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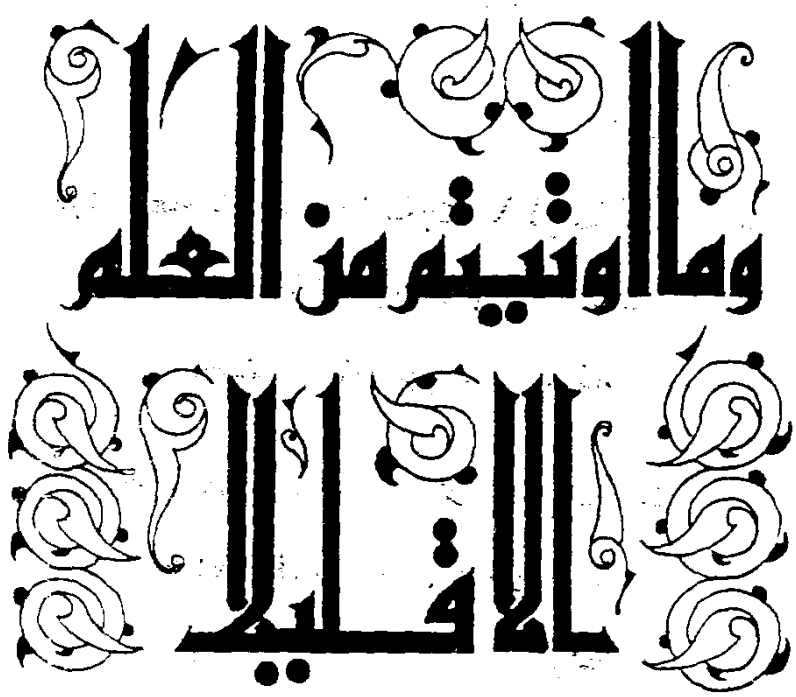


صدق الله العظيم

# *EPIDERMOPOIESIS AND EPIDERMAL GROWTH FACTOR*

AN ESSAY
SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE MASTER DEGREE
IN DERMATOLOGY AND VENEREOLOGY


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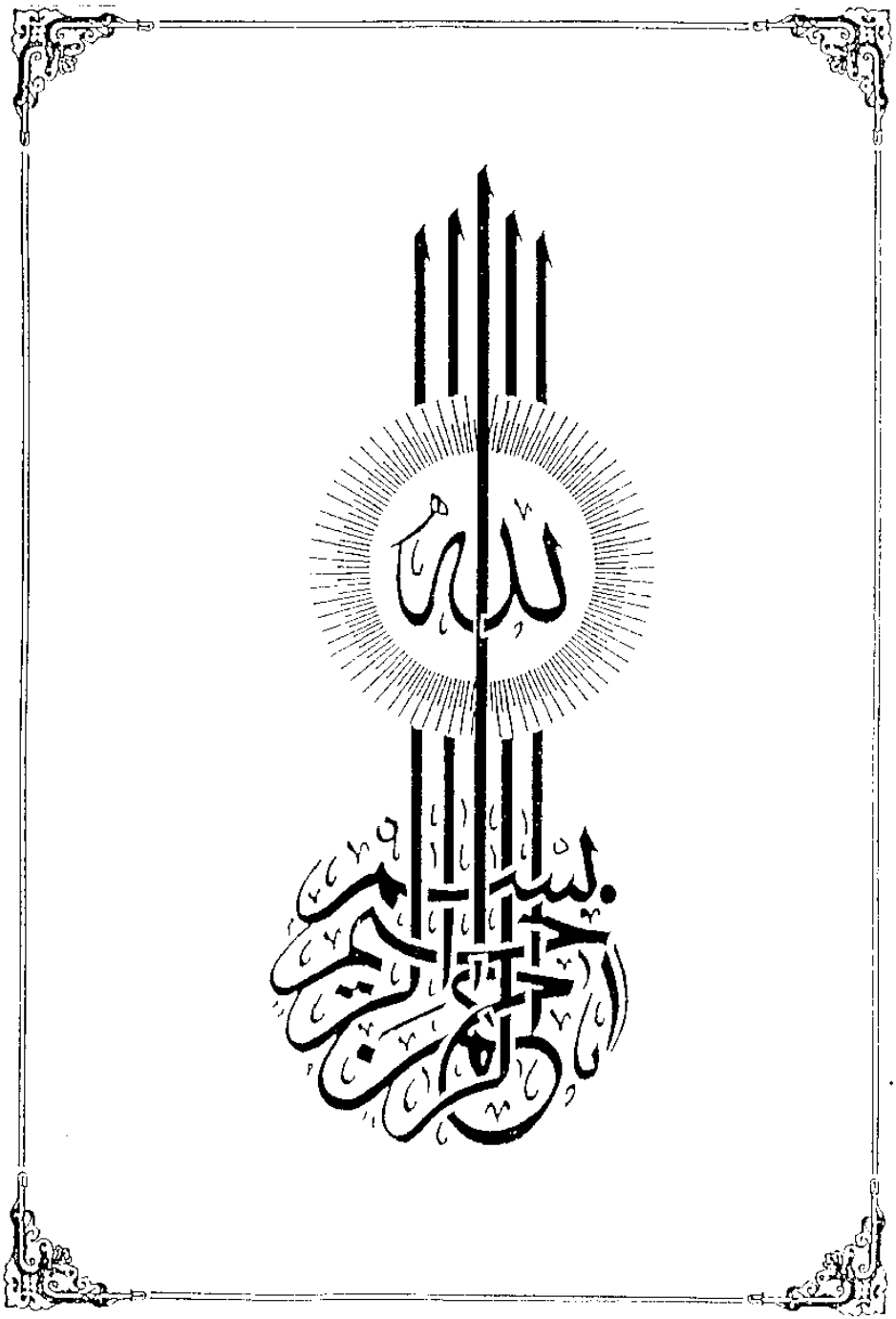

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# ABBREVIATIONS

| | |
|---|---|
| *(M)* | *Mitosis.* |
| *(G)* | *Post-mitotic growth phase.* |
| *(S)* | *A period of active DNA synthesis.* |
| *(G2)* | *Pre-mitotic growth phase.* |
| *EGF* | *Epidermal growth factor.* |
| *TA Cells* | *Transient Amplifying Cells* |
| *EPU* | *Epidermal Proliferative Units* |
| *[$H^3$]-TDR* | *Tritiated Thymidine* |
| *Ts* | *Duration of S phase.* |
| *TG2* | *Duration of G2 phase.* |
| *Tm* | *Mitosis time.* |
| *G0* | *Quiescent phase.* |
| *GF* | *Growth Fraction* |
| *Im* | *Mitotic Index* |
| *Is* | *Flash Labelling Index* |
| *cAMP* | *Cyclic 3',5' Adenosine Monophosphate* |
| *cGMP* | *Cyclic 3',5' Guanosine Monophosphate* |
| *EPP* | *Epidermal Pentapeptides* |
| *IFN* | *Interferon* |
| *TNF* | *Tumour Necrosis Factor* |
| *AA* | *Archidonic Acid* |
| *PG $E_2$* | *Prostaglandins $E_2$* |
| *1,25 $(OH)_2$ D* | 1,25 Dihydroxyvitamin D |
| *ETAF* | *Epidermal-Cell Derived Thymocyte Activating Factor* |
| *IL-1* | *Interlukin-1* |

| | |
|---|---|
| *EC-IL-3* | *Epidermal Cells-Interlukin-3* |
| *ENKAF* | *Epidermal-Cell Derived Mature Killer Cell Activating Factor* |
| *IL-6* | *Interlukin-6* |
| *IL-8* | *Interlukin-8* |
| *IL-4* | *Interlukin-4* |
| *TGFα* | *Transforming Ggrowth Factor-α* |
| *HBEGF* | *Heparin-binding EGF* |
| *AR* | *Amphiregulin* |
| *PI* | *Phosphotinositol* |
| *TGF-B* | *Transforming Growth Factor-B* |
| *FGF* | *Fibroblastic Growth Factor* |
| *aFGF* | *Acidic Fibroblastic Growth Factor* |
| *bFGF* | *Basic Fibroblastic Growth Factor* |
| *PDGF* | *Platelet-Derived Growth Factor* |
| *VEGF* | *Vascular endothelial growth factor* |
| *IGF* | *Insulin Growth Factor* |
| *NaCl* | *Sodium Chloride* |
| *ELISA* | *Enzyme-Linked Immunosorbent Assay* |
| *KGF* | *Keratinocyte Growth Factor* |
| *HLA-Dr* | *Human leukocyte antigen-DR* |
| *VDR* | *Vitamin-D receptor.* |

## LIST OF FIGURES

## LIST OF TABLES

# TABLE OF CONTENTS

# INTRODUCTION

# INTRODUCTION

The epidermis has classically been viewed as a stratified squamous epithelium, maintained by cell division. Renewing population are produced by rapid and continuous cell turnover from the small population of stem cell in the basal layer **(Ebling et al., 1992).**

In the epidermis, there are **"epidermal proliferation units"**, each is composed of a number of proliferative cells, a single Langerhans cell, two or three post-mitotic maturing basal cells, associated melanocytes, and a stock of differentiating cells. Thus, the basal layer in human epidermis is not simply a homogenous population of cells, but it is markedly heterogenous, containing stem, proliferative, and post-mitotic maturing cells **(Christophers and Potten, 1975).**

All proliferative cells move through what is called **cell cycle**, in which mitosis (M) is followed by the interphase, or post-mitotic growth phase ($G_1$), a period of active DNA synthesis (S), and a short resting or pre-mitotic growth phase ($G_2$). The interval between the mitosis of one basal cell and the next division of its daughter cell is called the **cell cycle time**. Using double labelling, a mean TGC of the complete cell cycle from

mitosis to mitosis was found to be 213 hours. **(Heeman and Galand, 1971).**

Differentiating cells leave the basal layer, and migrate through the Malpighian layer to the granular layer; then to the stratum corneum, with the latter losing cells from its external surface. The rate of cell loss from the stratum corneum should be balanced by the rate of cell production in the germinative compartment to produce the normal skin thickness. **(Ebling et al., 1992).**

The object of any **cell kinetic** investigation in a normal tissue, is to define the renewal system in kinetic terms. In the case of normal human epidermis, two of the proliferative indices. Two of them are partially useful, the mitotic index and the flash labelling index, which can be measured by labelling cells in S phase, with Tritiated Thymidine **(Christopher and Potten, 1975).** However, the more powerful measurement is the rate parameter, which is the rate at which cells enter any phase; this is done by using Calcemid or Vincristine, to arrest dividing cells in the metaphase. **(Ralfs et al., 1981).**

Epidermopoesis, like most biological systems, is under the control of both stimulatory and inhibitory signals. There are several factors which can inhibit the process of Epidermopoesis, as : **chalones**, which are the inhibitory polypeptide

influencing intracellular cyclic nucleotides(**Ebling et al., (1992)**; **interferon**, which reversibly inhibits the growth of human keratinocytes **(Morhen et al., 1987)**. **Tumor necrosis factor** has been shown to be reversibly cytostatic to keratinocyte **(Penicaet et al., 1984)**. Also increase concentration of **cyclic nucleotides** inhibit mitosis(**Halprin, (1976)**. **Steroids** lead to inhibition of mitosis **(Shahrad and Marks, 1977)**, **pentapeptides** inhibit mitosis rate by certain limited dose **(Elgio et al., 1986).** , and **Vitamin D analogues** inhibit proliferation, but stimulate differentiation **(Daniel et al., 1993)**.

On the other hand, there are some factors which have the ability to stimulate epidermopoesis as polyamines **(Herbest and Buchrach, 1970)**, and prostaglandins, which are the metabolic products of archidonic acid **(Hummorston et al., 1979)**. Also cytokines **(McKary and Leigh, 1991)**, growth factors **(Marti and Vincent, 1982)**, and Vit A, which is essential for the normal function of all epithelial tissues **(Jarrett and Spearman, 1970)**. Wound healing, provides a model to examine the changes in growth control that occur in establishing a new epidermis. Wound of the skin is followed by a wave of epidermal mitotic activity, which could represent the effects of diffusible factors spreading from the wound into surrounding tissues, such as growth factors **(Buckely et al., 1987).**

In recent years, the name **"growth factors"** has been given to proteins that are capable of enhancing cell mass, proliferations, and synthetic activity. However, the term **"growth factor"** is misleading, because of the multiplicity of their biological effects **(Marti and Vincent, 1989)**.

In recent years, the name **"growth factors"** has been given to proteins that are capable of enhancing cell mass, proliferations, and synthetic activity. However, the term **"growth factor"** is misleading, because of the multiplicity of their biological effects **(Marti and Vincent, 1989).**

There are five major families of growth factors that have been implicated in cell proliferation and wound healing. These families include epidermal growth factor family, platelets derived growth factor family, transforming growth factor family, insulin growth factor family, and fibroblast growth factor family. All the proteins of peptide growth factors families exert their biological effects by binding on target cells by large transmembrane glycoprotein receptors. When growth factors bind to a growth factor binding site in extracellular domain of receptor, initiation of a cascade of events occurs, that eventually stimulate cell to migrate or divide **(Neil and Gregory (part I), 1993).**

With the availability of large quantities of purified growth factor, the use of these agents for altering wound repair will become a reality. Experiments in animal models have shown that EGF and other growth factors treatment enhances healing of variety of wounds. Topical application of different growth factors promote healing of these wounds presumably by synthesis of epithelial cells, and by increasing the synthesis of proteins **(Gregory et al., 1986)**

Clinical trials have also assessed the effects of growth factor treatment on healing of chronic wounds in humans. The initial clinical results are encouraging. More research remain to be done to achieve the potential benefit of peptide growth factors treatment of chronic wounds **(Flanga, 1993).**