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p53: key conductor of all anti-acne therapies

Acne vulgaris is the most common inflammatory skin disease of developed countries affecting more than 80% of adolescents. In contrast, acne vulgaris is not epidemic or completely absent in populations living under Paleolithic conditions. During the last decade, Western nutrition has been identified as the most critical factor of the acne exposome of Westernized countries. In contrast to Paleolithic nutrition, Western diet is characterized by high glycemic load and cow´s milk consumption which both increase insulin and insulin-like growth factor-1 (IGF-1) signaling. Enhanced insulin/IGF-1 signaling activates the PI3K-AKT-mTORC1 pathway, which promotes sebaceous lipogenesis, the key driving force of acne featuring exaggerated sebum production. Increased AKT activation attenuates nuclear expression of metabolic transcription factors FoxO1 and FoxO3 but via activation of mouse double minute 2 (MDM2), promotes proteasomal degradation of p53. p53 is the key regulatory transcription factor, known as the guardian of the genome, that controls cell homeostasis, cell proliferation, cell survival and apoptosis. p53 attenuates the expression of IGF-1 receptor (IGF1R), androgen receptor (AR), mechanistic target of rapamycin complex 1 (mTORC1) activity, and sterol regulatory-element binding protein 1 (SREBP1), key transcription factors and metabolic regulators involved in acne pathogenesis. Furthermore, p53 induces the expression of FoxO1, FoxO3 and pro-apoptotic regulators such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Taken together, decreased p53 signaling is a central hallmark of acne nutrigenomics (Fig. 1).

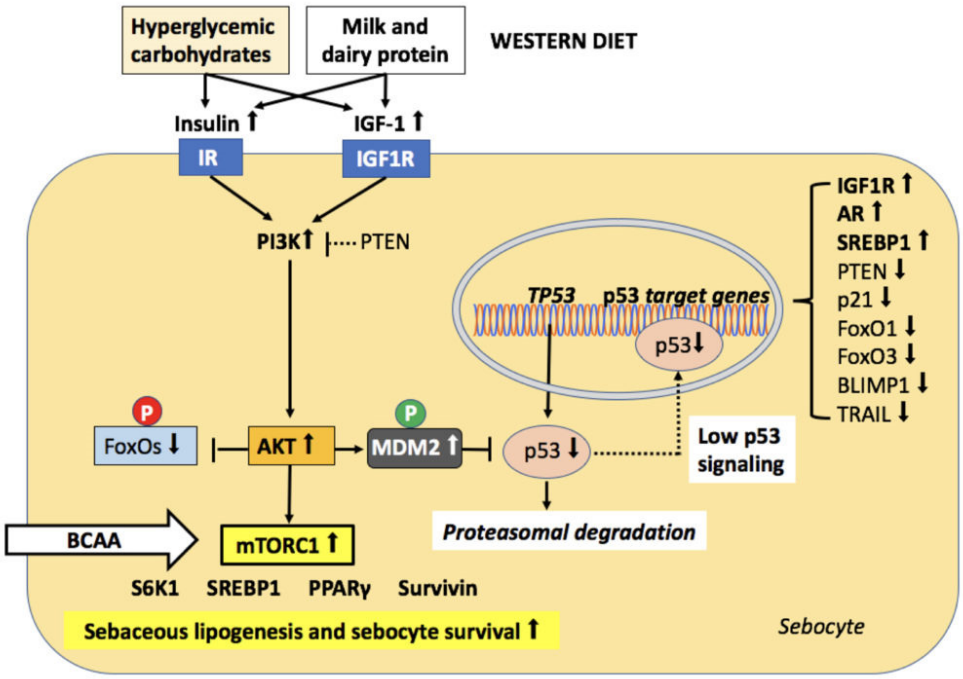

Fig. 1. Nutrigenomics of acne: Hyperglycemic carbohydrates and milk, prototypical components of Western diets, enhance insulin/IGF-1 signaling associated with activation of AKT and mouse double minute 2 (MDM2)-mediated degradation of p53, the key regulator of acne target gene expression.

All anti-acne therapies have been induced empirically without any clear mechanistic mode of action. However, translational evidence predicts that p53 is the key effector of all anti-acne therapies. All-trans retinoic acid (ATRA) and isotretinoin (13-cis retinoic acid) enhance p53 expression. Tetracyclines and macrolides via inhibiting p450 enzymes attenuate ATRA degradation, thereby increase p53. Benzoyl peroxide (BPO) and hydrogen peroxide (H_2O_2) elicit oxidative stress, which upregulates p53. Azelaic acid (AZA) leads to mitochondrial damage associated with increased release of reactive oxygen species inducing p53. Antiandrogens decrease AR-mediated expression of microRNA-125b, a key negative epigenetic regulator of p53. Paleolithic diets and exercise enhance p53 expression. Restriction of hyperglycemic carbohydrates decreases insulin and IGF-1 serum levels. Restriction of milk, an endocrine signaling system of mammals that enhances insulin/IGF-1 synthesis and transfers exosomal TP53-trageting microRNA-125b and DNA methyltransferase 1 (DNMT1)-targeting microRNA-148a, enhances p53 signaling. Thus, all anti-acne therapies and dietary interventions converge in upregulation of p53.

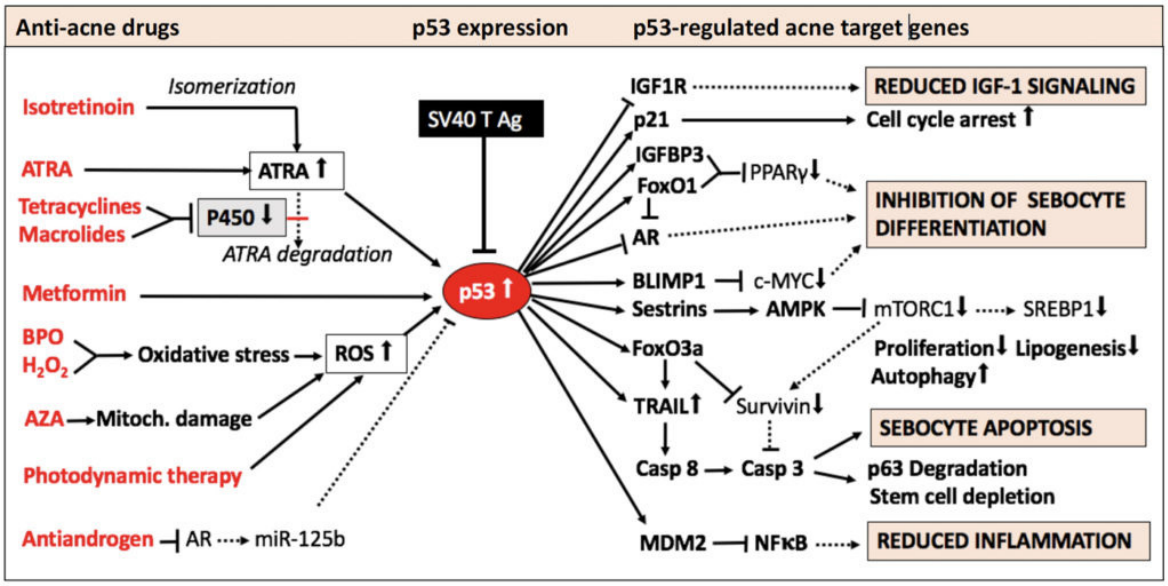

Fig. 2. Synoptic illustration of p53-inducing acne treatments and their impact of acne-related p53 target genes. Note, large SV40 T Ag, which immortalizes seboyctes, inhibits p53 activity, which does not reflect the reality of acne.

It is of critical concern that the majority of today´s acne researchers use immortalized sebocytes, which are transfected by Simian virus large T antigen (SV40 T Ag), a well-known inhibitor of p53. p53-inactivated, immortalized sebocytes are thus misleading *in vitro*-cell culture systems that should be used with caution in acne research and pharmacological studies of potential anti-acne drugs.

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Publications

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