

Regulation of Lipogenic Programs in the Meibomian Gland by MYC and Sterol Regulatory Element-Binding Protein 1 (SREBP1)

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Abstract

Introduction: Meibomian glands (MGs) are sebaceous glands of the eyelid which form the lipid layer of the tear film. Sebaceous carcinoma (SebCA) may arise following unchecked meibocyte proliferation. SebCA is a rare but aggressive cancer in which gain-of-function mutations and copy number variations at the *MYC* locus have been demonstrated. *MYC* upregulation activates SREBP1 and downstream metabolic pathways to promote tumor growth and invasion. We aimed to characterize the effects of *MYC* modulation on SREBP1 and lipogenesis and to define the impact of local fatty acid synthase (FASN) inhibition on *MYC*-mediated meibum alterations. **Methods:** Human meibocytes (hMGECs) and a primary human SebCA cell line were treated with *MYC* and fatty acid desaturase inhibitors with and without oleic acid (OA) or vehicle control (DMSO). Proliferation, apoptosis, differentiation, invasion, and SREBP1 binding activity were assessed. Adult wildtype (wt) and tamoxifen (4-OHT)-inducible *MYC*-overexpressing transgenic (TG) C57B6 mice were administered 4-OHT followed by topical application of a FASN inhibitor (C75) alone, or with OA, or DMSO. Tear Film Break-Up Times (TBUTs) were obtained before and after 4-OHT administration and following topical intervention. Eyelids were harvested and subject to assessments of morphology, differentiation, proliferation, apoptosis, and lipogenic transcript expression. **Results:** *MYC* inhibition suppressed SREBP1 expression and binding activity and impaired proliferation, clonogenicity, and invasiveness while promoting lipogenic stress and apoptosis in both cell lines. The addition of OA partially rescued this phenotype. FASN inhibition *in vivo* accelerated TBUTs, increased apoptosis, and attenuated *MYC* expression, proliferation, and lipid droplet formation in all mice. Lipogenic transcripts were upregulated in TG mice relative to wt littermates, and FASN inhibition downregulated these genes relative to DMSO controls. This phenotype was partially rescued by concurrent OA administration. **Conclusions:** *MYC* inhibition impairs SREBP1 activity and downstream lipogenic programs, leading to decreased proliferation and increased apoptosis in meibocytes. Topical FASN inhibition phenocopies key aspects of *MYC* inhibition, including tear film instability and altered lipid droplet formation. OA achieves partial lipotoxic rescue. SebCA's reliance on *MYC*-driven lipogenic programming unveils a metabolic vulnerability and represents a potential therapeutic target.

Key words: 10074-G5, fatty acid saturation, stearoyl-CoA-desaturase-1, PluriSIn, oleic acid, ocular adnexal sebaceous carcinoma