Expression of Sirtuin 1 and its relation to Tumor Necrosis Factor-Alpha in psoriatic plaques.

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Abstract

Background: Although it is now considered a prototypic Th1/Th17-mediated disease, several gaps still exist in our understanding of the pathogenesis of psoriasis. Sirtuins, a family of seven proteins that have generated huge interest in several fields including dermatology, have been proposed to contribute to the development of inflammatory and hyperproliferative disease. It has been proposed that changes in Sirtuin 1 (SIRT1), through its effect on pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), may contribute to the development of the psoriatic plaque.

Objective: Our aim was to study the degree of expression of Sirtuin 1 (SIRT1) and its relation to clinical disease parameters as well as its interactions with Tumor Necrosis Factor-alpha (TNF-α) in psoriatic skin.

Methods: 30 psoriatic patients and 22 age, sex and skin type matched controls were included. Full clinical examination was done and tissue levels of SIRT1 and TNF-α were measured by ELISA.

Results: SIRT1 was significantly downregulated in lesional psoriatic skin in comparison to controls and non-lesional skin ($p<0.001$). TNF-α was significantly upregulated in lesional psoriatic skin in comparison to controls and non-lesional skin ($p<0.001$). A significant negative correlation between non-lesional TNF-α and disease duration ($r=-0.483$, $p=0.007$), as well as a positive correlation between TNF-α and SIRT1 in non-lesional psoriatic skin ($r=0.451$, $p=0.021$) were detected.

Limitations: Small sample size

Conclusion: Our study concludes that the downregulation of SIRT1 in psoriatic plaques may be involved in the pathogenesis of psoriasis. This occurs through several mechanisms, including a possible unchecked pro-inflammatory TNF-α consequence.

Keywords: Psoriasis - Sirtuins - Tumor Necrosis Factor-alpha - Epigenetics - NF-κB

List of Abbreviations

ADP: Adenosine diphosphate

ADPRT: Adenosine diphosphate ribosyl transferase

AIF: Apoptosis-inducing factor

AMPs: Antimicrobial peptides

AP-1: Activation protein-1

APAF-1: Apoptotic protease activating factor 1

APCs: Antigen-presenting cells

APRIL: A proliferation-inducing ligand

BAFF: B cell-activating factor

Bak: BCL-2 homologous antagonist/killer

Bax: Bcl2 associated X protein

Bcl2: B-cell CLL/lymphoma 2

Bcl-xl: B-cell lymphoma-extra large

Bid: Bcl-2 interacting domain

BLyS: B-lymphocyte stimulator

cAMP: Cyclic adnosine monophosphate

CCL: Chemokine (C-C motif) ligand

CCR: Chemokine C-C Receptor

CD: Cluster of Differentiation

CDK4: Cyclin-Dependent Kinase 4

CLA: Cutaneous lymphocyte antigen

CREB: cAMP-responsive element-binding protein

CXCL: Chemokine (C-X-C motif) ligand

DC: Dendritic cells

DD: Death Domain

DDC: Dermal dendritic cells

DIABLO: IAP binding protein with low pI

DNA: Deoxyribonucleic acid

E2F: E2 Transcription Factor

ECAM: Endothelial cell adhesion molecule.

EGF-R: Epidermal growth factor receptor

ELISA: Enzyme linked immunosorbent assay

FADD: Fas-associated death domain

FLIP: FLICE/caspase-8-Inhibitory Protein

GDH: Glucose Dehydrogenase

GM-CSF: Granulocyte-macrophage colony-stimulating factor

GRO α: Growth related oncogene alpha

H: Histone

HAT: Histone acetyltransferase

HDAC: Histone deacetylase

HLA: Human leucocyte antigen

HPV: Human papilloma virus

IAP: Inhibitor of apoptosis

ICAD: Inhibitor of caspase activated DNase

ICAM: Intracellular adhesion molecule

IFN-α: Interferon alpha

IFN-γ: Interferon gamma

IGF-1: Insulin-like growth factor-1

IκB: Inhibitors of kappa-B

IKK: I Kappa B Kinase

IL: Interleukin

iNOS: Inducible nitric oxide synthase

Kc: Keratinocyte

kDa: Kilodalton

KGF: Keratinocyte growth factor

LFA: Lymphocyte functional antigen

Lys: Lysine

MHC: Major histocompatibility complex

MiRNA: microRNA

MMP-9: Metalloproteinases 9

mRNA: Messenger ribonucleic acid

mTOR : Mammalian target of rapamycin

n: Number

NAD: Nicotinamide adenine dinucleotide

NAM: Nicotinamide

NF-IL-6: Nuclear factor IL-6

NF-κB: Nuclear factor kappa-B

NGF: Nerve growth factor

NK: Natural Killer

O-AADPR: O-acetyl-ADP-ribose

PAI-2: Plasminogen activator inhibitor type 2

PASI: Psoriasis area and severity index

PBMCs: Peripheral blood mononuclear cells

PCNA: Proliferating Cell Nuclear Antigen

pDC: Plasmacytoid dendritic cells

PGE2: Prostaglandin E2

pRB: Retinoblastoma protein

RANKL: Receptor activator of NF-kB ligand

RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted

Rb: Retinoblastoma

RelA: V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A

RIP: Receptor interacting protein

RNA Pol 1: Ribonucleic acid Polymerase 1

RNA: Ribonucleic acid

rRNA: Ribosomal ribonucleic acid

SD: Standard deviation

Sir2: silent information regulator

SIRT: Sirtuin

SKALP: Skin-derived antileukoproteinase

SLE: Systemic lupus erythematosus

SMAC: second mitochondria-derived activator of caspases direct

SOCS3: Suppressor of Cytokine Signaling 3

STACs: Selective sirtuin activating compounds

STAT-3: Signal transducer and activator of transcription 3

TACE: Tumor necrosis factor alpha converting enzyme

TCR: T cell receptor

TGF: Transforming growth factor

Th: T helper

TLRs: Toll like receptors

TNFRI: Tumor necrosis factor alpha Receptor I

TNF-α: Tumor Necrosis Factor-alpha

TRADD: TNF receptor associated death domain

TRAF2: TNF receptor associated factor-2

TRAIL: TNF-related apoptosis-inducing ligand

Treg: T regulatory

TWEAK: TNF-like and weak inducer of apoptosis

Tyr: Tyrosine

UV: Ultraviolet

VCAM: Vascular cell adhesion molecule

VEGF: Vascular endothelial growth factor

VIP: Vasoactive intestinal peptide

VLA: Very late antigen

VPF: Vascular permeability factor

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Introduction