

# **EXPRESSION OF CYCLIN D1 AND P16 IN PSORIASIS BEFORE AND AFTER PHOTOTHERAPY**

Thesis  
submitted for partial fulfillment  
Of M.D. degree in  
**dermatology**

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2007

# Acknowledgement

*First, thanks to “God”*

I would like to express my deepest gratitude and profound thanks to **Prof. Dr. Mostafa Abou-Elela**, Professor of Dermatology, Faculty of Medicine, Cairo University, for his most valuable advice, laborious guidance and great help throughout this work.

I am also grateful to **Dr. Noha Nagui**, Assistant Professor of Dermatology, Faculty of Medicine, Cairo University, for her sincere help, kind supervision, meticulous guidance and continuous support.

Furthermore, I would like to thank **Dr. Laila Rashed**, Assistant Professor of Biochemistry, Faculty of Medicine, Cairo University, for her kind help in fulfilling the practical aspect of the study.

I would like also to thank **Dr. Dalia Ahmed**, Lecturer of community, Faculty of Medicine, Cairo University, for her great help and her valuable effort in the statistical analysis of this work.

Finally, I would like to thank all the Staff and Colleagues of Dermatology Department, Cairo University for their help and cooperation.

# ABSTRACT

As one of the most common hyperproliferative skin diseases, psoriasis vulgaris is characterized by keratinocyte hyperproliferation, profound changes in keratinocyte maturation and turnover rate. In addition, an abnormal resistance of psoriatic keratinocytes to apoptosis may contribute to the epidermal hyperplasia (**Wrone-Smith et al., 1997**).

Progression of cells from G 1 to S phase is regulated via pRb phosphorylation by cyclin D complexed with CDK 4 and 6, which are in turn regulated by CDKI, such as p16 INK4 protein (**Beasley et al., 2003**).

**KEY WORDS:** psoriasis, cyclin D1, P16, phototherapy

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# LIST OF ABBREVIATIONS

<b>ACE</b>	angiotensin-converting enzyme
<b>AP-1</b>	activator protein-1
<b>APC</b>	The anaphase-promoting complex
<b>APCs</b>	antigen-presenting cells
<b>ATM</b>	ataxia telangiectasia mutated
<b>ATR</b>	ATM and Rad3-related
<b>BMP-6</b>	Bone morphogenetic protein-6
<b>cAMP</b>	cyclic adenosine monophosphate
<b>CDKS</b>	Cyclin-dependent kinases
<b>CDKIs</b>	CDK inhibitors
<b>CE</b>	cornified envelope
<b>cGMP</b>	cyclic guanosine monophosphate
<b>Chk</b>	checkpoint kinase
<b>CLA</b>	cutaneous lymphocyte-associated antigen
<b>DCs</b>	dendritic cells
<b>DC-LAMP</b>	dendritic cell lysosome associated membrane protein
<b>EGF</b>	Epidermal growth factor
<b>eIF</b>	eukaryotic initiation factor
<b>FAE</b>	Fumaric acid esters

<b>G1</b>	GAP 1
<b>GM-CSF</b>	granulocyte-macrophage colony-stimulating factor
<b>GRO</b>	growth related oncogene
<b>HETE</b>	Hydroxyeicosatetraenoic
<b>HEVs</b>	high endothelial venules
<b>HIV</b>	human immunodeficiency virus
<b>HLA</b>	Human leucocyte antigen
<b>HSP</b>	heat shock protein
<b>ICAM</b>	intercellular adhesion molecule
<b>IFN</b>	Interferon
<b>Ig</b>	immunoglobulin
<b>IGF-I</b>	insulin growth factor-I
<b>IKB</b>	Inhibitor of Kappa Beta
<b>IL</b>	Interleukin
<b>ILVEN</b>	inflammatory linear verrucous epidermal naevus
<b>IM</b>	intramuscular
<b>IP-10</b>	Interferon gamma inducible protein -10
<b>IV</b>	intravenous
<b>K</b>	Keratin
<b>LCD</b>	Liquor carbonis detergens
<b>LFA</b>	lymphocyte functional antigen
<b>LT</b>	leukotrienes
<b>M stage</b>	mitosis

<b>MDC</b>	macrophage-derived chemokine
<b>MED</b>	minimal erythema dose
<b>MHC</b>	Major histocompatibility complex
<b>MIP</b>	Macrophage inflammatory protein
<b>MP</b>	mercaptopurine
<b>MRP-8</b>	migration inhibitory factor-related protein-8
<b>mTOR</b>	The mammalian target of rapamycin
<b>MTX</b>	Methotrexate
<b>NAPSI</b>	Nail Psoriasis Severity Index
<b>NAT gene</b>	natural antisense transcription
<b>NF-KB</b>	Nuclear factor Kappa Beta
<b>NSAIDs</b>	non-steroidal anti-inflammatory drugs
<b>PACAP</b>	pituitary adenylate cyclase activating polypeptide
<b>PASI</b>	Psoriasis area and severity index
<b>PCNA</b>	Proliferative cell nuclear antigen
<b>PDGF</b>	Platelet derived growth factor
<b>PDL</b>	pulsed dye laser
<b>PRP</b>	pityriasis rubra pilaris
<b>PUVA</b>	psoralen plus UVA
<b>RA</b>	rheumatoid arthritis
<b>RANTES</b>	Regulated upon activation normal T cell expressed and secreted
<b>RAPTOR</b>	TOR regulatory protein



<b>RARs</b>	retinoic acid receptors
<b>Rb</b>	retinoblastoma tumor suppressor gene
<b>RT-PCR</b>	Reverse transcriptase polymerase chain reaction
<b>SD</b>	Standard deviation
<b>S stage</b>	Synthesis
<b>SCC</b>	squamous cell carcinoma
<b>SKALP</b>	skin-derived antileukoproteinase
<b>SLC gene</b>	secondary lymphoid tissue chemokine
<b>SPF</b>	S-phase promoting factor
<b>TARC</b>	Thymus and activation-regulated chemokine
<b>Tc</b>	cytotoxic T cells
<b>TCR</b>	T cell receptor
<b>TGase K</b>	keratinocyte transglutaminase
<b>TGF-<math>\alpha</math></b>	transforming growth factor-alpha
<b>Th</b>	T-helper
<b>Tie</b>	Tyrosine kinase
<b>TNF-<math>\alpha</math></b>	tumor necrosis factor-alpha
<b>UVR</b>	ultraviolet radiation
<b>VCAM</b>	vascular cell adhesion molecule
<b>VEGF</b>	Vascular endothelial growth factor
<b>VIP</b>	Vasoactive intestinal polypeptide
<b>VLA-4</b>	very late antigen-4

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# INTRODUCTION

Psoriasis is a skin disease characterized by T cell activation and keratinocyte stem cell hyperproliferation. The proliferate cell population is approximately doubled in psoriasis, whereas the cell cycle is more than 8 times shorter and daily production of keratinocytes in psoriatic lesions is approximately 28 times greater than that in normal epidermis (**Krueger and Ellis, 2005**).

The cell cycle in an eukaryotic cell consists of **G1** (growth and preparation of the chromosomes for replication), **S** (synthesis of DNA), **G2** (preparation for mitosis) and **M** (mitosis) phases. The passage of a cell through the cell cycle is controlled by proteins in the cytoplasm. Among the main players are the cyclins and the cyclin-dependent kinases (Cdks) (**Miele, 2004**).

Cyclin D1 (a G1 cyclin) is a protein that is involved in cell cycle regulation by binding to Cdk4 thus signaling the cell to prepare the chromosomes for replication. The cyclin D1 gene product (*CCND1*, located at 11q13) phosphorylates retinoblastoma (Rb), leading to cell progression. The activity of cyclin D1 may be inhibited by many tumor suppressor genes including p16 (**Serrano et al.,1993**).

P16 is a tumor suppressor gene that acts to modulate cell proliferation; it is a Cdk inhibitor (CKI), specifically of cdk4. It binds cdk4, thereby preventing cyclin D from binding; cdk4 is kept inactive

as a result; cdk4 cannot phosphorylate RB, so RB remains active. The p16 gene is located at 9p21 (**Lukas et al., 1995**).

During malignant proliferation, epidermal keratinocytes (KCs) frequently acquire the capacity to by-pass cellular senescence, a response that normally limits their unrestricted proliferation. Despite growing interest in the role for senescence during aging of skin and cutaneous carcinogenesis little is known regarding the regulation of proteins encoded by the INK4a/ARF locus such as p16; which is a potential candidate marker for cellular senescence characteristic for psoriasis; in KCs. There is a great interest in studying the role of p16 and cyclin D1 in the pathogenesis of psoriasis (**Chaturvedi et al., 2003**).

Studying alterations in G (1)-S cell cycle regulatory proteins and proliferation in infiltrative cells were surprising and clearly indicated that invasion with an intact p16(INK4a)-cyclin D-retinoblastoma protein (Rb) pathway was equivalent to ceased proliferation (**Svensson et al .,2003**).

Ultraviolet (UV) light has been reported to induce an immediate G1 arrest by rapid clearance of cyclin D1 in the murine macrophage cell line Bac1.2F5 following UVR-induced V DNA damage to prevent further damage. The rapid disappearance of the cyclin D1 protein after exposure to UV was caused by at least two different mechanisms. In the first mechanism, cyclin D1 mRNA promptly disappeared within 1 min after UV irradiation, although cdk4 mRNA levels were unchanged. In the second mechanism, UV irradiation accelerated the degradation of cyclin D1 protein through the proteasome pathway.