
# Reduced RNA acetyltransferase NAT10 activity is associated with increased cellular stress in keratinocytes and enhanced inflammatory responses in mouse model of psoriasis

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Background: RNA modifications represent an important layer of post-transcriptional gene regulation, particularly in the context of mRNA. N4-acetylcytidine (ac4C), catalyzed by NAT10, enhances mRNA stability and translational efficiency and has been implicated in cellular stress responses, proliferation, and immune regulation. Here, we investigated whether ac4C is required for epithelial homeostasis and whether it plays a role in immune-mediated skin disease such as psoriasis. Method: To delineate NAT10 function, we performed siRNA-mediated knockdown (KD) of NAT10 in primary human keratinocytes as well as pharmacologically inhibited Nat10 activity in imiquimod-induced psoriasis mouse model. The effect of reduced NAT10 activity was assessed through transcriptomic, mRNA, and protein-level analyses. Results: We show that NAT10 expression is increased in lesional skin from psoriasis patients at both mRNA and protein levels. Additionally, transcriptome analysis revealed that NAT10 KD alters multiple inflammatory signaling pathways and induces a pronounced epithelial stress response in primary human keratinocytes. Specifically, NAT10 KD led to suppression of MYC signaling, alongside activation of TGF-β, IL-6, and STAT3 signaling pathways, and upregulation of genes associated with epithelial mesenchymal transition. Pharmacological inhibition of Nat10 in mice using Remodelin resulted in stronger skin inflammation in the imiquimod-induced mouse model of psoriasis. This was associated with increased expression of Ccl20, Cxcl1, and Il1b in the skin, and elevated Il6, Cxcl2, and Il17a mRNA expression in lymph nodes. Conclusion: Together, our findings identify NAT10-mediated RNA acetylation as a critical regulator of epithelial homeostasis and suggest that enhancing NAT10 activity may represent a potential therapeutic strategy in psoriasis.