What causes hidradenitis suppurativa?


Abstract: Hidradenitis suppurativa (HS) – a rather common, very chronic and debilitating inflammatory skin appendage disorder with a notoriously underestimated burden of disease – has long been a playground for the high priests of nomenclature: Ask a bunch of eminent dermatologists and skin pathologists to publicly share their thoughts on what causes HS, and they will soon get entrenched in a heated debate on whether this historical term is a despicable misnomer. Fortunately, the recently founded Hidradenitis Suppurativa Foundation (HSF; http://www.hs-foundation.org), to which EXP DERMATOL serves as home journal, has broken with this unproductive tradition and has encouraged publication of the current CONTROVERSIES feature. This is exclusively devoted to discussing the pathobiology of this chronic neutrophilic folliculitis of unknown origin. Although traces of terminological bickering remain visible, it does the HS experts in our virtual debate room credit that they engage in a constructive and comprehensive dissection of potential pathogenesis pathways that may culminate in the clinical picture we know under the competing terms HS or acne inversa. These experts sketch more often complementary than mutually exclusive pathogenesis scenarios, and the outlines of a conceivable consensus on the many open pathobiology questions begin to emerge in these CONTROVERSIES. Hopefully, this heralds a welcome new tradition: to get to the molecular heart of HS pathogenesis, which can only be achieved by a renaissance of solid basic HS research, as the key to developing more effective HS therapy.

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Prelude

Apocrine or not, that is the question…

In the context of HS, it has become foolhardy to speak of apocrine sweat glands ever since pathologists have demonstrated that the primary histological event was in the follicular duct, like in acne. It was then simple, if not to say simplistic, for many dermatologists to forget any major differences between acne and HS, and to rename the disease ‘acne inversa’, thus replacing one possible misnomer (HS) with another – and leading investigators to a dead end, and practitioners to use ineffective treatments.

Any hypothesis about HS must take two paradoxons into account:

1 Hidradenitis suppurativa lesions have a very specific topography which is a copy of the anatomical distribution of apocrine sweat glands: axillae and groin as the main areas; breast, perineum and buttocks as accessory regions. YET Apocrine glands are not the primary target of the pathological process.

2 Hidradenitis suppurativa is not primarily an infectious disease, and yet drugs that are conducive to infection, such as corticosteroids, immunosuppressive drugs and/or anti-TNF agents, may improve the disease YET One of the most useful drug regimens in cases of active inflammatory lesions is a combination of two antibiotics: rifadin and clindamycin (1).

Paradoxon 1

The topography of involvement may be explained by two – not mutually exclusive – hypotheses: (a) the distribution of apocrine glands; and (b) shearing forces, which originate in large skin folds, especially of overweight patients.

Obesity and overweight are frequent in HS and could be a risk factor (2). However, HS is not infrequent in inter-mammary folds and on the buttocks, where such shearing forces are absent. Moreover, individuals with low or normal body mass index also do develop HS. Thus, while obesity and overweight are strongly associated with severity in HS, they are insufficient to explain the specific topography of the disease.

So, what about apocrine sweat glands? The rejection of apocrine glands as a main factor in the pathogenesis of HS originates in the clear demonstration that they are spared
by the initial inflammatory and destructive process. The primary event is a follicular hyperkeratosis with plugging and dilatation of the hair follicle ensuing in inflammation, abscess and sinus tract formation. Apocrine involvement appears as a secondary phenomenon resulting from the diffusion of the granulomatous inflammation in deep structures of the skin.

The mechanism by which follicular plugging occurs in acne is not known; various candidates are hypersecretion of sebum, proliferation of P. Acnes favoured by an alteration of innate immunity and/or of inflammatory reactions, and possibly several others.

Here, the specific anatomical relationship of the apocrine gland with the follicular canal has to be taken into account: In contrast to eccrine glands, whose ducts open onto the skin surface, apocrine glands empty their content into the follicular canal, just above the sebaceous gland duct. In HS, hyperseborrhoea is definitely absent but the other factors may be at work:

An abnormal secretion – excess or absence – of a substance that is present in apocrine gland secretion under physiological conditions may therefore, after all, be the triggering factor of HS! Its morphologically recognisable effect could be in the acro infundibulum of the follicle, with the responsible gland disguising itself as an innocent bystander upon histology – a perfectly masked ‘criminal’.

Paradoxon 2

Hidradenitis suppurativa is a disease in which numerous bacteria are present and active (3), and in which various antibiotic regimens have definitely improved the condition in patients with severe inflammatory involvement (2). Surprisingly, numerous pro-infectious drugs have also been used with good results: corticosteroids, immunosuppressive drugs, anti-tumour necrosis factor (4,5). The coexistence of these two seemingly contradictory phenomena calls for a closer look at the properties of anti bacterial molecules which play a key role in innate and acquired immunity: the so-called anti-microbial peptides (6).

They are known to exert both pro- and anti-inflammatory functions; they alarm and activate the adaptive immune system and the keratinocytes that produce them. They induce keratinocytes migration, proliferation – a role in follicular occlusion? They are part of a complex network of cytokine and chemokine production. The absence or abnormality of one of these anti-microbial peptides would be a good candidate for explaining the infectious and inflammatory features of HS. Cathelicidins and defensins are the main representatives of this family identified today. New ones, psoriasin (7), are under consideration. Some of these peptides are produced by mature keratinocytes spontaneously or after stimulation, some are produced by eccrine sweat glands, and some are prominently subject to modulation by antibiotics (7–9).

However, until now, nothing is known about anti-microbial peptides that are specifically produced in apocrine sweat glands. This is where we need to search.

Conclusion

Hidradenitis suppurativa is as multifactorial as any chronic disease and probably heterogeneous. Here, I have only considered the role that apocrine glands may have, a role that might well be central – no matter, how much this gland has fallen out of fashion in HS research. The role of other factors – e.g. hair follicle anatomical/structural abnormalities (highly probable at least in a subset of HS patients), the role of obesity, the role of cigarette smoking – all deserve careful exploration. Any pathogenesis scenario, however, that completely discards apocrine glands and their specific distribution as key elements in the development of HS may soon turn out to have to be discarded itself!

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References