

Table SI. Notch-regulated targets disturbed in atopic dermatitis

Notch-regulated targets	Physiological function regulated by adequate Notch signalling	Disturbed Notch-regulation in atopic dermatitis (AD) and AD-like mouse models	Ref.
Epidermal differentiation Involucrin and TGM3 Filaggrin	Notch expression in suprabasal layers → p21-mediated growth arrest, epidermal homeostasis and barrier function Normal expression of involucrin and TGM3 → SCE formation Normal filaggrin processing maintaining low skin surface pH; suppression of <i>S. aureus</i> colonisation	Notch deficiency in AD epidermis → disturbed epidermal differentiation and disturbed barrier function Reduced expression of involucrin and TGM3 → disturbed SCE formation Disturbed filaggrin processing, higher skin surface pH and suppression of factors inhibiting <i>S. aureus</i> colonisation	20, 21, 30-32 34 30-33, 103, 104
Epidermal lipids	Normal barrier synthesis and function due to regular processing of SC barrier lipids	Reduced SC ceramides in AD dry skin; suppression of genes regulating epidermal lipid metabolism; reduced numbers of LBs → disturbed barrier function	24, 28, 33, 51
AP-1	Notch1-mediated repression of AP-1	Insufficient Notch1-mediated repression of AP-1 promoting AP-1-induced skin inflammation and enhanced IL-31 expression	58
TSLP	Notch-mediated suppression of c-Fos-on TSLP promoter; Notch-mediated inhibition of TSLP release	Enhanced c-Fos-mediated TSLP expression driving TH2 polarisation, IL-4-induced IgE and TSLP-induced pruritus	20, 21, 24, 25, 26, 28, 33, 106
GM-CSF	Normal Notch/c-Fos-mediated control of AP-1-promoted expression of GM-CSF	Over-expression of AP-1 in AD keratinocytes with enhanced GM-CSF expression and inflammatory cell infiltration	21, 56, 57
MKP-1	Normal Notch-mediated expression of MKP-1 and MKP-1-mediated feedback inhibition of innate immunity	Insufficient Notch-mediated feedback inhibition of innate immunity with activated macrophages and DCs.	81-84
FoxP3	Normal differentiation and function of Tregs with adequate suppression of TH2 activation	Insufficient Notch-mediated expression of FoxP3 → reduced Treg number and function with enhanced TH2 polarisation	88, 89, 93, 94
Interferon-γ	Normal Notch1-mediated expression of IFN-γ → adequate cutaneous viral defence	Decreased production of IFN-γ by T cells of AD epidermis increasing susceptibility for viral skin infections	97, 98
Claudin-1	Normal expression of claudin-1 with normal function of TJs and control of the paracellular barrier	Reduced expression of claudin-1 and -23 in AD epidermis → disturbed paracellular barrier	44-46
Aquaporin-3	Normal AQP3 expression with adequate control of TEWL	AQP3 over-expression in basal and suprabasal layers due to Notch1 inhibition → enhanced TEWL	38, 40
Sebaceous glands	Maintenance of sebaceous glands with normal sebum production	Sebaceous gland involution with reduced formation of sebum lipids → sebstasis	18, 28, 33, 55

TGM3: transglutaminase-3; SCE: stratum corneum envelope; SC: stratum corneum; AP-1: activating factor-1; TSLP: thymic stromal lymphopoietin; GM-CSF: Granulocyte/macrophage colony-stimulating factor; MKP-1: mitogen activated protein kinase phosphatase-1.