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Characterisation and novel treatments for atopic dermatitis endotypes: towards a molecular classification.

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Commentary on 'Distinct molecular signatures of mild extrinsic and intrinsic atopic dermatitis'

Since the 19th century the clinical syndrome of atopic dermatitis (AD) has been renamed at least 20 times ¹, whilst over the same time period, psoriasis has remained a well-defined, non-controversial diagnosis with multiple well recognised sub-types. It is likely that the constant attempts by different authors to redefine and reclassify AD, reflects a recognition that the clinical syndrome encompasses more than one disease entity. To date, sub-classification by algorithms based on phenotype have proved of limited use in clinical practice and do not define response to treatment or prognosis. A recent approach to address this issue in other complex diseases has been to define disease endotypes, which classify the disease based on pathogenesis through an analysis of both the clinical and molecular phenotype ².

Most experts currently agree that a defective skin barrier is central to the initiation of AD, but whether a putative distinction between intrinsic AD (primary defect in the skin) versus extrinsic AD (skin defect and allergy) is of clinical relevance, remains of interest. In the paper

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by Martel et al. in this journal ³, the authors set out to examine whether the transcriptome of mild AD reflects that of severe AD, and also to compare extrinsic AD (IgE >200 kU/L) and intrinsic AD. Interestingly, although the numbers studied were small, they showed distinct gene signatures for intrinsic AD versus extrinsic AD and that the transcriptome of the intrinsic form is more aligned to mild psoriasis than to extrinsic AD. Detailed analysis of the gene modules in the intrinsic AD signature suggested that the dominant pathways overlapping between intrinsic AD and psoriasis were inflammatory related, but additionally, genes involved in lipid metabolism were also upregulated in both conditions. Although, inflammation-related genes such as *IL13*, *MMP12*, *CCL18* and *CXCL10* were similarly upregulated in both intrinsic and extrinsic mild AD as for severe AD, distinct differences between the intrinsic and extrinsic AD were seen in key cytokine pathways such as increased *IL22*, *IL36A/G*, *IL36RN* and *CCL22* and decreased *IL37* expression in intrinsic AD. Thus this report provides evidence that the distinction between intrinsic and extrinsic AD reflects genuinely different molecular endotypes and the apparent transcriptomic similarity to psoriasis may suggest that a different therapeutic strategy is required for intrinsic AD. In addition, the shared inflammatory pathways in AD and psoriasis possibly suggests an explanation for disease overlap in mild disease, which is especially seen in children ⁴.

Surprisingly, given the association between filaggrin gene (*FLG*) mutations and allergy, this study did not find that filaggrin expression segregated intrinsic versus extrinsic AD, or even in those with or without heterozygous *FLG* mutations and the authors propose that this may be a result of compensation by the wild type allele. This supports the current paradigm that the presence or absence of heterozygous *FLG* mutations does not alter the clinical phenotype (beyond association with disease severity), or act as a molecular biomarker of Th2 skewing risk⁵. However, individuals with *FLG* mutations suffer more severe AD, and have increased risk of food allergy and asthma. Indeed, the transcriptomic profile is significantly different from filaggrin wild type AD ⁶. Therefore, although it seems possible that individuals with *FLG* mutations represent a distinct AD endotype, whether filaggrin status or IgE represents the most important distinction to define specific AD endotypes remains to be established.

Interestingly, despite the longstanding classification of psoriasis endotypes, recent findings in pustular psoriasis have uniquely shown a dysregulation of the IL-36 pathway which responds to IL-1RA antagonism ⁷. Whether AD endotypes may similarly reflect such striking differences in pathogenesis remains to be determined, but at the very least, combined molecular and clinical characterisation for patient stratification is likely to hold the key to the future success of new targeted therapies for AD (Table 1).

Table 1.

Phase	Target	Compound	Route
III	IL-4R	Dupilumab	S.C.
III	PDE4	Crisaborole	Topical
II	PDE4	Apremilast	Oral
II	IL-4	Pitrakinra	S.C.
II	IL-22	ILV-094	I.V.
II	IL-12/23	Ustekinumab	S.C.
II	IL-13	Tralokinumab	S.C.
II	IL-13	Lebrikizumab	S.C.
II	IL-31R	Nemolizumab (CIM331)	S.C.
II	CRTH2	Q301	Topical
II	CRTH2	Fevipirant (QAW039)	Oral
II	Neurokinin-1R	VLV-686	Oral
II	TSLP	Tezepelumab	I.V.
Suspended	IgE	Ligelizumab (QGE-031)	S.C.

I.V. intravenous infusion; S.C. Subcutaneous injection

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- Accepted Article
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