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On the TRAIL to truth, or on a road to nowhere?

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Abstract

In this issue of Experimental Dermatology, dr. Melnik presents the hypothesis that acne is caused by inappropriate survival of cells in the sebaceous duct and gland. He proposes in particular that TRAIL mediated apoptosis is inhibited by ductal hypoxia. If it works out, this intriguing idea would suggest interesting new therapies.

In my comment, I offer a critical appraisal – the TRAIL to acne pathogenesis might be rather different from what dr. Melnik would have us believe.

Acne is by far the most common skin disease. In some countries, its incidence amongst adolescents is approaching 100%. The disorder can be very distressing and causes considerable psychological and social morbidity.

Mild disease will spontaneously resolve. Moderate to severe acne, however, requires medical intervention. Several treatments are available. For most, there is no evidence for efficacy or superiority over other options. Examples include photodynamic therapy, pulsed dye laser and azelaic acid. The treatments with proven efficacy have important disadvantages (1). They all take a long time to act and must be used daily. Topical retinoids can induce cumbersome skin irritation. The antibiotics used to treat acne can cause bacteria to become resistant. As an aside, they are effective even in patients with resistant *Propionibacterium acnes* (2). This observation further challenges the already tenuous notion of *P. acnes* having any pathogenic role in acne. The most effective systemic drug, 13-cis retinoic acid (13RA), has undesirable side effects and is highly teratogenic. There are also persistent reports of suicidal ideation associated with its use. These disadvantages preclude 13RA from being prescribed routinely, even if it can cure acne and prevent scarring.

There is thus a clear need for new drugs that can treat acne quickly and have fewer disadvantages. However, no new drug classes have been developed since 13RA was introduced in 1982. This lack of innovation is due to our incomplete

understanding of the molecular events underpinning acne. What are the mechanisms that drive comedogenesis? What causes inflammation and scarring? Despite decades of research, the underlying cellular pathways remain elusive and no novel drug targets have been identified.

A prolific and original thinker, dr. Bodo Melnik has over the past several years outlined interesting new hypotheses on the pathogenesis of acne (3). Even though these remain to be rigorously tested, they have helped to rekindle interest in the fundamentals of acne. In this issue of Experimental Dermatology, dr. Melnik offers up his latest idea (4). Deftly weaving together his previous thinking and published data obtained in seemingly disparate systems, he arrives at the conclusion that inappropriate pro-survival signaling could be an important factor in acne. Specifically, dr. Melnik proposes that hypoxia in the sebaceous duct and increased PI3K/Akt signaling in sebocytes conspire to inhibit TRAIL-mediated apoptosis in the sebaceous gland and associated structures. Abnormal apoptosis might affect the differentiation of infundibular keratinocytes, contributing to comedo formation. Enhanced sebocyte survival could contribute to the altered sebum production implicated in acne. Isotretinoin would then work by enhancing apoptosis, which is consistent with previously published observations (5).

This line of reasoning is interesting and eminently testable. Certainly, inappropriate protection from apoptosis would be an actionable mechanism that is relatively easy to assay in high-throughput screens. That said, key assumptions underlying dr. Melnik's hypothesis could be challenged. For instance, it is assumed that cornification and sebum production both are based on apoptosis, but there is no

good evidence that they are (6). It is also surmised that acne is, at least in part, a sebocyte disorder. However, it is, at heart, a disease of the infundibulum (7). That is where the comedo forms. There is no good evidence that abnormal sebocyte function, as reflected in altered sebum production, has a causal role. Of particular note, comedone formation is well known to be associated with sebaceous gland atrophy (7).This phenomenon conflicts with a key prediction of dr Melnik's hypothesis: the sebaceous gland should become larger due to sebocytes being protected from apoptosis. Of course, one might argue that the pro-survival effect is limited to the infundibulum alone. But in that case, one would have to explain where this limitation comes from. It is also difficult to reconcile a lack of oxygen with the increased keratinocyte proliferation observed in comedones (8).

Finally, positing ductal hypoxia as a trigger mechanism gives rise to an interesting conflict with one of dr. Melnik's previously published hypotheses. Hypoxia inhibits mTORC1 signaling. If the pilosebaceous unit is truly hypoxic (and it might be), a role for increased mTORC1 activity in the pathogenesis of acne seems less likely. That doesn't rule out pathological activation, but this is more typically associated with malignancy (9).

With so many, sometimes conflicting hypotheses ready for falsification, these are exciting times for acne researchers. The road ahead may not be clear, but the trail blazed by dr. Melnik at least gives us some guidance. Here we go!

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