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مقدمة من

الطبيبة/مروة هلال مُحمد الخضَري

(بكالوريوس الطب والجراحة)
كلية الطب- جامعة عين شمس

تحت إشراف

الأستاذة الدكتورة/مي حسين السَّماحي

أستاذ الأمراض الجلدية والتناسلية وأمراض الذكورة

كلية الطب – جامعة عين شمس

الدكتورة/ نجلاء سمير أحمد

أستاذ مساعد الباثولوجي

كلية الطب – جامعة عين شمس

الدكتورة/ عزَّة عصمت مصطفى

مدرس الأمراض الجلدية و التناسلية وأمراض الذكورة

كلية الطب – جامعة عين شمس

كلية الطب

جامعة عين شمس

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Expression of Matrix Metalloproteinases in Skin Aging

Thesis

Submitted for Partial Fulfillment of Master Degree in Dermatology, Venereology and Andrology

Presented by

Marwa Helal Mohammed El Hadary
(M.B, B.Ch.)
Faculty of Medicine – Ain Shams University

Supervised by

Prof. Dr. May Hussein El Samahy
Professor of Dermatology, Venereology and Andrology
Faculty of Medicine – Ain Shams University

Dr. Naglaa Samier Ahmed
Assistant Professor of Pathology
Faculty of Medicine, Ain Shams University

Dr. Azza Esmat Mostafa
Lecturer of Dermatology, Venereology and Andrology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
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List of Abbreviations

ADAMs	A disintegrin and metalloproteinases
AP-1	Activator protein-1
BCC	Basal cell carcinoma
bFGF	Basic fibroblast growth factor
bp	Base pairs
ºC	Degree centigrade
cAMP	Cyclic adenosine monophosphate
CA-MMP	Cysteine array MMP = MMP-23A
Cdk	Cyclin dependent kinases
Cy	cytoplasmic domain
DAB	Diaminobenzedine
DEJ	Dermal-epidermal junction
DHEA	Dehydroepiandrostrone
DHEAS	Dehydroepiandrostrone- Sulphate
DNA	Deoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
ECM	Extracellular matrix
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
ERK	Extracellular signal-regulated kinases
FGF	Fibroplast growth factors
FN	fibronectin
Fu	Furin
GAGs	Glycosaminoglycans
GM-CSF	Granulocyte macrophage colony stimulating factor
GPI	Glycosylphosphatidylinositol
H&E	Hematoxylin and Eosin
HgCl2	Mercuric chloride
HS	Highly significant
Ig	Immunoglobulin
IGFBP	Insulin-growth factor binding protein
IL	Interleukin
JNK	c-Jun amino-terminal kinase
LCs	Langerhans cells
MAPk	Mitogen-activated protein kinases
MMPs	Matrix metalloproteinases
µm	Micrometer
mm	Millimeter

List of Abbreviations (Cont..)

mRNA	Messenger ribonucleic acid
mRNP	Messenger ribonucleoprotein
MT-MMPs	Membrane-type MMPs
NADPH	Nicotinamide adenine dinucleotide phosphate
ND	Not determined yet
NE	Neutrophil elastase
NS	Non-significant
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
$^1O_2$	Singlet oxygen
$O_2^{\bullet-}$	Superoxide radical
OG	O-glycosylated
$^{\bullet}OH$	Hydroxyl radical
ox-LDL	Oxidized low density lipoprotein
P	Probability value
PAF	Platelet activating factor
PBS	phosphate buffered saline
PDGF	Platelet derived growth factor
PGE 2	Prostaglandin E 2
RASI-1	Rheumatoid arthritis synovium inflamed-1=MMP-19
RECK	Reversion-inducing cysteine-rich protein with kazal motifs
ROS	Reactive oxygen species
S	Significant
S-S	Disulfide bond
SA	Signal anchor
SCC	Squamous cell carcinoma
SD	Standard deviation
SDS	Sodium dodecyl sulfate
-SH	Thiol-group (-SH)
SPSS	Statistical package for Social Science
TGF	Transforming growth factor
TIMPs	Tissue inhibitors of matrix metalloproteinases
TM	Transmembrane
TNF α	Tumour necrosis factor α
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
Zn2+	Zinc

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INTRODUCTION

Cutaneous aging is a complex biological phenomenon affecting the different constituents of the skin [(1)]. There are two independent, clinically and biologically distinct, processes affecting the skin simultaneously. The first is the innate or intrinsic aging, 'the biologic clock' that affects the skin by slow, irreversible tissue degeneration. The second process is the extrinsic aging, which is the result of exposure to out-door elements, mainly, ultraviolet (UV) irradiation; namely 'the photoaging [(2)].

Intrinsic skin aging is characterized clinically by fine wrinkles, thin and dry skin, loss of underlying fat and hair loss. Histologically, such skin manifests epidermal and dermal atrophy, flattening of the epidermal rete ridges, as well as reduced numbers of fibroblasts and mast cells [(3)]. In addition, collagen in aged skin is characterized by thickened disorganized fibrils. Besides, lower level of collagen is synthesized by aged fibroblasts. The ratio of collagen types found in human skin also changes with age. In young skin, collagen type I comprises 80% and collagen type III comprises about 15% of total skin collagen. In older skin, the ratio of type III to type I collagen increases, due to an appreciable loss of collagen type I [(4)].

Nevertheless, Photoaging affects sun-exposed areas and is characterized clinically by fine and coarse wrinkling,

roughness, dryness, laxity, telangiectasias, loss of tensile strength, pigmentary changes and the development of a variety of benign and malignant neoplasms [(5)].The histologic hallmark of photo-aging is dermal elastosis which largely consists of thickened, granular amorphous elastic structures. This elastotic material is postulated to result from direct ultraviolet-mediated damage to the dermal fibroblasts which then produce abnormal elastin, or it may result from chronic low-grade enzymatic digestion of extracellular matrix by proteases elicited by inflammatory mediators [(6)].

Normally, the level of collagen is maintained by ensuring a balance between collagen synthesis by fibroblasts in the dermis and enzymatic degradation by matrix metalloproteinases (MMPs). The later comprise a family of zinc-containing proteinases that are responsible for degrading extracellular proteins [(7)]. MMPs are classified as collagenases, gelatinases, stromelysins and membrane-type MMPs according to their substrate specificities and whether they are secreted soluble proteins or bound to cell surface membrane [(8)].Collagenases-1 (MMP-1) degrades collagens, while gelatinases A and B (MMP-2 and MMP-9) degrade elastin. Other MMPs, such as stromelysin 1 (MMP-3), are involved both in the collagen and elastin degradation. MMP levels in skin increase as a function of age [(9)] and also as a response to UV irradiation [(10)].

Ultraviolet irradiation causes alternations of dermal collagen through two primary pathways: **1)** stimulation of

collagen breakdown, resulting in fragmented, disorganized collagen and **2)** inhibition of procollagen biosynthesis, resulting in loss of collagen content. MMPs are key mediators of collagen degradation that is observed in photoaged skin. UV has been postulated to elevate at least three different MMPs in human skin namely; MMP-1, MMP-3 and MMP-9 **(11)**. This induction of increased levels of MMPs is brought about by a series of events involving signaling mechanisms, deoxyribonucleic acid (DNA) and protein damage, and an intricate dynamic process of interaction between keratinocytes and fibroblasts **(12,13)**.

It is evident that the activity of the MMPs is one of the keys of the skin aging and that these enzymes have thus to be the target of therapeutic activities **(14)**. Our understanding of the complex process of skin aging has increased significantly in recent years. Elucidating the underlying mechanisms involved in skin aging is of paramount importance for the design of specific effective therapeutic and protective strategies.