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

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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

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

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

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

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

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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.