SKIN DISORDERS

Inhibiting sebum production to treat acne

Sebum oils play critical functions in the human skin, ranging from thermoregulation to antimicrobial defence. However, excess sebum production can contribute to the development of acne vulgaris. Writing in *Science Translational Medicine*, Esler and colleagues now demonstrate that human sebum production is highly dependent on sebocyte de novo lipogenesis (DNL) and flux through this pathway is elevated in patients with acne. Furthermore, small-molecule inhibition of acetyl-CoA carboxylase (ACC) — the rate-limiting enzyme in the DNL pathway — reduced sebum production in humans.

The metabolic pathways underlying increased sebum production in humans with acne remain incompletely understood. Although sebaceous glands are known to be capable of DNL and contain functional ACC, the importance of this pathway in humans for sebum biosynthesis, relative to the utilization of circulating lipids derived from other sources (including diet, adipose tissue or the liver), is unknown.

To investigate the role of local DNL in sebum biosynthesis, Esler and colleagues used an inhibitor of ACC (ACCi), PF-05175157. This ACCi inhibits both isoforms of ACC and has been part of a metabolic disease drug discovery programme at Pfizer.

In rats, oral administration of PF-05175157 for 7 days induced morphological changes in sebaceous glands consistent with reduced sebum lipid content: glands were atrophied and sebocytes decreased in size with less cytoplasm and lipid vacuolation. Furthermore, the ACCi suppressed DNL in cultured human sebocytes, reducing concentrations of triglyceride — the major lipid species in human sebum — by up to about 90%.

DNL-derived fatty acids may be synthesized locally in the sebaceous glands or synthesized in other lipogenic organs and delivered via the circulation and subsequently incorporated into sebum. Therefore, the authors next determined the role of the local DNL pathway in human sebum production.

To do this, 22 healthy individuals received deuterium-labelled water daily by oral administration for 2 weeks. The incorporation of this deuterium into sebum palmitate and circulating very-low-density lipoprotein (VLDL)–triglyceride palmitate represents fatty acids synthesized de novo from acetyl-CoA.

Plasma and facial skin sebum samples were collected and analysed, revealing that the percent contributions of DNL to sebum lipid palmitate and plasma VLDL–triglyceride palmitate were 80% and 20%, respectively. This finding indicates that the human sebaceous gland preferentially synthesizes fatty acids de novo rather than using circulating lipids for sebum biosynthesis. Similarly, 80% of sebum sapienate — a monounsaturated fatty acid found exclusively in human sebum — was derived from local DNL.

> “small-molecule inhibition of acetyl-CoA carboxylase … reduced sebum production in humans”

Next, to confirm that PF-05175157 inhibits DNL in humans, the authors assessed the suppression of hepatic DNL in 32 healthy humans. DNL was measured as incorporation of [1-^{13}C]-acetate into VLDL–triglyceride palmitate. Labelled acetate was infused intravenously to isotopically enrich the precursor pool of hepatic, cytosolic acetyl-CoA. Each individual received a single oral dose of PF-05175157 and a 10-hour oral fructose load throughout the period of plasma sampling. The ACCi was found to dose-dependently inhibit fructose-stimulated DNL.

Next, the authors assessed the effect of PF-05175157 on human sebum production. Oral administration of the ACCi to 15 healthy individuals twice a day for a period of 2 weeks was well-tolerated, suppressing the total sebum excretion rate by 49% and reducing sebum triglycerides by 66%.

Finally, the authors assessed whether elevated DNL flux underlies increased sebum production rate in humans with acne. In nine individuals with acne, administration of deuterium-labelled water followed by sebum and plasma sampling revealed that the total rates of sebum production and of flux through the DNL pathway were >20% higher than in healthy volunteers.

Interestingly, two widely used animal models of sebum production, the Syrian hamster ear skin model and Göttingen minipigs, were shown to rely on circulating lipids for sebum biosynthesis and not local sebocyte DNL. This finding questions the use of these animal models in future studies.

In summary, these findings demonstrate the role of the sebocyte DNL pathway in the overproduction of sebum lipids in humans with acne and highlight the potential of ACC inhibition to suppress sebum production. Clinical evaluation of this pathway for the treatment of acne is warranted.

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