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We Need to Talk About Notch: Notch Dysregulation as an Epiphenomenon in Inflammatory Skin Disease

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Main Text:

The Notch signaling pathway is a highly evolutionarily conserved signaling pathway comprised of four type 1 transmembrane receptors¹. Canonical Notch signaling is stimulated by Jagged and Delta ligands resulting in translocation of the Notch Intracellular domain (ICD) to the nucleus resulting in activation of transcription factor CSL¹. Increased Notch activity is associated with epidermal keratinocyte maturation, proliferation and innate immune activation through maturation of dendritic cells, T cells and macrophages¹. Dysregulation of Notch signaling has been proposed as a component of the pathogenesis of Hidradenitis Suppurativa (HS)², Psoriasis³, Atopic Dermatitis (AD)⁴ and Lichen Planus (LP)⁵. Toll like receptor (TLR) activation can activate canonical and non-canonical Notch signalling¹ and elevated levels of Interferon gamma (IFN- γ) can suppress Notch signaling¹. TLR play a significant role in the pathogenesis of all the aforementioned cutaneous conditions, and IFN- γ , being a key component of Th1 immune response, plays a major role in HS, Psoriasis and LP.

In examining the relationship between reported Notch activity, keratinocyte proliferation, maturation and IFN- γ (Table 1) a number of contradictions emerge. Keratinocyte hyperproliferation is present HS², Psoriasis³, Chronic Atopic Dermatitis⁴ and Lichen Planus⁵, with decreased maturation present in Atopic Dermatitis in association with decreased epidermal barrier function⁴. IFN- γ is elevated in psoriasis³, HS² and LP⁵ and decreased in AD⁴. However, Notch has been identified as downregulated in HS², AD⁴ and LP⁵ (Table 1). If Notch signaling was a major contributor to the pathogenesis of these conditions, then a strong association with both inflammatory mediators and degree of keratinocyte proliferation would be expected.

Additionally, evidence in murine models are used to support the potential role of Notch in inflammatory cutaneous disease, including the Notch-AhR (Aryl-hydrocarbon receptor)-IL-22 pathway^{4,6}. The role of IL-22 as the primary mediator of epidermal hyperproliferation in these diseases is well established⁶. It is also well established that the Notch-AhR-IL-22 pathway is significantly different between murine and human models of disease⁶. Although murine models showed modulation of IL-22 due to Notch signaling, this was unable to be

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replicated in human subjects⁶. Hence the evidence from mouse studies that Notch signaling can influence inflammatory cytokine levels in these diseases needs to be interpreted with caution. Further, no GWAS studies in Psoriasis, LP, AD and preliminary data from HS GWAS have implicated Notch associated genes as strong risk-associated loci for disease.

It is more consistent to consider keratinocyte Notch dysregulation as an epiphenomenon presenting in multiple inflammatory skin diseases. This may be related to the immune-mediated keratinocyte hyperproliferation and alterations to keratinocyte maturation which is dictated by the extracellular cytokine and immunological milieu specific to the disease state.

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References:

1. Shang Y, Smith S, Hu X Role of Notch signaling in regulating innate immunity and inflammation in health and disease *Protein Cell* 2016;7(3):159–174 [PubMed: 26936847]
2. Xiao X, He Y, Li C, Zhang X, Xu H, Wang B. Nicastrin mutations in familial acne inversa impact keratinocyte proliferation and differentiation through the Notch and phosphoinositide 3-kinase/AKT signalling pathways. *Br J Dermatol* 2016 3;174(3):522–32. [PubMed: 26473517]
3. Ota T Takekoshi S, Takagi T, Kitatani K, Toriumi K, Kojima T, Kato M, Ikoma N, Mabuchi T, Ozawa A. Notch signaling may be involved in the abnormal differentiation of epidermal keratinocytes in psoriasis. *Acta Histochem Cytochem* 2014 8 29;47(4):175–83. [PubMed: 25392571]
4. Melnik BC. The potential role of impaired Notch signalling in atopic dermatitis. *Acta Derm Venereol* 2015 1;95(1):5–11. [PubMed: 24853951]
5. Nowwarote N, Osathanon T, Dysregulation of Notch signaling related genes in oral lichen planus *Asian Pacific Journal of Tropical Biomedicine* 2017;7(7):666–669
6. Weidenbusch M, Rodler S, Song S, Romoli S, Marschner JA, Kraft F et al. Gene expression profiling of the Notch-AhR-IL22 axis at homeostasis and in response to tissue injury *Biosci Rep* 2017;37(6): BSR20170099.

Table 1:

Relationship of Notch Dysregulation to Keratinocyte Hyperproliferation, Keratinocyte Maturation, and role of IFN- γ in inflammatory skin disease

Inflammatory Skin Disease	Notch Dysregulation	Keratinocyte Hyperproliferation	Keratinocyte Maturation	IFN- γ	Reference
Hidradenitis Suppurativa	Downregulation	Increased	Increased	Increased	2
Psoriasis	Upregulation	Increased	Increased	Increased	3
Atopic Dermatitis	Downregulation	Increased	Decreased	Decreased	4
Lichen Planus	Up and Down Regulation	Increased	Increased	Increased	5