THE ROLE OF LANGERHANS CELLS IN BASAL CELL CARCINOMA AND SKIN MALIGNITY

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Abstract: *The Langerhans cells, dermal dendritic cells, and the group of dendritic cells, in which they are included, have as a common activity, the presentation of antigens in the lymph nodes where they are migrating to. The Langerhans cells stimulate the function of cytotoxic T lymphocytes, while the dendritic dermal cells, the function of the B lymphocytes. Recent studies mention the implication of Langerhans cells and of dermal dendritic cells in the antitumor immunotherapy with promising success in the epicutaneos immunization in the carcinoma of the skin.*

Cuvinte cheie: *celule Langerhans, celule dendritce, imunoterapie, imunizare epicutanată*

Rezumat: *Celulele Langerhans, celule dendritice dermale □i grupul de celule dendritice din care fac parte au ca activitate comună prezentarea de antigeni limfocitelor la nivelul ganglionilor limfatici unde acestea migrează. Celulele Langerhans stimulează func□ia limfocitelor T citotoxice, iar celulele dendritice dermale ale limfocitelor B. Studii recente sustin ideea implicării celulelor Langerhans □i a celulelor dendritice dermale în imunoterapia antitumorală, strategii terapeutice de imunizare epicutanate pentru carcinoamele pielii sunt promi□ tătoare de succes.*

Dendritic cells (DCs) represent an important part of the immune system. They have different subtypes, the best known being the Langerhans cells (LCs) (discovered over 140 years ago and later described by Steinman and Cohn, in 1973) and the proper dendritic cells recently mentioned and studied.(1)

DCs, especially LCs have the function of processing antigenic proteins and of presenting immunogenic peptides at the cell surface linked to the class II major histocompatibility complex molecules (MHC) to CD4+ T cells.(2)

More recently, Stoitzner, demonstrated that LCs take up and process exogenous skin antigens, and afterwards present the antigenic peptides associated with class I MHC molecules to CD8+ T cells.(3)

DCs play an important role in the skin, by stimulating immune responses to exogenous skin pathogens, and also by maintaining the peripheral immune tolerance to self antigens present in the skin.(4) Therefore, LCs and dermal DCs are the main activators of the immune system in the skin. They are functionally different, as the first are generated by CD34+ precursors and stimulate the T cell response, while the second induce antibody secretion by B cells.(5)

LCs migrate in the T cells areas of the lymph nodes and dermal DCs in the lymph nodes follicles that contain B cells.(6)

Lipton (2000) classified the DCs according to their location and functions in the following subtypes: DCs located in peripheral areas (migrant cells); LCs located in the epidermis, cervix, vagina, esophagus, stomach (antigen presenting cells); timic DCs (involved in immune tolerance); interstitial DCs located in parenchimatous organs, except for the brain (cells that take up and present antigens); follicular DCs in the germinative centers of lymph organs (involved in antigen presentation to B cells and their maintenance); dermal dendrocytes (unknown function).(7)

LCs and DCs are generated in the hematogen bone marrow from pluripotent hematopoietic stem cells, having the same progenitor (CD34+ cells) as macrophages.

Recent experimental studies that used stimulating cytokines such as tumor necrosis factor (TNF) alpha of bone marrow progenitors suggest that DCs have a common origin with granulocytes, especially with macrophages, despite their distinct membrane phenotypes, DCs having higher levels of class II MHC molecules and CD1, CD83, p 55, and S100 molecules compared with macrophages.

The proliferative precursors of DCs, via LCs pass from the bone marrow into the circulation similarly to monocytes. Precursors exit the blood torrent into the tissues, were they proliferate and undergo functional differentiation into antigen presenting cells.(8)

LCs' structure presents a large euchromatic nucleus in an eccentric position within the cell, with small nucleols, and a cytoplasm with numerous mitochondria and other organits, such as endoplasmic reticulum, Golgi complex and rare lysosomes. Cytoplasmic characteristic elements are the Birbeck granules (tennis racket shaped pentalaminated structures) and an enzymatic ATP-ase reaction. Also, characteristic for these cells and the entire DCs group are the cytoplasmic extensions that these cells are named after.

LCs and the DCs group have functions in the following processes:

a) Immune processes
b) Autoimmune processes
c) Inflammatory processes
d) Malignant processes

The role of LCs in the immune processes is best known. LCs process antigen and present immunogenic peptides associated with class II MHC molecules at the cell surface to

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naïve CD4+ T cells (Romani et al., 2003) and with class I MHC molecules to CD8+ T cells, which, once activated, produce IFN-gamma, having a cytotoxic action.(9)

The most studied function of LCs and DCs lately is the antitumoral function, these cells being involved in the fight against epidermal premalignant and malignant tumours, among which, we may mention the actinic keratoses, the basal cell and squamous cell carcinomas.

The actinic or senile keratosis is the most frequent premalignant dermatosis and results from prolonged exposure to ultraviolet radiations. It can progress to "in situ" or invasive squamous cell carcinoma.(10)

The squamous cell carcinoma, a relatively common skin tumour, has a progressive course, it is characterized by metastatic spread of tumoral cells, often representing the cause of death. The keratinocyte masses present cellular atipia that ranges from well differentiated cells to anaplastic cells. They pass into the dermis and afterwards into the lymph nodes.(11)

LCs are isolated, irregularly dispersed in the premalignant epidermal tumours, located in the basal and suprabasal layers, while in the squamous cell carcinoma, they are concentrated at the periphery of the tumour.

In both diseases (i.e. actinic keratosis and squamous cell carcinoma), the number of LCs-DCs is reduced, indicating a deficiency of skin immunity.(12)

The basal cell carcinoma is a frequent malignant skin tumour, whose incidence increased in the last few decades, that generally appears on photoexposed skin areas and in the patients with leucoderma. It arises in the epidermal basal layer, therefore the formation and evolution of the tumour influence the histophisiological and chemical polimorfism of this type of carcinoma. The histopathologic aspects of the tumour play an important role in establishing the prognosis, indicating the aggressiveness of the disease and the potential of metastatic spread. Thus, the least aggressive nodular form is characterized by an increased number of LCs in the epidermis adjacent to the tumor and of DCs in the dermis subjacent to the tumour. In basal cell carcinomas, many LCs have round or deformed shapes. Dendrites are shorter or completely absent. Moreover, important variations of ATP-ase activity can be noticed. Due to these changes, some authors introduced the term "dendritic index", measured by an image analyzer.

The structural changes of LCs in the basal cell carcinoma suggest the idea that this tumour can develop in areas in which the morphology and/or activity of the immune cells is altered. Such histological alterations could sometimes be the effect of malignant cells over the morphology of LCs.

The conjunctive tissue adjacent to the basal cell carcinoma seems to be arranged in parallel bands around the tumour and discretely infiltrated with lymphocytes. (13)

The increase in LCs numbers in the peritumoral epidermis in the case of nodular basal cell carcinoma, a type of basal cell carcinoma with low aggressiveness, indicate an increased immunologic resistance that limits the development of the tumour and the metastatic spread of the tumoral cells.

The behavior of LCs and DCs in basal cell carcinomas and also in squamous cell carcinomas reflect the participation of these cells, along with a series of cytokines, IFN, TNF (released by these cells) in the immune response that takes place in the skin, stimulating the immunologic function of CD4+ T cells and CD8+ B cells.(14)

The skin immunologic system is made up of LCs (the main immunologic factors) and other cells (keratinocytes, lymphocytes, macrophages and, perhaps, granulocytes), as well as of chemical substances, such as immunoglobulines, cytokines, and immune complexes.

Bos and Kapsenberg (1986) suggested the name of skin immune system (SIS) for the immunologic complex of cells + chemical substances released by them. McArdle et al., in the same year of 1986, asserted that the skin oncogenesis is more specific in the case of basal cell carcinoma regarding the density, morphology, and the pathologic response compared with other premalignant or malignant epidermal tumours, such as squamous cell carcinoma, actinic keratosis and Bowen disease.(15)

Apart from these data on the role of LCs and dermal DCs, recent observations state the existence of another cell subtype in the DCs group, specifically a smaller cellular population located in the superior dermis, named dermal langerin DCs. This cell subtype express the marker of LC langerin CD207, a C-type lecitin-receptor, through which these cells take part in the skin immune responses, but have a functional independence.(16)

In vitro, and less often, in vivo studies showed that LCs are equipped with stimulatory mechanisms for cytotoxic T cells. The efficiency of these mechanisms in destroying the malignant cells amplified the investigations regarding the immunization and immune therapy strategies in malignancies.

The LCs and the subset of DCs induce antitumoral responses. The faster these cells are able to migrate from the epidermis/dermis towards peripheral lymphoid organs, the more powerful these responses are. LCs possesses the greatest migration speed, whereas dermal DCs, except langerin+ cells situated in the profound dermis migrate at a much lower speed. Due to the presence of langerin marker at the surface of these cells, which is characteristic to LCs, the two DC types are more potent in inducing the antitumoral immune response.

The immunization strategies through skin-lymph nodes developed lately on the bases of new experimental and practical knowledge on the involvement of DCs in the treatment of malignant tumours.

The aim of the treatment known as epicutaneous immunization is the activation of T lymphocytes and arming them with the power to start the antitumoral attack. Normally, the tumoral antigens are self antigens to which the immune system is tolerant. The immunotherapeutic procedures aim at blocking this tolerance and attacking the tumoral cells.

The increase in numeric density of LCs at the level of the tumour indicates that the malignant cells produce a factor or multiple factors that stimulate the migration of LCs precursors into the epidermis, the increase of mitoses in immunogenic cells and the decrease of their migration in lymph nodes.(17)

The alternatives for epicutaneous immunization are either the use of antigen protein or peptide antigens conjugated with target antibodies. The objective is to target the tumoral antigen towards the patient's DCs and to deposit it directly on LCs in order to induce CD4+ and CD8+ T cell responses in lymph nodes.(18)

The peptide or protein antigens are introduced either directly on injured skin, with a broken barrier induced by repeated applications of adhesive bands, or on intact skin (19) in combination with adjuvants such as choleric toxin or ligands that contain imiquimod (Aldara) in the form of creams.(20)

The existing data on these procedures indicate their therapeutic efficiency in stopping malignant tumour growth, especially that of epidermal carcinomas.

An intense stimulating response is obtained by conjugating the antigen with antibodies specifically attached to the surface of DCs, the target conjugates belonging to the family of type C lectin receptors.

The antigen-antibody conjugates are usually administered by intradermic injections.

Nevertheless, these strategies represent the first promising steps in epicutaneous immunization, in which DCs, in particular LCs, are called to exert antitumoral actions. It seems that they can be successfully used for the treatment of malignant skin tumours.

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