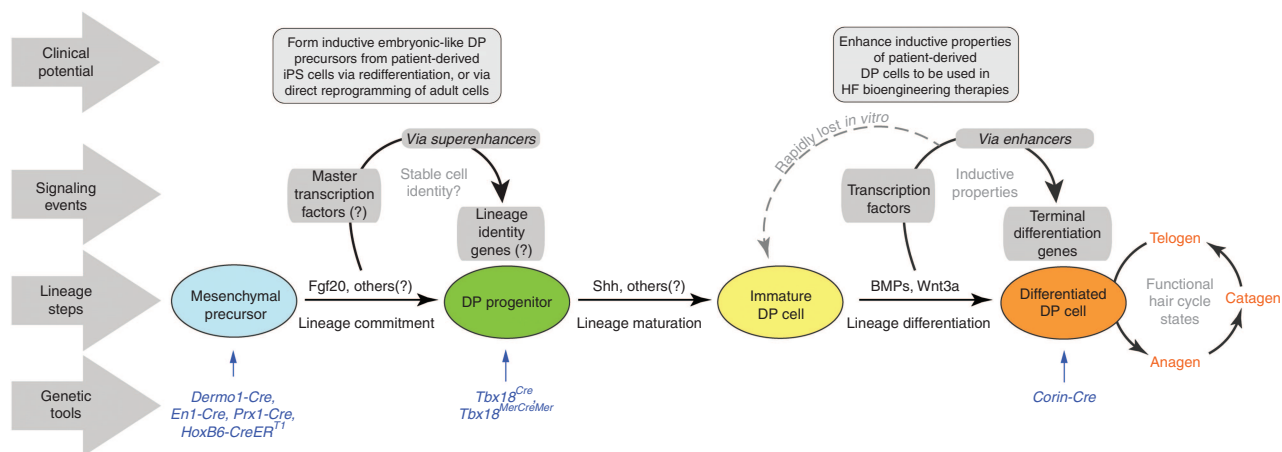# COMMENTARY

Figure 1. Dermal papilla (DP) lineage program. DP cells form during embryonic HF development from initially uncommitted mesenchymal precursors. Formation of the DP lineage likely follows a stereotypical cell lineage program, which starts with the commitment event. Although DP lineage commitment is likely associated with stable gene expression changes, signaling characteristics of differentiated DP cells are unstable and can be rapidly lost in culture. Signaling networks of DP lineage can now be studied using several stage-specific *Cre* lines. Mechanisms of the DP lineage commitment and differentiation can be exploited for developing optimized HF bioengineering therapies for alopecia (listed at the top). iPS, induced pluripotent stem; Shh, Sonic hedgehog.

of this issue map out a novel genetic strategy for systematically examining the functional significance of DP signature genes both in its own lineage specification and, more broadly, in HF morphogenesis. Future gene ablation studies using DP-specific *Cre* lines will undoubtedly reveal the molecular identity of DP lineage master regulators. An in-depth understanding of the DP lineage commitment program will help devise protocols for achieving highly inductive patient-specific DP cells and improve prospects for HF bioengineering therapies for alopecia.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES
Chen D, Jarrell A, Guo C et al. (2012) Dermal β-catenin activity in response to epidermal Wnt ligands is required for fibroblast proliferation and hair follicle initiation *Development* 139:1522–33

Clavel C, Grisanti L, Zemla R et al. (2012) Sox2 in the dermal papilla niche controls hair growth by fine-tuning BMP signaling in differentiating hair shaft progenitors. *Dev Cell* 23:981–94

Enshell-Seijffers D, Lindon C, Kashiwagi M et al. (2010) Beta-catenin activity in the dermal papilla regulates morphogenesis and regeneration of hair. *Dev Cell* 18:633–42

Fu J, Hsu W (2013) Epidermal Wnt controls hair follicle induction by orchestrating dynamic signaling crosstalk between the epidermis and dermis. *J Invest Dermatol* 133:890–8

Greco V, Chen T, Rendl M et al. (2009) A two-step mechanism for stem cell activation during hair regeneration. *Cell Stem Cell* 4:155–69

Grisanti L, Clavel C, Cai X et al. (2013a) Tbx18 targets dermal condensates for labeling, isolation, and gene ablation during embryonic hair follicle formation. *J Invest Dermatol* 133:344–53

Grisanti L, Rezza A, Clavel C et al. (2013b) Enpp2/autotaxin in dermal papilla precursors is dispensable for hair follicle morphogenesis. *J Invest Dermatol* 133:2332–9

Huh SH, Närhi K, Lindfors PH et al. (2013) Fgf20 governs formation of primary and secondary dermal condensations in developing hair follicles. *Genes Dev* 27:450–8

Rendl M, Lewis L, Fuchs E (2005) Molecular dissection of mesenchymal-epithelial interactions in the hair follicle. *PLoS Biol* 3:e331

Rendl M, Polak L, Fuchs E (2008) BMP signaling in dermal papilla cells is required for their hair follicle-inductive properties. *Genes Dev* 22:543–57

Woo WM, Zhen HH, Oro AE (2012) Shh maintains dermal papilla identity and hair morphogenesis *via* a Noggin-Shh regulatory loop. *Genes Dev* 26:1235–46

Psoriasis and Cardiovascular Disease: Where Is the Risk?

Catriona M. Maybury[1], Jonathan N. Barker[1] and Catherine H. Smith[1]

In this issue, Dowlatshahi *et al.* publish results from their population-based study in Rotterdam showing that, despite an increase in body mass index and smoking, individuals with psoriasis have no increased risk of incident cardiovascular disease. These results should be interpreted with caution: the study included relatively small numbers of patients with psoriasis, most of whom had mild disease.

Background to psoriasis and cardiovascular risk
Psoriasis is now recognized as a chronic inflammatory skin disease that is more than "skin deep." The reported association between psoriasis and cardiovascular disease (CVD) has attracted considerable interest in the last decade

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Clinical Implications (from the Rotterdam Study)

- Patients with mild psoriasis, managed in the community, can be reassured that the absolute risk of developing cardiovascular disease (CVD) is not significantly different compared with the rest of the general population. However, they may still have an increased risk of developing traditional CVD risk factors such as hyperlipidemia.
- Dermatologists treating patients with moderate-to-severe psoriasis should remain vigilant in detecting and managing CVD and should refer to their relevant guidelines for the management of CVD, such as the recently published UK NICE Psoriasis guidelines (http://publications.nice.org.uk/psoriasis-cg153).
- The pathogenic mechanisms linking psoriasis and CVD remain uncertain, requiring further research.

since Mallbris et al. (2004) reported data from a large cohort study comparing CVD mortality in hospitalized patients with psoriasis, outpatients with psoriasis, and the general population. They observed no increased mortality for outpatients with psoriasis, but they did identify a significantly increased risk of death from CVD for patients with psoriasis requiring hospital admission. In 2006, the first population-based study indicating that psoriasis may confer an independent risk of myocardial infarction (MI) was published in the journal JAMA (Gelfand et al., 2006). Subsequent studies showed that psoriasis is also a risk factor for stroke and thromboembolism. A recent systematic review and meta-analysis of 17 studies reporting the incidence (as opposed to the prevalence) of CVD events in individuals with psoriasis indicates that CVD risk predominates in individuals who have severe disease, with marked increases in the incidence of MI, stroke, and all-cause CVD mortality (Samarasekera et al., 2013). The relative risks appear to be greatest in younger individuals, although the absolute number of CVD events attributable to psoriasis per year remains modest and especially low for young individuals and for those with mild disease. The review also highlights the difficulties in interpreting these data: descriptors of disease severity rely largely on surrogate markers such as healthcare use (for example hospitalization or use of systemic therapy), and inter-study hetero-geneity exists for all CVD outcomes. Discrepancies are likely to reflect important differences in study design, how the diagnosis and disease severity of psoriasis was ascertained, and whether the patients were drawn from a primary or secondary care setting. Although, on balance, the literature supports an association between psoriasis and CVD, Wakkee et al. (2010) concluded that psoriasis may not be an independent risk factor for CVD as indicated by rates of hospitalization due to ischemic heart disease in people with psoriasis compared to those without. Notably, this study was also based in Rotterdam, and the majority of participants had mild disease.

Cardiovascular disease and psoriasis: proposed pathogenesis

Although an association between psoriasis and CVD is, with a few exceptions, reported consistently, it is less certain that the relationship is causal. It is important to state that all possible mechanisms are theoretical. In the 1960s, Framingham epidemiologists identified hypertension, smoking, diabetes, and hyperlipidemia as coronary risk factors (Ridker et al., 2007). These "traditional" risk factors are more common in individuals with psoriasis and could account for some, if not all, of the increased risk of CVD in this group. More recently, the metabolic syndrome has entered medical terminology to describe the clustering of insulin resis-tance or diabetes, abdominal obesity, hypertension, and hyperlipidemia, and it is strongly associated with CVD. In a large population-based study, Langan et al. showed an increased prevalence of metabolic syndrome in individuals with psoriasis in the UK. This associa-tion was "dose dependent" and increa-sed with disease severity (Langan et al., 2011).

Inflammation has been hypothesized as an independent CVD risk factor (recognized through the addition of high-sensitivity C-reactive protein to more recent cardiovascular risk scoring) (Ridker et al., 2007). The burden of chronic inflammation in psoriasis may confer a degree of risk that is indepen-dent of traditional coronary risk factors or in a manner that may exacerbate their impact. In particular, overproduction of Th-1 cytokines in psoriasis (such as TNF-α, IFN-γ) may disturb endothelial function (Pietrzak et al., 2013). In an animal study using mice with psoriasi-form dermatitis (KC-Tie2 mice) and an absence of comorbidities, aortic root inflammation was present in 33% of the affected KC-Tie2 group compared with 0% in the controls ($P = 0.04$). Bio-markers of CVD risk, including C-reac-tive protein and TNF-α, were also elevated in the KC-Tie2 group. After treatment of skin inflammation, the aortic root lesions resolved. These data suggest that at least in murine models skin inflammation alone promotes vas-cular inflammation and thrombosis (Wang et al., 2012). Again, not all data are consistent with this hypothesis: Martyn-Simmons et al. (2011), for exam-ple, detected no difference in endothe-lial dysfunction in a cross-sectional cohort of patients with severe psoriasis without traditional CVD risk and controls.

Areas of uncertainty

Therefore, although significant progress in knowledge regarding CVD risk in patients with psoriasis has been made, fundamental questions remain, including the following: What are the pathogenic mechanisms for the development of CVD in this group? How important is psoriasis-associated inflammation as a risk factor for CVD? Does treatment of psoriasis attenuate CVD risk?

COMMENTARY

"Psoriasis and cardiovascular events: the Rotterdam Study," Dowlatshahi et al.

In this issue of the Journal, Dowlatshahi et al. (2013) report results from a prospective population-based study aimed to assess the risk of subclinical atherosclerosis, coronary heart disease, stroke, and heart failure in patients with psoriasis. This was performed as part of the larger 'Rotterdam Study' (http://www.epib.nl/research/ergo.htm), using data from individuals over 55 years living in one Dutch suburb. Cases were identified via a search of general practitioner records for a physician diagnosis of psoriasis or evidence of medication for psoriasis. The reference population was subjects with no medical or drug history related to psoriasis. The medical records of all participants were assessed continuously over a decade for significant events. The primary outcome was incident cardiovascular disease (morbidity and mortality). Secondary outcomes were components of CVD (MI, stroke, heart failure) and subclinical measures of atherosclerosis.

Data were collected for 262 patients with psoriasis and 8,009 reference subjects. The mean age of the patients was 64 years; 44% were men. Psoriasis area severity index (PASI) scores were available for 14% of patients and ranged from 0.4 to 12.7. The majority of patients (75%) had mild disease (defined as a PASI <10 or using no therapy or topical therapy alone). Psoriasis patients smoked more, had an increased body mass index, and used more lipid-lowering medication than reference subjects. There were no significant differences in the incidence of CVD, MI, stroke, and heart failure between those with psoriasis and the control group. There were no significant differences in carotid intima-media thickness or coronary artery calcification (subclinical markers of atherosclerosis) between the groups. Seventy-two percent of psoriasis patients were identified to have a carotid plaque compared with 65% of the reference population ($P = 0.09$).

Strengths and weaknesses of study

This was a prospective population-based study, drawn from a community setting, avoiding the significant ascertainment bias of many previous hospital-based case–control studies. Earlier population studies using health records data formulated their evidence on information obtained via international disease classification (ICD) or Oxford Medical Information System (OXMIS) coding, which could introduce misclassification bias. Therefore, this study is unique in assessing individuals across the whole spectrum of disease, in the community setting and not in a healthcare setting, and by the fact that the psoriasis diagnosis was made either by a doctor or through a validated algorithm, with follow-up taking place over a 10-year period. Furthermore, because the aim was to investigate CVD, the Rotterdam group gathered comprehensive data on cardiovascular risk factors that other databases failed to capture: the study looked at both surrogate markers of CVD health and hard CVD end points with correction for confounders.

The main drawback is the small number of participants with psoriasis (259) and the low number of cardiovascular events in the psoriasis group during the study period (28). Individuals were categorized as having moderate-to-severe psoriasis if they were using either phototherapy or a systemic drug. This was a minority of patients (63 patients or 24% of the psoriasis cohort). Rotterdam participants were predominantly in late middle age, an age group in which other studies indicate that the relative risks of MI are lower. Previous population-based studies demonstrating a positive association between psoriasis and CVD included much larger numbers of individuals with psoriasis of all severities. For example, in the study by Gelfand et al. (2006), the number of patients with severe disease (based on those receiving systemic therapy) was 3,837. Therefore, the Rotterdam Study may have been underpowered to detect a difference between the groups. A power calculation was not made at the outset to determine adequate sample size, and this introduces the risk of a type-11 error (the effect is interpreted as not significant when the association does exist).

Disease severity scoring (PASI) data were only available in 14% of the patients; therefore, attribution of disease severity was, in common with most other studies, judged by medication use. Participants were classified as having either mild (no or topical therapy) or moderate-to-severe psoriasis (using either phototherapy or systemic therapy).

Supplementary Figure 2: Incidence estimates for MI in people with psoriasis compared to people without stratified by age—(A) mild psoriasis; (B) severe psoriasis (Samarasekera et al., 2013).

Conclusion

The Rotterdam Study supports existing data that individuals with mild psoriasis do not have an increased risk of developing CVD. However, the majority of published literature suggests that there is an increased risk of developing CVD in individuals with severe psoriasis. The low numbers of individuals with severe disease in this study means that their results are not powerful enough to negate such prior evidence.

REFERENCES

Dowlatshahi EA, Kavousi M, Nijsten T et al. (2013) Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study. J Invest Dermatol 133:2347–54

Gelfand JM, Neimann AL, Shin DB et al. (2006) Risk of myocardial infarction in patients with psoriasis. JAMA 296:1735–41

Langan S, Seminara N, Shin D et al. (2011) Psoriasis is associated with an increased prevalence of metabolic syndrome that varies directly with objectively measured severity. J Invest Dermatol 131:S36

Mallbris L, Akre O, Granath F et al. (2004) Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 19:225–30

Martyn-Simmons CL, Ranawaka RR, Chowienczyk P et al. (2011) A prospective case-controlled cohort study of endothelial function in patients with moderate to severe psoriasis. Br J Dermatol 164:26–32

Pietrzak A, Bartosinska J, Chodorowska G et al. (2013) Cardiovascular aspects of psoriasis: an updated review. Int J Dermatol 52:153–62

Ridker PM, Rifai N et al. (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 297:611–9

Samarasekera EJ, Neilson JM, Warren RB et al. (2013) Incidence of cardiovascular disease in people with psoriasis: a systematic review and meta-analysis. J Invest Dermatol 133: 2340–6

Wakkee M, Herings RM, Nijsten T (2010) Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based Dutch cohort. J Invest Dermatol 130: 962–7

Wang Y, Gao H, Loyd CM et al. (2012) Chronic skin-specific inflammation promotes vascular inflammation and thrombosis. J Invest Dermatol 132:2067–75

Mechanisms of Contact Sensitization Offer Insights into the Role of Barrier Defects vs. Intrinsic Immune Abnormalities as Drivers of Atopic Dermatitis

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Atopic dermatitis (AD) is a common inflammatory skin disease characterized by wet, oozing, erythematous, pruritic lesions in the acute stage and xerotic, lichenified plaques in the chronic stage. It frequently coexists with asthma and allergic rhinitis, sharing some mechanistic features with these diseases as part of the "atopic march." Controversy exists as to whether immune abnormalities, epidermal barrier defects, or both are the primary factors responsible for disease pathogenesis. In AD patients, there is often a coexisting irritant contact dermatitis (ICD) or allergic contact dermatitis (ACD) that is sometimes clinically difficult to distinguish from AD. ACD shares molecular mechanisms with AD, including increased cellular infiltrates and cytokine activation (Gittler et al., 2013). In this issue, Newell et al. (2013) used an experimental contact sensitization model with dinitrochlorobenzene (DNCB) to gain insight into the unique immune phenotype of AD patients.

Epidermal barrier defects characterize lesional and nonlesional AD skin

The stratum corneum, including terminal differentiation proteins such as filaggrin (FLG), corneodesmosin, and loricrin, is a first-line defense against irritants and allergens. The genomic expression of key barrier molecules, which comprise the epidermal differentiation complex on chromosome 1q21, have been previously shown to be downregulated in AD patients in both lesional and nonlesional skin (Suárez-Fariñas et al., 2011).

Furthermore, frequent mutations in the FLG gene (found in up to 30–50% of AD patients) have been associated with the severity of AD (as identified by the Scoring of AD (SCORAD) index). These differentiation abnormalities contribute to the barrier defect in AD, ultimately resulting in increased transepidermal water loss, xerosis, and greater penetration of various agents (Gittler et al., 2013). In humans, FLG deficiency has been linked to increased risk of the other atopic diseases, as well as to greater

susceptibility to common triggers of AD (including allergens and microbes). Murine models with reduced FLG exhibit greater passive transfer of protein allergens and reduced thresholds to irritants (Irvine et al., 2011). These studies provide the basis for the "outside-in" hypothesis of AD, which states that transfer of external triggers across a dysfunctional barrier elicits the disease's characteristic immune responses. Although FLG and other defects in the barrier have been linked to AD pathogenesis, there are notable limitations to this hypothesis. For example, an inverse correlation has been established between the expression levels of several terminal differentiation molecules and AD disease severity (as measured by the SCORAD index) (Suárez-Fariñas et al., 2011). This raises the possibility of a reactive epidermal barrier to a primary immune insult. Furthermore, impressive reductions in key terminal differentiation molecules, extending far beyond FLG, have been found even in nonlesional AD skin. In addition, a majority of AD patients do not harbor FLG mutations, and even those with them have been shown to outgrow the disease (Guttman-Yassky et al., 2011). Collectively, these observations suggest that barrier dysfunction is not the sole contributor to disease pathogenesis.

AD is primarily Th2 and Th22 polarized

The historical immune paradigm for AD characterized it largely as a T helper type 2 (Th2)-mediated disease with high levels of IL-4, IL-13, and Th2-polarizing chemokines (i.e., CCL17, CCL18, and CCL22). Recent work has implicated additional key Th2-associated cytokines and factors, including IL-31, thymic stromal lymphopoietin (TSLP), and OX40. Th2 signaling has been demonstrated to produce many of the molecular findings seen in AD skin, with the exception of the characteristic epidermal hyperplasia. Allergen-specific Th2 T cells can be found in AD but not in nonatopic controls (Ardern-Jones et al., 2007). More recently, Th22 T cells and their cytokine, IL-22, have been shown to have a key role in the pathogenesis of AD, potentially accounting for the increased epidermal thickness. Langerhans

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