TISSUE LIVER X-RECEPTOR ALPHA (LXRα) LEVEL IN ACNE VULGARIS

Thesis

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BY

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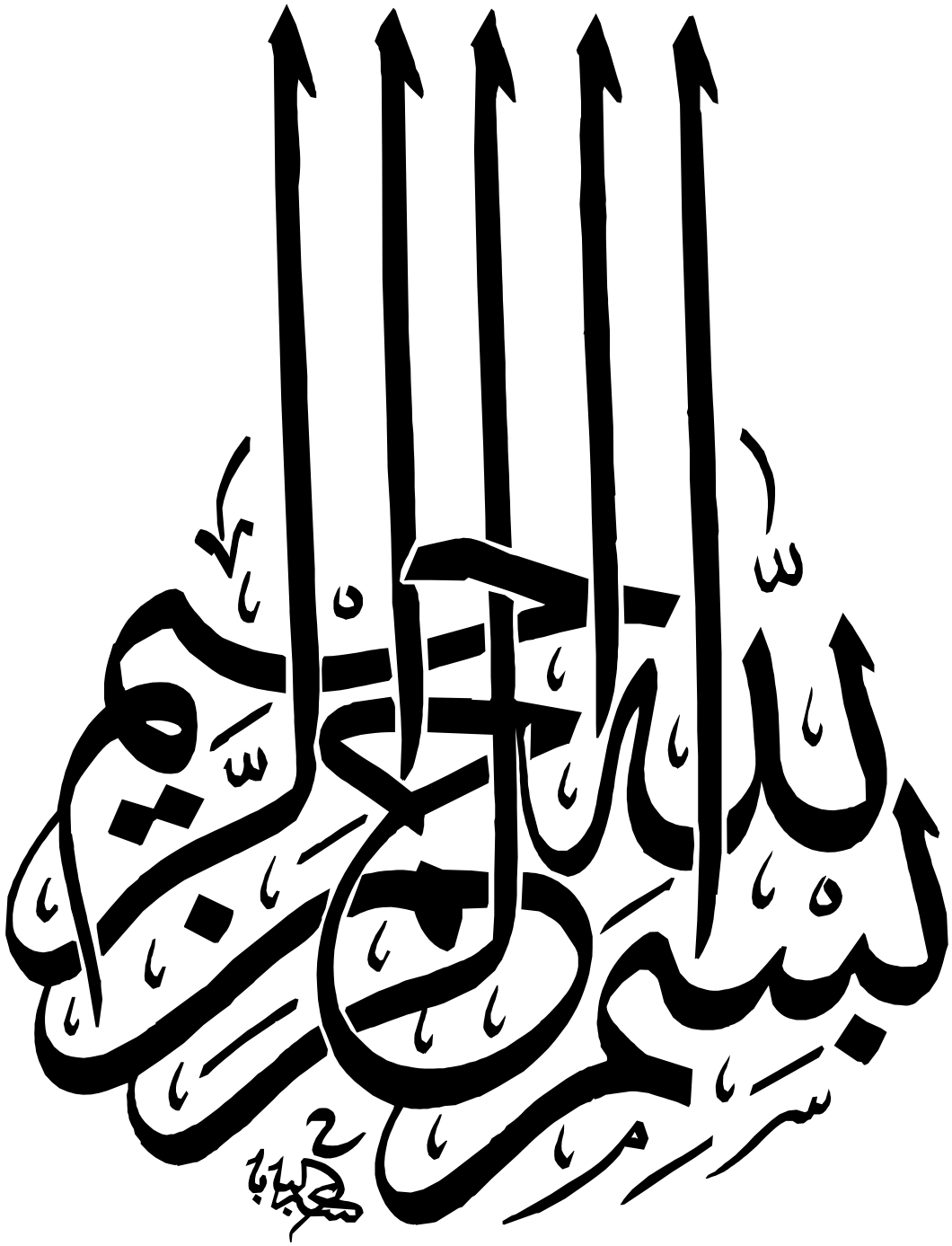
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Contents

List of Abbreviations

ApoE : Apolipoprotein E.

cDNA : Complementary deoxyribonucleic acid.

COX-2 : Cyclooxygenase-2.

DBD : DNA- binding domain.

DHEAS : Dehydroepiandrosterone sulphate.

DHT : Dihydrotestoterone.

DNA : Deoxyribonucleic acid.

EcR : Ecdysone receptor.

EFA : Essential fatty acids.

FXR : farnesoid X receptor.

GR : Glucocorticoid receptor.

HSD : hydroxysteroid dehydrogenase.

IGF : Insulin-like growth factor.

IL : Interleukin.

LBD : Ligand binding domain.

LRH : Liver receptor homologue.

LXR : Liver X receptors.

LXREs : Lxr response elements.

mRNA : Messenger Ribonucleic acid.

NCoR : Nuclear receptor corepressor.

NF-kB : Nuclear Factor-Kappa B.

NO synthase : Nitric oxide synthase.

NR : Nuclear receptor.

P. acnes : Propionobacterium acnes.

PCR : Polymerase chain reaction.

PPAR : Peroxisome proliferator-activated receptor.

PPRE : Peroxisome proliferator response element.

PUFA : Polyunsaturated fatty acids.

PXR : Pregnane x receptor.

RT-PCR : Reverse transcription polymerase chain reaction.

RXR : Retinoid x receptor.

SHP : short heterodimer partner.

SREBP : Sterol regulatory element binding proteins.

TLR : Toll like receptor.

TNF : Tumor necrosis factor.

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ABSTRACT

Background: Acne vulgaris is a disease of the pilosebaceous unit. Increased sebum lipogenesis by sebaceous gland is the major factor in the pathophysiology of acne. LXRα have been recognized in the regulation of genes involved in lipid biosynthesis. Activation of LXRα inhibits proliferation, increase lipogenesis and improve differentiation of sebocytes.

Aim: To investigate the level of tissue expression of LXRα in inflammatory and non inflammatory acne lesions and in comparison with normal skin.

Patients and methods: Seventeen patients with inflammatory and non inflammatory acne lesions and sixteen age and sex comparable healthy volunteers as control were included in the study. Punch skin biopsies were taken from the acne lesions and normal skin of the volunteers for detection of gene expression of LXRα by RT- PCR.

Results: the level of LXRα was significantly higher in the lesional skin either inflammatory (with a mean of 1188.52 ± 129.5) or comedonal acne (with a mean of 892.52 ± 66.08) in a statistically significant manner than the controls (with a mean of 600.50 ± 95.30) where the P value was <0.001. In addition, the

level of LXRα was significantly higher in inflammatory acne (with a mean of 1188.52 ± 129.5) in a statistically significant manner) than comedonal acne (with a mean of 892.52 ± 66.08) where the P value was <0.001.

Conclusion: the significant increase in the level of LXRα in acne lesions compared to controls suggesting that LXRα may have a role in the pathogenesis of acne vulgaris itself and is not a consequence of inflammation. In addition, it may play a role in the progression of the disease from comedonal to inflammatory. Further studies are recommended to evaluate the therapeutic benefits of the use of LXRα antagonists as a new therapeutic modality for acne vulgaris.

Keywords: Acne vulgaris, Pathogenesis, Liver x receptors (LXR), Polymerase chain reaction (PCR).

Introduction

Acne vulgaris is a disease of the pilosebaceous unit resulting from the interplay of different factors: seborrhea, *P. acnes* colonization, hyperkeratinization of the follicular duct and release of inflammatory mediators. Increased sebum lipogenesis by sebaceous gland is considered, among all features, the major one involved in the pathophysiology of acne. On average, acne subjects excrete more sebum than normal ones and secretion rates correlate well with the severity of clinical manifestations ***(Picardo et al, 2009).***

It was thought that the primary change in the sebaceous follicle is the alteration in the pattern of keratinization within the follicle. Initial alteration is in the infrainfundibular portion where there is hyperproliferation. The keratin is also qualitatively altered as it tends to become densely packed along with monofilaments and lipid droplets ***(Gollnick et al, 2003).***

Propionobacterium acnes colonises the follicular duct and proliferates, breaking down the sebum to triglycerides, irritants that contribute to the development of inflammation. When the follicular epithelium is invaded by lymphocytes it ruptures, releasing sebum, micro‑organisms, and keratin into the dermis. Neutrophils, lymphocytes, and foreign body giant cells

accumulate and produce the erythematous papules, pustules, and nodular swelling characteristic of inflammatory acne ***(Ayer and Burrows, 2006).***

Inflammation is the key component of acne and the major reason for its morbidity and sequelae (pigmentary disturbances and scarring). Inflammation, for a long time was believed to be a secondary process in the pathogenesis of acne. New data indicates that immunological events led by perifollicular helper T-cells in genetically predisposed individuals may in fact be a primary process, initiating comedogenesis through elaboration of IL-1. Further; inflammation may upregulate sebum production through production of inflammatory mediator leukotriene B4 that binds to receptors on the sebocytes ***(Kubba et al, 2009).***

It was indicated that sebocytes, as major components of pilosebaceous unit, may act as immune cells and may be activated by *P. acnes* that recognize altered lipid content in sebum, followed by the production of inflammatory cytokines ***(Knor, 2005).***

Liver X-receptor (LXR) is a member of the nuclear receptor family of transcription factors and closely related to nuclear receptors such as peroxisome proliferator-activated receptors

(PPAR), retinoid X receptors (Rxr). Two isoforms are present LXRα and LXRβ ***(Willy et al, 1995).***

LXRα have been widely recognized in the regulation of genes involved in innate immunity, inflammation and lipid biosynthesis, whereas LXRβ have been shown to be involved in keratinocyte differentiation and epidermal permeability barrier function ***(Gupta et al, 2010).***

Activation of LXRs stimulates keratinocyte differentiation and improves permeability barrier homeostasis by a number of mechanisms, including stimulating epidermal lipid synthesis, increasing lamellar body formation and secretion, and increasing the activity of enzymes required for the extracellular processing of lipids in the stratum corneum, leading to the formation of lamellar membranes that mediate permeability barrier function ***(Schmuth et al, 2008).***

Differentiation of sebocytes is strongly associated with enhanced lipid synthesis and accumulation in the cells. Sebocytes express LXRα, the application of natural 22(R)-hydroxycholesterol or synthetic ligands of LXRα significantly inhibit proliferation, increase lipogenesis and improve differentiation of sebocytes ***(Hong et al, 2008).***

Aim of the work:

Based on these findings, the aim of this study was to investigate the level of tissue expression of LXRα in inflammatory versus non inflammatory acne lesions and in comparison with normal skin. Suggesting that LXRα could be one of the most important therapeutic targets for the treatment of acne. Thus, it would be advantageous to develop selective LXR antagonists to regulate sebaceous lipogenesis and inflammation.

Chapter One

Acne Vulgaris

Definition:

Acne is a term derived from the Greek word “acme” in which the Greeks used this word to mean a point or a spot on the face. In the sixth century AD the term “acne” was first used by the emperor Justinian’s physician, Aetius Amidenus who translated it from Greek into Latin, and through these translations confusion arose regarding its original meaning ***(Goolamali and Andison, 1977).***

Acne is a chronic disease of the pilosebaceous follicle that causes polymorph cutaneous lesions, among them comedones (as a primary lesion), papules, cysts, pustules, and abscesses, which after regression may leave scars ***(Degitz et al, 2007).***

The face, anterior trunk, and upper back are the most commonly affected areas due to their greater concentration of sebaceous glands in these areas It is characterized by periods of exacerbation alternated with periods of stability ***(Ramos-e-Silva and Carneiro 2009).***