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Elucidating The Role Of Langerhans Cell

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Abstract
Apart from the keratinocytes that make up the bulk of the epithelium in the oral mucosa is a subpopulation of cells called non-keratinocytes among which is the Langerhans cell (LC) discovered in 1868. LCs were found to be antigen presenting cells that function as the most peripheral outpost of the immune system. A more complex role for the cell has been elucidated in the last few years which could help us understand their role in early carcinogenesis.

Key Words
Langerhans cell, non-keratinocyte, langerin

Introduction

The basic histology of the oral mucosa consists of an epithelium underlying which is the connective tissue. Apart from the cells that collectively make up the epithelium referred to as keratinocytes, are a resident subpopulation of permanent or transient cells, heterozygous in their origin, structure and function called non-keratinocytes which include melanocytes, Merkels cells, Langerhans cells and lymphocytes.

The article traces the story of the Langerhans cell (LC) from its humble beginnings as an obscure epithelial cell to its current status as a distinctive member of oral mucosal immunity.

Origin

It was Paul Langerhans[1] who first noted a population of dendritic cells in human epidermis and named it the Langerhans cell. But further studies on the cell remained dormant for almost a century until in 1961 Birbeck et al.[2] using transmission electron microscopy observed a microtubular structure in the cytoplasm unique to the LC and named it the Birbeck granule.

The lack of desmosomal junctions and tonofilaments along with the presence of lysosomal granules confirmed its origin distinct from keratinocytes while the presence of an abundance of hydrolytic enzymes supported the view that the LC could be a macrophage. Currently we know that keratinocytes elaborate cytokines, growth factors, and hormones that influence LC phenotype and function.[3]

Immediately following the implication that they could be related to the monocyte series,[4] Silberberg and her associates[5] spotted the specific apposition of mononuclear cells to LCs in animals sensitized to contact allergens and found these cells not only in the lymphatic vessels but also in the lymph node, reiterating their role in the immune process - as part of the reticulo-epithelial system.

Today, we know for certain that LCs are dendritic, antigen presenting cells of bone marrow origin residing within the stratified squamous epithelium of skin, oral mucosa, upper gastrointestinal and female genital tract. In the epithelium LCs take up and process antigenic moieties in situ and upon receiving danger signals start to mature phenotypically and functionally and migrate to the T-cell zones of regional lymph nodes. Then in the lymph node, they come into prolonged contact with antigen-specific, naive resting T cells leading to their activation.

Important to note is that under homeostatic, non-dangerous conditions, LCs would be exposed to innocuous substances but this encounter would neither entice them to migrate nor induce immunological maturation.

Distribution

They populate the supra-basal layers of the epithelium by about the seventh week of intrauterine life and in normal conditions make up 2-8% of the epithelial cell population with considerable variation in their numbers[6] **(see Table 1)** from site to site within the oral mucosa.

Table 1

Site	Cells/mm length of epithelium	P value
Dorsum of Tongue	28.3	0.05
Buccal Mucosa	25.2	0.05
Lip	22.4	-
Lateral Border of Tongue	17.6	<0.05
Hard Palate	17.6	<0.05
Floor of the Mouth	16.7	<0.05

The lowest LC counts are in the floor of the mouth. However, the only site where Birbeck-granules-containing LCs could not be demonstrated was the junctional epithelium though they were present in sulcular epithelium.[7]

LC Kinetics

Although it is widely believed that dendritic leukocytes are end cells and therefore incapable of cell division, mitotic figures have been demonstrated in epidermal LC[8] as well as after labelling with 3H-Thymidine injected intradermally.[9] Flow cytometric analysis[10] of the cell cycle performed on OKT6+ LCs also demonstrated the cell in various phases of the cell cycle suggesting that the majority of LCs are able to proliferate in situ in normal

human epidermis.

During wound healing LCs migrated with the epidermal cells over the wound during the process of re-epithelialization[11] suggesting that they respond to injury by both migration and increased mitosis. Much later Murphy et al.[12] observed the sequential depletion and subsequent repopulation of LCs in the skin of acute leukemic patients after allogenic bone marrow transplant.

During the repopulation phase clusters of T6+ cells containing Birbeck granule-like structures first accumulated around superficial dermal vessels leading researchers to agree that : (i) LCs were capable of division and thus self-perpetuating (ii) they can be induced to proliferate. Their proliferation and turnover rate was found to be slower than keratinocytes.

New developments in LC research in the last decade[13] have markedly changed the perception about this cell beginning with the discovery of a molecule called "langerin" expressed specifically on LC surface and also a major constituent of Birbeck granules.[14]

In 2007 a distinct type of dendritic cell was detected in murine dermis.[15],[16] Until then, whatever langerin+ cells was found in the dermis was considered to be LCs that just happened to be in transit from the epidermis through the dermis toward lymph nodes. But experts believe these represent another population of langerin+ dendritic cells in the dermis.

LCs role in early neoplasia

Until 1995apart from a brief comment on LC numbers correlating positively with lymphocytes in the stroma of pulmonary cancers no one had raised its immunological role in oral malignancy.[17] Research hasn't provided any conclusive evidence so far on their positive or negative role in neoplasia, yet throws some interesting perspectives.

Shklar et al.[18] observed an increase in the LCs in leukoplakic lesions associated with smokeless tobacco and attributed it to an attempt at epithelial protection. Later researchers[19] also suggested that it could be an adaptive response of the peripheral immune system to the increase in functional demand due to the penetration of antigens - in this case nicotine and its by-products, through the mucosa.

Therefore, a role for LC could be possible in squamous cell carcinoma only if they recognized early antigenic changes on the cell membrane and instigated early destruction of a neighboring keratinocyte undergoing malignant change. Evidence came from Cruchley et al.[20] who demonstrated an increase in numbers of CD1a+ LC in smokers, at sites often affected by carcinoma viz. lip and lateral border of the tongue. Similarly, density of HLA DR+ LC in lateral border of tongue was increased in smokers.

Similar to their behaviour in different stages of gingivitis where they migrate into the gingival epithelium during early gingivitis [21],[22] and migrating out as the gingivitis becomes more chronic say after 21 days[23] it is possible they may play an active role in early pre-malignancy. It was suggested that their powerful antigen presenting capacity could be used to overcome tumor tolerance and induce anti-tumor immunity when loaded with tumor antigens.

Conclusion

The Langerhans cell has generated considerable interest ever since its accidental discovery almost a century and half ago. A more complex role for the cell has been elucidated in the last few years which could help us understand their role in early carcinogenesis. The spate of research on this cell - the 'most peripheral outpost of the immune system' - has contributed immensely to our understanding of how the oral mucosa responds to antigens, be it microbial or tumor.

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