbit-polyclonal anti-NFAT 1 antibody, goat anti-rabbit FITC, propidium iodide (50 μg/ml) and visualized using a Biorad confocal microscope. These results are representative of 3 experiments on keratinocytes derived from 3 independent donors. *Scale bar*, 25μM.

Treatment	**NFAT 1**	
	% cells showing nuclear positivity	Number of cells counted
Medium control*	8.9	225
DMSO control†	10.2	225
LiCl 2h¶	8.0	225
LiCl 4 h¶	11.1	225
LiCl 24 h¶	78.2‖	225
LiCl 72 h¶	83.6‖	225

* Low calcium (70 μM) medium,
† Vehicle control,
‡ Ionomycin (1 μM),
¶ LiCl (2 mmol/ml),
‖P<0.0001 compared to DMSO (vehicle control).

Table 1: Lithium induces nuclear translocation of NFAT 1 in human keratinocytes.

Lithium is a mood stabilising drug used to treat manic-depressive (bipolar) disorders (Thase & Sachs, 2000). Psoriasis is known to be induced or exacerbated by lithium compounds (Abel et al., 1986; Skoven & Thormann, 1979). Lithium therapy also provoked both palmoplantar (White, 1982)and generalised pustular psoriasis (Lowe & Ridgway, 1978). GSK-3β is an enzyme that regulates diverse functions in different intracellular signalling pathways including the wnt pathway (Grimes & Jope, 2001). GSK-3β also phosphorylates conserved serines necessary for nuclear export of NFAT (Beals et al., 1997a). Lithium inhibits GSK-3β action on NFAT and thereby increases the duration of NFAT residence in the nucleus (Ohteki et al., 2000). As expected, lithium increased the proportion of NFAT 1 within the nucleus of keratinocytes, although the time course was longer compared to nuclear translocation observed in response to differentiation promoting agents. Lithium was shown to modulate the cell communication of psoriatic keratinocytes with cultured lymphocytes by targeting the secretion of different cytokines such as IL-2 (Ockenfels et al., 1996). The cultured skin in the presence of lithium showed cell crowding of keratinocytes in the lower part of the epidermis, suggesting that lithium might act directly on dividing cells of the epidermis (Wolf et al., 2000). Together these data suggest a role for NFAT in mediating lithium-exacerbated psoriasis. Finally, these observations provide further evidence that Calcineurin/NFAT pathway is functionally active in human keratinocytes.

Conflict of Interest

The Author Declares No Conflict of Interest

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