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COMMENTARY

Smoking and Psoriasis: From Epidemiology to Pathomechanisms

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Smoking is a well-established environmental risk factor for psoriasis. It should be carefully considered in genetic studies because smoking can modify risk estimates for genetic markers. Genome-wide association studies may facilitate the analysis of genetic–environmental interaction in psoriasis.

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Multifactorial heredity, the interaction between genetic predisposition and environmental factors, is hypothesized to cause several chronic inflammatory disorders, including psoriasis. According to this model, susceptibility for the development of psoriatic lesions depends on both genetic and extragenetic predisposing factors, which are shared by the whole skin ("pre-psoriasis"). Disease expression, in terms of visible lesions, is influenced by extragenetic precipitating or initiating factors. Smoking and a high body mass index (BMI) are well-established environmental predisposing factors for psoriasis (La Vecchia *et al.*, 2005).

Environmental influences should be carefully considered in genetic studies because they can modify the effects of genetic factors (Figure 1). This consideration has commonly been given only marginal importance in the genetic studies of psoriasis, but the report by Duffin *et al.* (this issue) is a welcome departure. This paper presents evidence that polymorphisms in the *IL13/IL4* region (especially rs1800925*T) may be associated with protection from developing psoriatic arthritis and that this effect may be abrogated by smoking. It is unclear from the data presented whether smoking *per se* was associated with psoriatic arthritis.

Genetic–environmental interactions involving smoking have been proposed in other studies of patients with psoriasis. In a letter to this journal, a stronger association between smoking and psoriasis in subjects with a nonvariant CYP1A1 genotype has been presented, suggesting that sequence variation in genes coding for phase 1 and II enzymes, including members of the cytochrome P450 (CYP) family, may alter individual susceptibilities to the development of psoriasis in smokers, similar to the effects documented in cancer and coronary artery disease (Krämer and Esser, 2006). In another study, the risk of psoriasis for smokers with HLA-Cw6 increased about 11-fold over that for nonsmokers without HLA-Cw6 (Jin *et al.*, 2009). In principle, these studies point to possible multiple actions (and interactions) of smoking in psoriasis. However, drawbacks of these studies are their limited statistical power and their failure to document significant heterogeneity across the strata of smoking status, despite variations in risk point estimates. This underlines the difficulties in studying genetic–environmental interactions and the need for very large sample sizes (on the order of thousands of individuals rather than hundreds) to obtain reliable estimates.

Current genome-wide association studies using gene chips, large sample sizes, and case–control designs, instead of linkage analysis, may facilitate the investigation of genetic–environmental interactions and thereby address questions about disease pathomechanisms. One disadvantage to such studies is that they may result in large numbers of hints, which then require validation studies.

Cigarette smoking as a complex risk factor

In principle, smoking might influence the pathomechanisms of psoriasis in many ways. For example, it may accelerate the formation of autoantigens in the skin or trigger innate immunity (Sopori, 2002). Alternatively, genes involved in behaviors associated with smoking and tobacco dependence may be the real players.

Tobacco smokers are exposed to a cocktail of more than 4,000 chemicals, which makes it difficult to identify agents responsible for tobacco's wide-ranging effects, both detrimental and otherwise (Table 1). Nicotine is the principal alkaloid in tobacco. It is rapidly absorbed through the lungs, skin, and gut and is metabolized mainly by the liver to cotinine and other metabolites, some of which are also pharmacologically active. Nicotine exerts its effects by activating several subtypes of nicotinic

Table 1. Main chemicals in tobacco smoke

Particulate phase
Polycyclic aromatic hydrocarbons
N-heterocyclic amines
Hydroquinone
Nicotine
Phenol, cresol
Naphtylamine
Benzo(a)pyrene
Indole, carbazole
Trace metals (e.g., arsenic)
Vapor phase
Carbon monoxide
Hydrocyanic acid
Acetaldehyde
Acrolein
Ammonia
Formaldehyde
Nitrogen oxides
Nitrosamines
Hydrazine
Vinyl chloride

The particulate and vapor phases are described operationally as fractions of cigarette smoke that are retained or passed through a Cambridge filter, respectively.

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acetylcholine receptors (nAChRs), which are classically found in the nervous system and adrenal medulla, but which have also been identified in nonneuronal tissue, such as keratinocytes in skin, bronchial epithelium, and cells involved in inflammation, such as monocytes, dendritic cells, and microglial cells. Interaction of nicotine with nAChRs results in an initial transient stimulation of ganglionic transmission, followed by a more persistent depression (biphasic effect) and the release of catecholamines from the adrenal medulla and postganglionic sympathetic neurons. The effect of nAChRs on nonneurologic tissue such as keratinocytes and monocytes is less clear, but in the former they might facilitate cell-to-cell communication, keratinocyte adhesion, and upward migration in the epidermis, and in the latter they have an immunomodulatory effect. Other components of tobacco smoking have been related to inflammatory and vascular events. For example, acrolein, an unsaturated aldehyde, affects neutrophil function, whereas chronic exposure to benzo(*a*) pyrene induces dose-related decreases in the mass and cellularity of lymphoid tissue (Sopori, 2002). As confirmed in a recent meta-analysis, the effects of smoking might also be modulated by gender, with females at higher risk compared with males for overall morbidity and mortality associated with smoking at both low and high levels (Mucha *et al.*, 2006). This potential gender effect should be taken into account in genetic analyses and interaction studies.

> Smoking may affect psoriasis by more than one mechanism.

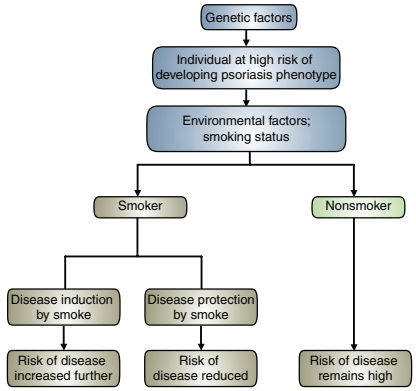

Figure 1. Risk estimates and interaction between smoking and genetic factors

Smoking and immune-related disease

Cigarette smoking is a risk factor for more than two dozen diseases, and it is the single greatest cause of preventable mortality worldwide. In addition to its well-known association with cardiovascular disease, chronic obstructive pulmonary disease, peptic ulcer, and several cancers (especially but not limited to those of the respiratory tract), smoking appears to be associated with a number of inflammatory immune system–related diseases (Sopori, 2002).

Passive exposure to cigarette smoke both *in utero* and during early life increases individuals' subsequent risk of developing asthma. Moreover, it is now recognized that patients with asthma who smoke have an impaired response to treatment with corticosteroids. It has been proposed that interleukin-1 receptor antagonist gene polymorphism rs2234678 and polymorphisms in *IL13* interact with maternal smoking to increase the risk of childhood asthma (von Mutius, 2009).

Smoking is associated with an increased risk of Crohn's disease and also has a detrimental effect on its clinical course. In contrast, it decreases the risk of ulcerative colitis and, possibly, primary sclerosing cholangitis. It has been suggested that Crohn's disease is caused by an impaired host response to luminal bacteria; the documented association of Crohn's disease with mutations in the *CARD15* (*NOD2*) gene, which seem to be associated with decreased production of antimicrobial peptides, supports this theory. Smoking in Crohn's disease might further compound any deficiency in the host response to luminal bacteria (Thomas *et al.*, 2005).

Despite their reduced immunoglobulin levels, smokers have increased levels of autoantibodies, notably antinuclear rheumatoid factors (Sopori, 2002). The duration and intensity of smoking have been linked to a corresponding development of rheumatoid arthritis, with an especially high risk in postmenopausal women. Smoking has also been associated with an increase in both the severity of rheumatoid arthritis and the disease activity. A Swedish population-based case–control study has documented that the risk of developing rheumatoid factor-positive disease substantially increased in smokers carrying double copies of the *HLA DRB1* shared epitope (relative risk (RR) = 15.7) compared with smokers with no copies of these genes (RR = 2.4). Recent research has also demonstrated additive and multiplicative interactions between *PTPN22* and heavy cigarette smoking (Oliver and Silman, 2009).

An excess risk of more than 10-fold in tobacco smokers has been documented for discoid lupus erythematosus (DLE). In addition, DLE and subacute cutaneous lupus erythematosus patients who are smokers are less likely to respond to antimalarial therapy than are nonsmokers (40% vs. 90% response rate). A meta-analysis of nine studies, including seven case–control and two cohort investigations, gave a summary RR for systemic lupus erythematosus in smokers of about 1.50 (95% confidence interval = 1.09–2.08) (La Vecchia *et al.*, 2005).

At variance with rheumatoid arthritis, no clear documentation of an association of psoriatic arthritis with smoking has been produced. Tobacco smoking has been strongly associated with palmoplantar pustulosis (La Vecchia *et al.*, 2005).

The genetics of smoking habits

Both environmental and genetic influences on tobacco dependence exist, and these factors, which affect behavior, may, in turn, play a role in

the development of smoking-related diseases. Low socioeconomic status, peer smoking, and maternal smoking during pregnancy are well-documented environmental factors that affect smoking behavior. On the other hand, twin studies provide strong evidence that a range of diverse smoking phenotypes—including age at initiation, intensity, nicotine dependence (expressed by the Fagerstrom test), and cessation propensity—have a substantial hereditary component (Caporaso *et al.*, 2009). Results from linkage analysis studies have generally been heterogeneous and short on conclusive findings. Gene association studies have been focused until recently on genes in a few candidate pathways, particularly genes in opioid, serotoninergic, dopaminergic, drug-metabolizing enzyme, and nicotinic and muscarinic cholinergic receptor pathways. Results from these studies have been largely equivocal. Genome-wide association studies may offer better information with which to identify causal relationships. A few such studies point to a region on chromosome 15q25.1, spanning the nicotinic acetylcholine receptors CHRNA5, CHRNA3, and CHRNB4, as being associated with smoking intensity (i.e., number of cigarettes smoked per day or dichotomized smoking intensity). Future research into the genetics of smoking behavior should take into account the interaction between genetic influences and environmental factors, whereas studies focused on the role of smoke in disease causation should consider the genetic component of smoking behavior.

What next?

Psoriasis is a phenotypically heterogeneous disorder, and our understanding of its clinical variations remains fragmentary. Psoriatic arthritis, which represents an interesting conundrum of a "disease within a disease," adds to its complexity. Epidemiologically, psoriatic arthritis is difficult to study because it is not easy to disentangle whether the risk factors revealed are for the complete disease phenotype (arthritis and psoriasis) or for one of its components. Studies that compare psoriatic arthritis patients with healthy controls are as yet not able to address this issue. A well-designed case–control study, however, should have the ability and power to separate the genetics of susceptibility to psoriatic arthritis from those of its constituent parts by choosing, for example, different control groups simultaneously (such as a control group of patients who have psoriasis without arthritis and one with inflammatory arthritis without psoriasis). Large numbers would be required to allow subgroup analyses, stratifying the psoriatic arthritis data set for type of psoriasis and pattern of joint involvement. A study powered adequately to allow dissection of skin and joint involvement at a genetic level would be a major contribution to our understanding of the psoriasis–arthritis connection. Smoking should be considered in these studies as a possible risk modifier. Moreover, as genetic studies of smoking behavior move forward, the possible roles of genes influencing smoking attitude and tobacco dependence should be carefully considered.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Adoptive Cell Transfer in the Treatment of Metastatic Melanoma

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Adoptive cell therapy (ACT) for metastatic cancer is the focus of considerable research effort. Rosenberg's laboratory demonstrated a 50% response rate in stage IV melanoma patients treated with *in vitro* expanded tumor-infiltrating lymphocytes (TILs) and high-dose IL-2 administered after nonmyeloablative conditioning (Dudley *et al.*, 2002a). Because early attempts to use expanded TILs in melanoma therapy failed to demonstrate better efficacy than high-dose IL-2 (Rosenberg *et al.*, 1994), the efficacy of TILs and nonmyeloablative conditioning in combination implies that patient conditioning is crucial to clinical success. The 2002 data represent a milestone in cellular cancer therapy and a turning point for ACT in cancer treatment.

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Expansion of TILs for clinical use is labor intensive and requires a significant investment in infrastructure, equipment, and staff, as well as a high degree of expertise in both the clinic and the laboratory. This explains, at least in part,

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