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THE SKIN: NEURO-IMMUNE AND ANTI-RADIATION SCOUT

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The skin and its annexes are the interface between human body and the environment. This organ is a multi-structural and multifunctional, being able to protect the subjacent structures from the various mechanical, thermal, chemical, physical (various radiations) or biological (microbes, viruses, fungi and parasites) aggression factors. The skin has a multi-structural architecture and here we will refer to the manner in which the two main components (peripheral nerve endings and immune system) act in conjunction, as part of the "conservation instinct". The epidermis is the main component of the neuro-immune and anti-radiation protective scout whose function is ensured on one side by the numerous nervous terminals found in the skin which are able to induce various sensations: touch, pressure, vibration, changes in temperature (toward warm or toward cold), and by other side by the three specialized cells: keratinocytes (physical protection against abrasion), melanocytes (anti-radiation protection) and the Langerhans cells (immune protection). Melanocytes are the specific cells present in the basal layer of epidermis. The color of the skin does not depend on the number of melanocytes, but rather upon the melanogenetic activity of these cells, the production of melanin. LAMTOR (Lysosomal Adaptor and Mitogen activated protein kinase and Mammalian Target of Rapamicine [mTOR] activator/regulator) is a molecular complex involved in the generation and maintenance of the Langerhans cell homeostasis. These epidermal network of these cells is considered by us to be the main immune guards, regulating immune response and tolerance as a part of the neuroimmune shield of the body through the skin. Langerhans cells have a very important function in the defense system of the human body without knowing when they arrive there, when they became mature and how do they work and especially, how long do they live and when they die and how are they replaced afterward. Dermatoglyphics are ridged patterns on the palmar and plantar surfaces of humans (fingerprints, palm prints and foot prints, in glabrous skin). The epidermal ridges may serve as a diagnostic tool for a number of diseases that have a strong hereditary background**.**

Keywords: keratocytes, Langerhans cell, Stratum lucidum, dermatoglyphics.

INTRODUCTION

The human body is one of the most complex biological known organ/tissue which works in a medium with only a relative predictability and sometimes hostile. Today, in 24 hours one can arrive from the North Pole (extremely cold) to the Tropics (extremely hot) and in the next part of the same day from there to South Pole. The adaptation possibility to various conditions suppose the existence of the refined neuro-behavioral rectification mechanisms. The physiologists, biochemists, psychologists, sociologists and lastly philosophers try to know and to understand their signification.

THE BRAIN AND SKIN

The skin and his annexes is the interface between human body and the environment. It is the biggest organ, for a reference adult has a weight of about 3.6 kg and a surface of about 1.5–1.8 m^2. This organ is a multi-structural and multifunctional, being able to protect the subjacent structures from the various mechanical, thermal, chemical, physical (various radiations) or biological (microbes, viruses, fungi and parasites) aggression factors.

Embryologic, the ectoderm layer of the skin and the brain have a common origin. Between these two important structures there is a continuous flux of information whose processing is performed automatically.

The multistructural architecture of the skin made the object of a high number of anatomic and histochemical studies which can be found in various specialty treaties. Here we will refer to the manner in which the two main components (peripheral nerve endings and immune system) act in conjunction, as part of the "*conservation instinct"*, which functions independently of our will and often outside our consciousness. The only

conscious sensations are that which became painful and unpleasant due to their high intensity. Some sensations are unexpected (touching a burning object or pricking a surface with fingers), this triggers a defending reflex reaction (involuntary and sudden retraction of the hand), which is involuntary but conscious in the end.

The skin is a stratified structure including epidermis, dermis and sub-dermis represented by the subcutaneous adipose tissue. In this paper we focus on the epidermis, mentioning that its function depends on the dermal rich vascular network (arterial, venous and lymphatic).

The epidermis is the main component of the *neuro-immune and anti-radiationprotective scout* whose function is ensured on one side by the numerous nervous terminals found in the skin which are able to induce various sensations: touch, pressure, vibration, changes in temperature (toward warm or toward cold), and by other side by the three specialized cells: keratinocytes (physical protection against abrasion), melanocytes (anti-radiation protection) and the Langerhans cells (immune protection).

GENERAL CHARACTERISTICS OF THE SKIN

Epidermis, an ectodermal epithelium is a dynamic structure in which the vast majority of cells are *keratocytes*. These cells have the capacity that along a cycle of about 30 days undergo a differentiation process that results in keratinisation. The original cells (stem-like cells) are in the deepest, basal layer of epidermis, with a specific ondulatory architecture (Fig. 1). They migrate upward slowly and synchronized, forming successively *spinous layer, granulosum stratum, lucidum layer and finally the corneous, exfoliative layer*. These evolution depends of the quality of the extracellular matrix, in which harbor also specific imported cells: melanocytes (from which depends the color of the skin and hair), Langerhans cells (from which depends the immune defense against various pathogens), Merkel cells, monocytes and occasionally other immune cells. There are also other obstacles to avoid: the bulb of hair with erector muscles and sebaceous glands, upper part of sudoral channel of sweat glands located in dermis and free nerve terminals which build up neuro-immune network with Langerhans cells in granulosum layer and neuro-melanocytes network in spinosum layer, where melanosomes are distributed to keratocytes giving their the final color of the skin.

How such a dynamic and apparently non synchronized tissue succeeded in maintenance a strong interconnection trough forces of cohesion ensuring the continuity of the epithelium, is a mystery. The stability of epidermis with its upward directional flow depends of the basal membrane complex which keep together the epidermis to dermis and its upper corneal layer of epidermis. It is well known today that the connection between various layers is ensured by continuous tight-junctions (also called zonula occludens) microfilament bundles adhesion belt, tonofilament bundle desmosomes or hemidesmosomes and gap junctions.

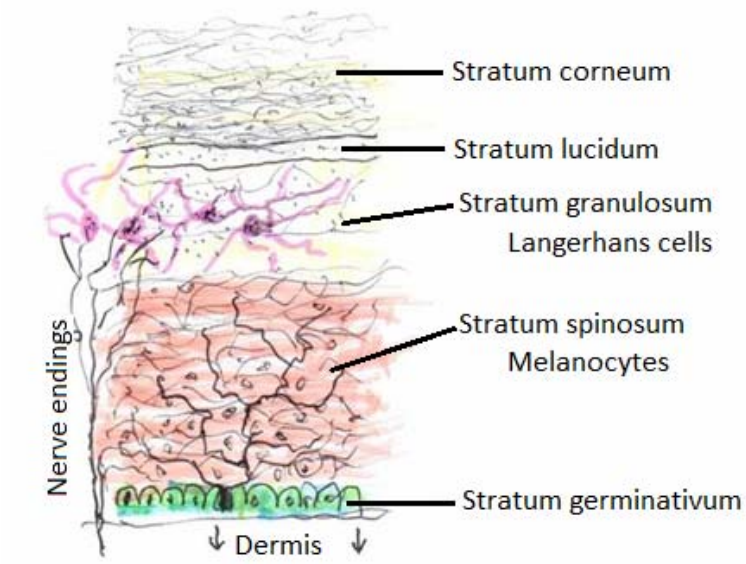

Figure 1. General structure of the skin.

THE COLOR OF THE SKIN

Some fish, reptiles and amphibian have the ability to change the color of their skin for various purposes: thermoregulation, camouflage, or "social communication". To do that, the melanin granules (black and brown) are moving into or out of the pigment-carrying cells, called *melanophores*. These are under the control of a variety of hypothalamic hormones or neurotransmitters, such as melanocyte stimulating hormone (MSH,α or β), melanin concentrating hormone, melatonin and catecholamines. For humans (and other mammals), who have no melanophores, the color of the skin depends on the production of melanin by melanocytes.

POMC (pro-opiomelanocortin) is a gene encoding multiple molecules, most of them hormones (such as ACTH), but also α and β MSH (melanocyte stimulating hormone). The observations that a yeast protease is able to activate a yeast prohormone, shows that this POMC is a big polyprotein molecule (encoded in a single gene) and it can yield different sets of polypeptides that can vary among different tissues.

Melanocytes are the specific cells present in the basal layer of epidermis. Their density ranges between about 550–1200 /mm^{2}and even more. The highest concentrations are in the anal-genital area. The color of the skin does not depend on the number of melanocytes, but rather upon the melanogenetic activity of these cells. These cells change their size and shape as they move upward, replacing cells that are lost during normal cell shading. The black and brown melanin pigment granules that give the color of the skin are transformed by the melanocytes threadlike cytoplasmic-filled extension to the keratinocytes.

The ability of melanocytes to synthetize melanin depends on their capacity to produce tyrosinase, an enzyme which converts the aminoacide tyrosine to a precursor of melanin. The genetic lack of this enzyme results in lack of pigment of the skin, hair and iris of the eye called *albinism.Vitiligo* is due from the patching loss of melanin.

The last product of melanocytes is the *melanosomes,* a vesicle-like structure generated after post-translational processing of tyrosinase which takes place in *endoplasmic reticulum* (ER) and *Golgi apparatus* of melanocytes. This processes are quite similar with those who happen in the pancreatic β-cells, where the main product is not melanosomes, but insulin containing secretory vesicles (SV). In fact, the melanocyte is a true "factory" of melanosomes, just like the β-cell is a "factory" of SV containing mainly insulin[1].

Melanin ensures a physical protection against various pathogenic radiation by scattering them when are excessive. For humans, the melanocytes are present in the inter-follicular epidermis, with one melanocyte corresponding to 5–6 basal keratinocytes.

A special "follicular melanin unit" is associated to the hair cycle. In the proximal hair bulb, the ratio of keratinocytes and melanocytes is 1:1. Melanogenesis and melanin transfer to keratinocytes takes place during their upward migration and maturation. These cells ultimately form the hair shaft. The color of the hair depends on the quantity of melanin transferred to either the keratinocytes or the hair cells. It is interesting to note that hair melanin dose not ensure a protection against UV radiation, because the radiation does not reach the hair follicle. However, the UV radiations has an important role in the transformation of inactive provitamin D in active D vitamin, and by extension with an indirect contribution in hematopoiesis.

LAMTOR (Lysosomal Adaptor and Mitogen activated protein kinase and Mammalian Target of Rapamicine [mTOR] activator/regulator) is a molecular complex that contributes to the signal transduction of the extracellular signaling-regulated kinase (ERK) and the mTOR cascade. Recently, Sparber *et al.*[2] found that late endosomal adaptor molecule p14 (LAMTOR 2) is deep involved in the generation and maintenance of the Langerhans cell homeostasis. These epidermal network of these cells is considered by us to be the main immune guards, regulating immune response and tolerance as a part of the neuroimmune shield of the body through the skin.

The p14 molecule (LAMTOR2) belongs to a LAMTOR family, consisting in p18 (LAMTOR 1), MP1 (LAMTOR3, HPXSP (LAMTOR 4) and C7 or fi5 (LATOR 5).

In a state of art study, Romani, Storzer *et al.*[3] showed successively that:

a. CD11 - specific depletion of p14 results in loss of LCs;
b. Adult CD11c-p14 deleted mice lack epidermal LCs in the skin and draining LNs;
c. Loss of LCs is due to LC-intrinsec depletion or ablation of p14
d. CD11c-specific depletion of p14 led to a decrease of LCs neonatal mice and maturation of langerin$^+$ cells;
e. CD11c specific depletion of p14 leads to increase LC apoptosis;
f. CD11c-specific depletion of p14 inhibits mitosis of LCs;

g. Depletion of p14 impairs mTORC1 and ERK signaling in dendritic cells;
h. CD11c-specific depletion of p14 leads to residual expression of the LAMTOR complex and impaired ERK and mTORC1 signaling.

The most interesting message of this article is considered to be the following: the Langerhans cells in their full structural assembly are different from the classical dendritic cells, which are found also in the skin, without knowing yet their pathway from the bone marrow, where they are supposed to be originated, to the skin. We know that Langerhans cells have a very important function in the defense system of the human body without knowing when they arrive there, when they became mature and how do they work and especially, how long do they live and when they die and how are they replaced afterward.

HISTORY OF LANGERHANS CELLS

The skin Langerhans cells had a longer history. In his paper from 1848, Langerhans (1847–1888), a student of the great pathologist Rudolf Virchow (1821–1902), interpreted these cells to be the intra-epidermal nervous terminals due to their impregnation with gold chloride and also by the cell prolongations suggesting axons or neural dendrites. In 1942, Weddell *et al.*[4] considered these cells due to their morphological feature to be the Schwann cells devoid of melanin. Only in 1960, using the electron microscopy, Bierbeck showed that the Langerhans cells lack the melanin granule, but possess other specific granule which have been named Bierbeck granule and the cells, temporarily named "B cells". Hashimoto in 1968[5] considered Langerhans cells (LCs) as being self-perpetuating intra-epithelial phagocyte system possessing macrophage-like functions. In 1979, Kats[6] established the hematopoietic nature of LCs. Finally, the identification of MHC class I and II expression on their surface, suggested their role as antigen presenting cells (APCs). After 40 years of persistence studies of dendritic cells, Ralph Steinman (1943–2011) showed that these cells are presenting antigen cells as versatile controllers of the immune system and received the Nobel Prize two days after his death, the first time when this Prize has been awarded after his death, contrary to the rules imposed by the founder of this Prize (to give the Prize to a living scientist). For an important achievement, we considered that some rules could be adjusted as this event shows us that in a certain exceptional situation exception could be made.

STRATUM LUCIDUM

The Greek "hydros" means "glass" and the translucent appearance might be due to the glycosaminoglycans, hyaluronic acid. At the physiologic pH, hyaluronate contains alternate residues. Some studies show that several enzymes can be identified in the stratum lucidum level. Their role is possible related with protection against some environmental factors[7]. It is worthy to note that *stratum lucidum* can be considered as a draw line between life (below this layer) and the dyeing cells in upper (cornified) layer, which will detach sequentially after about 20–30 days since their apperance in the basal (germinative) layer.

A possibility to explain the "lucidum layer" of the skin might be due to the structure of the glycosaminoglycans, which can fill a space with a gel-material similar to the one of the extracellular matrix, which holds the cells together. They may form a selectively permeable structure, permitting the diffusion of the oxygen, CO_2 and other small molecules to individual cells. Because the hyaluronic acid is a containing alternating glycosaminoglycans (as hyaluronate residue of D-glycuronic acid and N-acetil glicuronic), as the physiological pH, the about 50.000 repeates of this two basic disaccharide units (molecular weight >1 million), they form a jelly (clear) structure, highly viscous in consistency. Very rare in this thin layer could be seen some flattened structures considered to be a non-functional nucleus. In fact, this lucidum layer represent the limit between the cornified dead cells in the upper / external exfoliative layer and granular layer. Indeed, bellow this stratum in the granular layer there are a lot of nerves terminals which together with the Langerhans cells form a network of neuro-immune structure, as a component of defense instinct sustained mainly by nervous system and immune system. This supposition is sustained by the lower number of the Langerhans cells in both, autoimmune diabetes in children[8] and in diabetic neuropathy in type 2 diabetic patients. Some years ago[7], the lucidum stratum has been interpreted as "*plasmalemal barrier*" containing a number of enzymes and molecules (phosphatase, ATP, DNA and SH thiolic groups) produced by the cells of the granular layer, being well developed not only in the skin, but also in the buccal mucosa (for humans and also for ruminant animal)[7].

A large part of any tissue is made up of an extracellular matrix that is a complex mixture of molecules produced by cell and being a part of and

continuing the cell membrane. Glycose-aminoglycans are linked to protein molecules (proteoglycans). Fibrous proteins (collagen and elastin), but also fibrous adhesion proteins (fibronectin and laminin) ensuring both, elasticity and resistance (fermity) of the skin. There are many numbers of these two molecular classes which can be found in any biochemistry treaty. Collagen is the most common skin forming hard-fibered that seems as the structural framework of the skin, ligaments and many other hard structures.

Reticular layer belongs to dense irregular connective tissue, formed predominantly of collagen fibers and of cells. Such a layer is formed in the dermis of the skin, ensuring its strong resistance.

DERMATOGLYPHICS

Dermatoglyphics are ridged patterns on the palmar and plantar surfaces of humans (fingerprints, palm prints and foot prints, in glabrous skin), which develop approximately between the 13th and 18th weeks of gestation. They have complex genetic backgrounds that are currently not fully explained, but polygenic multifactorial inheritance is the most agreed upon inheritance mechanism[9, 10].

Among the numerous quantitative and qualitative dermatoglyphic traits, commonly assessed variables include: finger patterns (whorl, loop and arch), finger ridge counts (total TRFC and absolute AFRC, palmar angle ('atd', 'adt' and 'dat'), palmar a-b ridge counts and palmar axial triradius position (t, t', t''). An example is described in Fig. 2 and Fig. 3.

The epidermal ridges may serve as a diagnostic tool for a number of diseases that have a strong hereditary background.

The importance of dermatoglyphic studies in clinical medicine is that, during development, ridge formations is affected by maternal environment, gene deviants, and chromosomal aberrations but once formed, they are age, development and environment stable, becoming a reliable indicator of gene damage.

Dermatoglyphic investigation is high cost/effective, requires no hospitalization and can help in anthropologic analysis of various populations, and also for identification of different genetic determined diseases or syndromes, including diabetes mellitus[11, 12, 13].

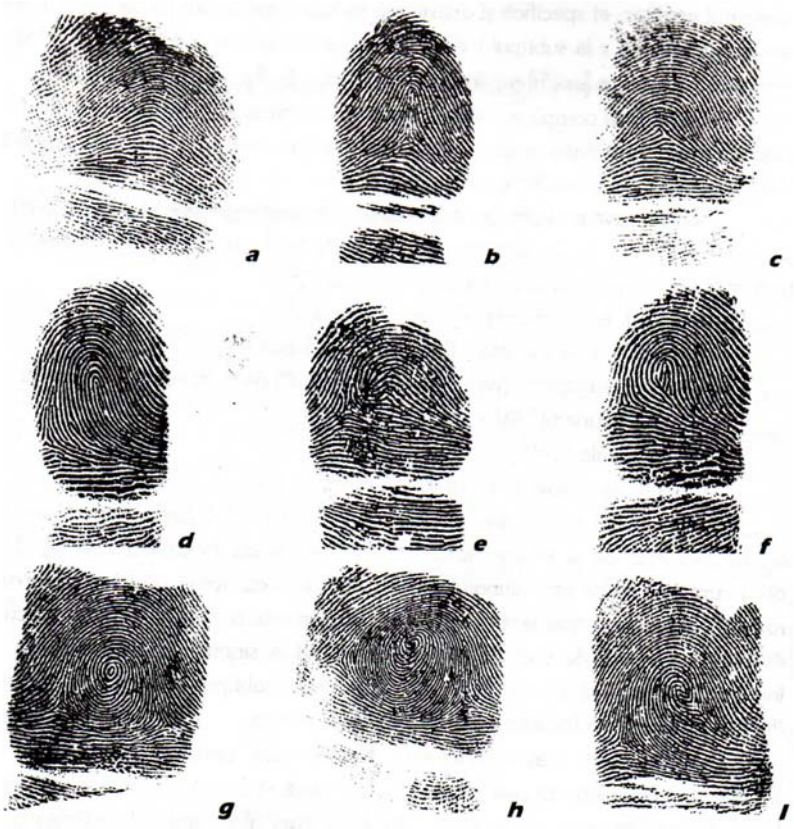

Figure 2. The three basic fingerprint patterns: (a, b, c) arches; (d, e, f) loops; (g, h, i) whorls
(Adapted after Lidia Cotutiu. Dermatoglifele in practica medicala si judiciara, Ed. PsihOmnia, Iasi, 1998).

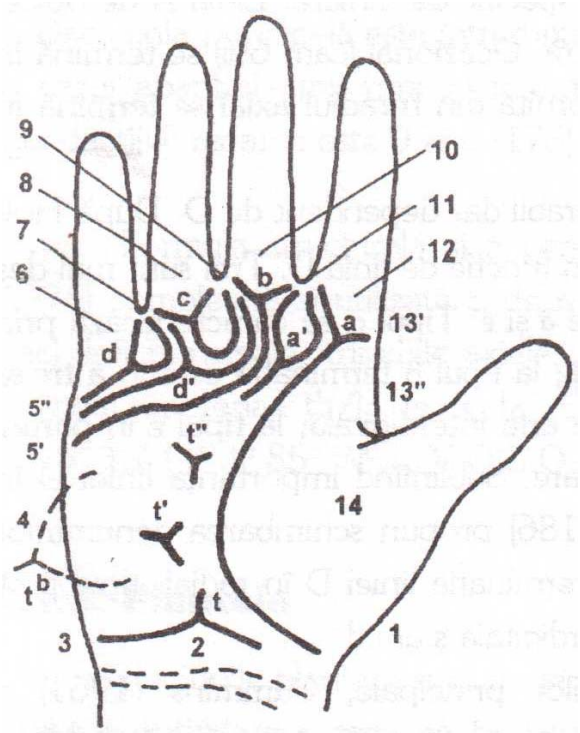

Figure 3. Different palmar triradii (t, t', t''), A, B, C, D lines and the palmar numbering
(Adapted after Lidia Cotutiu. Dermatoglifele in practica medicala si judiciara, Ed. PsihOmnia, Iasi, 1998).

The word "dermatoglyphics" is derived from the Greek word "*Derma*" meaning skin and "*Glyphae*" meaning curve. The dermatoglyphics scientific study has began with the work of Jan Evangelista Purkinje (1787–1869), in 1823[14], but the term as we know it today, was introduced by Harold Cummins (1894–1976). He is universally acknowledged as father of dermatoglyphics. Each dermatoglyphic configuration is unique for each individ. Even for monozygotic twins there are not identical. For that the dermatogryphes are used in criminology investigations.

Cummins proposed that the direction of epidermal ridges was determined by growth factors and contours of volar skin at the time of ridge formation. These epidermal ridges form well-defined patterns that characterize individuals and they have been found useful in the clinical diagnosis of various genetic and acquired disorders with a genetic influence[15].

Also the interest was granted in the past, half of century ago and a sudden interest occur barely in the last period[11, 12, 13]. The interest must be twice: to found some differences between the three main types of diabetes (type 1 diabetes, intermediary diabetes and type 2 diabetes) and to check if some particular dermatoglyphic patterns could predict the diabetes, in agreement with the known genetic determinants.

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