REVIEW

Langerhans cells in health and oral diseases - A review

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Abstract

The oral mucosa is constantly exposed to pathogens and harmless foreign antigens like bacteria. It shows the presence of Langerhans' cells (LCs) which are the important antigenpresenting cells. LCs are responsible for detecting the antigens, recruiting Tcells, and thereby initiating the immune response. Main hallmark of LCs is the presence of Birbeck's granules. LCs originate prenatally in the epidermis by yolk sac macrophages. While, oral mucosal LCs are derived post-natally in the bone marrow by pre-dendritic cells. Main markers of LCs include- CD1a, S-100, Langerin with Langerin being the most specific marker. All the major lesions of oral cavity are influenced mainly by CD1a. Oral mucosal LCs are capable of engaging and internalizing a wide variety of pathogens. Hence they have been found in various diseases affecting oral cavity like oral candidiasis, oral lichen planus, periodontal diseases, gingivitis, median rhomboid glossitis, various periapical inflammatory conditions/ cysts, various premalignant lesions and conditions, and oral squamous cell carcinoma.

This literature review aims to comprehensively analyze existing literature on LC, focusing on its structure, origin, classification, and its influence on oral mucosal diseases.

Scientific databases were searched for the literature and relevant articles were selected for the review. Articles published in electronic databases like PubMed, Scopus, Science Direct and Research gate were selected and reviewed. Eligible study materials were original case reports, review articles in English related to immunohistochemistry, LCs in different oral mucosal diseases, and pathophysiology of LCs.

LCs are a critical component of primary immune response, capable of capturing protein antigens in the oral epithelium and presenting them to specific T cells in the context of MHC II molecules. Their density and distribution in oral pathologic conditions may reflect different immunological mechanisms involved in the pathogenesis of these diseases.

Keywords: Langerhans' cells, Birbeck granules, Epidermis, Oral mucosa, Yolk sac macrophages, CD1a, S-100, Langerin

Introduction

Immune response to any antigen is brought about by three types of cells- "Antigen presenting cells, T cells and B cells.

Langerhans cells (LCs) are the antigen presenting cells present in the epithelia of the skin and mucosa. They are myeloid cells residing in the epidermis of skin, and epithelium of corneal, buccal, gingival and genital mucosa. They were initially considered as neuritic in origin, but later of bone marrow origin. They express high levels of MHC II proteins. They act as sentinels in the early detection of foreign antigens. These cells were discovered by Paul Langerhans in 1868, but later named as 'Langerhans Cells' by Sigmund Merkel (1875). Because of their efficient antigen trapping properties and their capacity to generate strong co-stimulatory signals, LCs play a key role in the primary immune response. They are also able to secrete inflammatory chemokines that contribute to the recruitment of effectors cells such as macrophages, granulocytes, and additional dendritic cells to early inflammatory lesions. Now, LCs are re-classified as macrophages.

The immune system plays a noticeable role in wide varieties of oral pathological conditions- such as gingivitis, periodontitis, gingival enlargements, oral malignancy and premalignancy, mucosal infections, periapical inflammatory

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conditions ect. This presentation explains the distribution of LCs cells in normal oral mucosa and in different pathological conditions of the oral cavity.

Microstructure of LCs:

LCs in situ possess 5-9 dendritic processes, extending out in horizontal plane(Fig 1). Desmosomes and tonofilaments are generally absent. Nuclei appear as clefts, and many cell organelles like lysosomes, centrioles, golgi vesicles, small amount of RER, and mitochondria are present. The most distinctive feature of LCs is the presence of Birbeck's granules, which are abundant in golgi complex. Birbeck granules are 100 nm to 1μ in size. They exhibit disk-shaped structures with central linear density, giving it zipper-like pattern or periodic striations. They show a tennis-racket like appearance, when terminal vesicle is present. These granules were described first by Birbeck and were referred to as "Langerhans cell granules". The function of Birbeck granules is unknown and has been associated to antigen-trapping and antigen-presenting function. (Table 1)

Origin of LCs:

The embryonic origin (prenatal) of LCs is from the erythromyeloid progenitors present in the yolk sac. They also differentiate from hematopoietic stem cells, which migrate through the fetal liver. The first myeloid cells, called yolk sac macrophages, at around 16-18 days of human gestation, are generated from EMPs. These macrophages are c-myb independent cells. EMPs, due to their restricted potential, can't produce HSC (hematopoietic stem cells, which are the produced in the aorta-gonad-mesonephros (AGM) region at around 32nd day in humans. They migrate first to the fetal liver and then to the bone marrow. Late EMPs migrate through fetal liver and modify themselves as c-myb and flt3 dependent liver monocytes which together with HSC pass to the bone marrow. Minor contribution in LC formation is by the third component i.e., hematopoietic stem cells.(Fig 2 and Fig 3)

Postnatally, the homeostasis of LCs is maintained by transforming growth factor β1. It plays a key role in the differentiation of LCs from CD34+ hematopoietic progenitor stem cells recruited from bone marrow. Bone morphogenic protein 7, along with the ALK3 receptor and phosphorylation of SMAD1/5/8, also maintains the homeostasis of LCs. In the epidermis, LCs are derived from CSF-1 precursors, which also originate from the bone marrow. The oral mucosa and intestines are exposed to large amounts of antigens, whereas in the skin not such a diverse microbiota is harbored. Hence the quantity of antigenic exposure is also proportionately low in epidermal LCs. This difference in antigenic load demands different immune responses.

In case of oral mucosa LCs, they are derive post-natally from bone marrow derived pre-dendritic cells and monocytes. Also they are continuously replenished throughout the life. Oral mucosal Langerhans cell comprise of three different subsets: CD103+, CD11b+LC2 and moLC. The regulation of oral mucosal LCs is by microbiota. Origin of three different subsets is by different cells- CD103+ by Pre DC1, CD11b+LC2 is by Pre-DC2 and moLC is by monocytes. (Fig 3)

Langerhans Cells in Normal Oral Mucosa:

LCs are found in all oral mucosal surfaces except the junctional epithelium and the base of the tastebuds. Their density is more in non- keratinized than in keratinized mucosa. LCs originate in bone marrow, and have antigen presenting activity by the receptor for MHC class II antigens and various complements.

In normal oral mucosa, LCs are present above the basal layers of oral epithelium. They lack desmosomal attachments to surrounding cells and therefore appear as a clear cell in histologic sections. Ultrastructurally, they are characterized by small rod or flask shaped granules known as 'Birbeck granules.'

Langerhans Cells in Epidermis:

LCs are critical component of skin immunity. Here also they play a role in T-cell responses directed against different variety of antigens, not only peptide antigens but also lipid antigens. Recently, an MHC independent pathway of lipid antigen presentation has been identified and is mediated by molecules of the CD1 family- CD1a, CD1b, CD1c and CD1d.

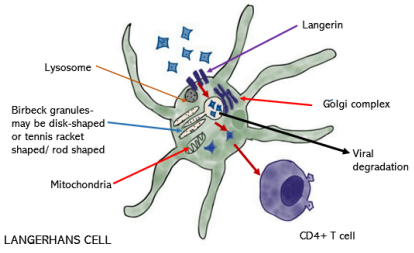

Fig 1: Microstructure of Langerhans cell showing all organelles

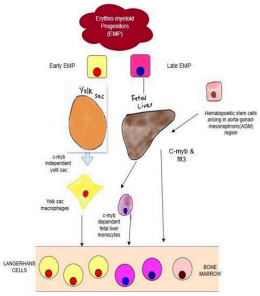

Fig 2: Prenatal origin of Langerhans' cells

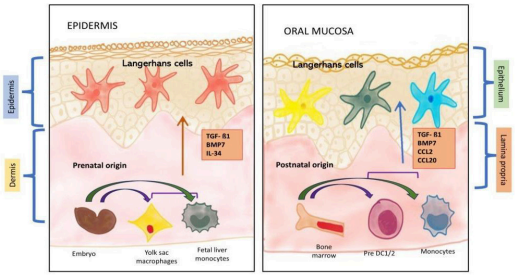

Fig 3: Hemostasis and differentiation of LC in skin (left) and oral mucosa (right). In skin, LC promote inflammatory immune responses. They originate prenatally from yolk sac macrophages and fetal liver monocytes. Oral mucosal LC comprises of three subsets: CD103+(yellow), CD11b+LC2(green) and moLC(blue). They arise post-natally from bone marrow derived monocytes and dendritic cells.

Because LCs are professional antigen- presenting cells and express CD1a molecules prominently, it is considered that they might play a role in T cell responses directed against various types of antigens.

There are few differences between LCs in epidermis and in oral mucosa (Table 2)

Functional Properties of Langerhans Cells:

Antigen Presentation: LCs function as antigen-presenting cells (APCs). When they encounter pathogens, they engulf them and break them down into protein fragments. These fragments are then displayed on the cell surface, where they can stimulate other immune cells, particularly naïve T cells, to mount an immune response. They primarily present exogenous antigen-derived peptides via MHC proteins to CD4+ helper cells. They also generate MHC class I restricted cytotoxic CD8+ T-cell responses.

Migration to Lymph Nodes: After encountering a pathogen, Langerhans cells migrate to the lymph nodes. There, they present the antigens to naïve T cells, activating the adaptive immune response.

Immune Suppression: Langerhans cells also play a role in immune suppression. In the presence of non-pathogenic bacteria, they coordinate immune tolerance, preventing an unnecessary immune response.

Production of m-RNA: LCs produce spontaneous mRNA encoding IL-α, IL-β, IL-6, IL-7, IL-12, IL-15, IL-18, TNF-α, TGF-β, M-CSF, and GM-CSF. They are also responsible for production of prostaglandin PGD2.

Molecular Markers for LCs:

S-100 protein: Originally isolated from nerve cells of the brain, derives its name from its 100% solubility in ammonium sulphate. Once thought to be unique to the central nervous system, it has subsequently been identified in numerous other cells outside the nervous system, including LCs

CD1 family: CD1 a, b, c and d are expressed by the LCs. Because of their professional antigen presenting property, they prominently express CD 1a molecule.

Langerin (CD207): It is a type II, Ca+2 dependent, lectin displaying, mannose-binding, specific molecule, exclusively

Table 1: Identification and expression of Langerhans' cells (structure)

Identification of LCs	Expression
Histology	Clear cells under microscope
Histochemistry	Dendritic cells with 5-9 dendritic processes
Ultrastructure	Intracytoplasmic Birbeck granules- morphological hallmark
Immunohistochemistry	CD1, CD14, CD23, CD45, CD69, CD74, CD83, HLAA/B/C, HLADR/DP/DQ, S100, MIP1α. Four CD1 genes have been cloned and they are designated as CD1 a, b, c, d. LCs are highly positive for CD1a and CD1c. CD1a is the most specific marker

Table 2: Comparative features of Epidermal Langerhans cells and Oral mucosal Langerhans' cells

Location	Epidermis	Oral mucosa		
Development	Prenatal	Post-natal		
Origin	Yolk sac macrophages, fetal liver monocytes	Bone marrow- Pre DC1/2		
Subtypes		Pre-DC1	Pre DC-2	Monocytes
General features	Radioresistant	Radiosensitive		
	Self-renewal	Replenishment via circulation		
	Immature	Immature, and activated		
General Phenotype	CD11c+, MNCII+, CD24+, CD11b+, Langerin (CD207)	CD11c+, MNCII+, CD24+, EpCam+ (CD326), E-cadherin, Langerin+ (CD207)		
Subset-specific phenotype	F4/80+, EpCam+(CD326), E-cadherin	$CD11b^{low}$, CD103+	CD11b+	CD11b+, CD64+, CX_3CR1+
Transcription factors	Id2, IRF2, IRF8, RunX3	Id2, IRF8, FLT3 (partially)		---
Signaling cytokines	TGF-β1 (ALK5), BMP7(ALK3)	TGF-β1 (ALK5), BMP7(ALK3)		
Chemokines receptors	----	CCL2 (CCR2), CCL20 (CCR6)		

expressed by Langerhans cells. It is a potent inducer of membrane superimposition and zippering leading to the formation of Birbeck granules. Induction of these granules is a consequence of the antigen capture function of Langerin, allowing routing into these organelles and providing access to a nonclassical antigen processing pathway.

Sylvie Seguier, Agnes Bodineau, Gaston Godeau, Bernard Pellat and Nicole Brousse (2003) conducted a comparative and quantitative immunohistochemical study on Langerin +ve Vs CD1a +ve LCs in human gingival tissue, and concluded that Langerin is the most specific marker for the study of LCs.

LANGERHANS CELLS IN VARIOUS ORAL DISEASES:

LCs in Chronic Gingivitis:

The LCs in gingival epithelium respond to the buildup of plaque. They migrate into the site during acute gingivitis, and out of site during chronic gingivitis. As plaque accumulates, no. of CD1+a LCs increase, as compared in normal healthy gingiva. The number and distribution of LCs in the epithelia of chronically inflamed gingiva is always variable. This may be because of the result of the different bacterial antigens elucidating different responses or alternatively, reflect different responses to similar plaque antigens penetrating the surfaces of oral epithelium.

LCs in Chronic Periodontitis:

The number of LCs in the oral epithelium and interstitial dendritic cells in the lamina propria is increased in gingivitis compared to periodontitis, which may contribute to the different pattern of host response in these diseases. LCs play an important role in presentation of antigen during all phases of periodontal diseases, and represent key pathogens in pathogenesis of the disease. There is increase in no. of S100+ LCs in gingival epithelium and connective tissue of periodontitis specimen. There is functional alteration of Langerhans cells in periodontal disease.

Table 3: Oral diseases and molecular markers

Oral diseases	Molecular marker of LCs
Gingivitis	CD1a
Periodontitis	S-100
Drug induced gingival enlargement	CD1a
Chronic hyperplastic Candidiasis	CD1a
Lichen planus	CD1a
CEOT	CD1a
OSCC	Cd1a and S-100
Langerhans cell histiocytosis	Langerin- highly sensitive and specific marker CD1a, S-100 – Confirmatory marker

LCs in Drug Induced Gingival Enlargements:

In the drug-induced gingival enlargements, such as those caused by anticonvulsants (e.g., phenytoin), immunosuppressants (e.g., cyclosporine), and calcium channel blockers (e.g., nifedipine), LCs can be involved in the inflammatory response. The exact mechanism by which the drugs cause gingival enlargement is unknown, but it is believed that the host response in plaque antigens alter the number and functions of Langerhans' cells in the gingival tissues, both epithelium and the connective tissue. This alteration can contribute to the inflammatory processes that lead to gingival enlargement. Density of CD1a labeled LCs is significantly lower than in normal gingiva. There is no specific explanation for how the antihypertensives, immunosuppressants and antiseizure drugs reduce their density.

LCs in Oral Candidiasis:

In chronic hyperplastic candidiasis, the LCs are distributed throughout the epithelium with variable quantity. There may be a close association between their number in the epithelium and the intensity of candidal yeasts and hyphae. A possible CD1a LCs-mast cell interaction has also been described in chronic hyperplastic candidiasis. They are present in all layers of the epithelium, at the basement membrane and as mononuclear round cells in the lamina propria.

LCs in Oral Lichen Planus:

Lichen planus is a common dermatological disease related with cell mediated immunity. For such immunity to develop, T-cells must be sensitized by information from antigen presenting cells, such as LCs. Oral Lichen planus is an auto-immune disease caused by cytotoxic CD8+ T cells. LCs are immunologically active and play a role in disease progression. They are the target cells involved in primary immune response. Oral Lichen Planus lesions show an increase in expression of CD1a- like antigens. This increase demonstrates an increased capacity of Langerhans' cells to detect and present antigens to epithelial T-lymphocytes. Considerably more LCs are seen in buccal mucosa with OLP than in normal buccal mucosa. High density of LCs in buccal mucosa compared to the other oral mucosal sites may be one of the causes for the predilection of OLP for the buccal mucosa.

LCs in Periapical Inflammatory Lesions:

LCs can be found intra-epithelially in all the periapical lesions. CDla-positive LCs in a few periapical granulomas with well differentiated epithelia have been reported. The LCs distribution appears to be associated with the degree of differentiation of the epithelia. LCs density is associated with the severity of infiltration of chronic inflammatory cells. LCs are present in the basal and suprabasal layers in the cystic epithelium and may be concentrated in distinct regions of the epithelium. In granulomas, LCs are only observed in granulation tissue, showing discrete immunostaining density. In Periapical cysts, LCs exhibit both a round and a dendritic shape in all epithelial layers. LCs in radicular granulomas are associated with local defense reactions as stronger antigen-presenting cells as compared with macrophages.

LCs in Odontogenic Neoplasms:

There are some cases reported in the literature of some odontogenic tumors containing LCs. LCs present in Calcifying epithelial odontogenic tumour were +ve for CD1a, CD68, HLA-DR and S-100. The pathologic significance regarding the presence of LCs in CEOT is not yet clear. While it is suggested that both the oral epithelium and LCs originate from the Oral Ectoderm. They may undergo phagocytosis and present the processed antigens to T lymphocytes in the regional lymph nodes. There are chances that LCs may be present in other odontogenic tumours also. LCs can be detected in the nests or strands of odontogenic epithelia of Odontogenic fibromas.

LCs in Potentially Malignant Disorders:

Langerhans cells (LCs) play a significant role in the immune response within oral premalignant lesions and conditions. Localized absence of epithelial LCs has been shown to affect systemic immune responses, allow microbial colonization, and play a possible role in carcinogenesis. LCs help in detecting and presenting antigens from potentially malignant cells to T-cells, initiating an immune response to eliminate these malignant cells. LCs regulate the inflammatory conditions within the premalignant lesions, which in turn, contribute in the progression or regression of these lesions. Any kind of alteration in the number or function of these cells act as a biomarker for the risk of malignant transformation. Studies on density of LCs in smokeless tobacco associated oral mucosal lesions describe that the altered oral mucosa due to tobacco habit contain fewer LCs than the normal oral mucosa, regardless of increased epithelial thickness or changes in keratinization.

LCs in Oral Carcinomas:

In OSCC tumor-bearing sites, LCs are antigen-presenting cells that interact with T-cells by MHC class I restricted proteins. This leads to the generation of tumor specific effector T-cells capable of recognizing and eliminating tumor cells.

The density of LCs in verrucous carcinomas may be significantly higher than those in intraepithelial tissues of adjacent normal mucosa. CD1a+ and S-100+ are increased in number in oral carcinomas. In well-differentiated variant, it is localized to usual suprabasal layer, while in anaplastic epithelium, they are scattered randomly. A pronounced decrease of LCs in poorly differentiated OSCC, as compared to their well-differentiated variant has been reported. The density and distribution of LCs in oral carcinomas are prognostically important as greater density of LCs suggest better immune response and in turn better prognosis. Predisposing factors impact LC presence. Factors like tobacco and alcohol consumption, cause an increase in LCs, while smokeless tobacco cause decrease in number of LCs, probably due to inhibitory effect of tobacco absorption.

LCs in Human immunodeficiency virus infection:

The target cells for HIV infection are the LCs. They are the first cells to get infected. The infected cells migrate to the regional lymph nodes to present the antigens to T lymphocytes. They disseminate the infection among T-cells. They influence the pathogenesis and protective mechanisms of HIV-1 at several levels. The first action of the HIV-1 antigen is to infect immature dendritic cells. Second, different types of dendritic cells sequester and transmit infectious HIV-1, leading to productive infection in T-cells. C-type lectin, DC-SIGN/CD209 plays a pivotal role in the transmission of the virus to T-cells. Third, LCs are efficient antigen-presenting cells for HIV-1. Then CD4+ and CD8+ T-cells are stimulated by the infected LCs. On the other hand, dendritic cells and MHC Class I act by exogenous pathway; they inhibit the replication of viral antigens. Therefore, the interaction of HIV-1 with dendritic cells is complex, and how these viruses disrupt immune function and elicit immune responses is difficult to estimate. However, it is determined that LCs act as vectors for HIV-1

CD1a and Antitumor Immune Response:

The density of CD1a +ve dendritic cells within human tumours has been associated with survival, by involving in first steps of immune response in number of malignancies. Moreover, the presences of a high number of DCs in the tumoral or peritumoral area, as well as in the draining lymph nodes, are suggestive of a better prognosis. CD1a plays a role in presenting tumour-associated lipid antigens to T cells. This helps activate the T cells, which can then target and destroy cancer cells. The presence and activity of CD1a can influence the ef-

Table 4: Role of Langerhans cells in oral mucosal diseases and effect on density of LCs

Diseases	Role of Langerhans cells	Density of LCs
Periodontitis	Functionally altered cell	Less than normal
Drug induced gingival enlargement	Inflammatory mediators	Less than normal
Chronic hyperplastic Candidiasis	Phagocytosis	Depends on the intensity of candidal and yeast infestations
Oral Lichen planus	CD1a like antigen	Increased
Periapical lesions	Inflammatory mediator	Depends on the intensity of inflammation
Odontogenic tumors	Phagocytosis	
Premalignant lesions and conditions	Immune mediator cells	Less than normal
Oral Carcinomas	Immune mediator cells	Increased in well-differentiated, decreased in poorly differentiated lesions
Langerhans cell histiocytosis	Tumor cells	

fectiveness of the immune response against tumours, making it a significant focus in cancer immunology research.

Langerhans Cells Histiocytosis

Langerhans cell histiocytosis is a rare disease marked by proliferation of Langerhans-type cells that share immunophenotypic and ultrastructural similarities with antigen-presenting LCs of mucosal sites and skin. It represents a type of histiocytosis with unclear etiology and incompletely recognized pathogenesis. Clinically, it shows broad spectrum of manifestations. Most of the cases concerns children, usually around 1 to 15 years of age. The lesions of LCH are composed of cells that are 12 to 15 μm in diameter. They are round to oval in shape, with or without dendritic processes, with abundant eosinophilic cytoplasm. The nucleus shows irregular folds and grooves, fine chromatin and indistinct nuclei. Using immunohistochemical methods, specific markers can be detected in cells, including CD1a, Langerin and S-100 protein. Expression of CD68 is variable. CD1a, CD207, CD68, and S100 are the confirmatory markers for LCH whereas Langerin is a highly sensitive and specific marker. The final confirmation of LCH involves the detection of Birbeck granules, appearing as elongated, zipperlike cytoplasmic structures measuring 200 to 400 nm x 33 nm under the electron microscope.

Other Mucosal Diseases:

Median Rhomboid Glossitis:

As compared to normal tongue, median rhomboid glossitis shows huge reduction in LCs. This contribute to the development of tolerance to antigens, and promote chronicity of the lesion.

Aphthous Stomatitis or Behcet's Syndrome:

There is increase in number of LCs in areas of lesions with Behcet's syndrome than the normal mucosa, there may be degenerating LCs also demonstrated in these lesions.

Future Directions:

Since many pathologies exhibit the presence of LCs. Therefore both qualitative & quantitative analysis of LCs should be done to understand their role in pathogenesis. Also comparative analysis of LCs in potentially malignant disorders & malignancy should be done to assess their usefulness in prognosis as well as treatment planning.

Conclusion

LCs are a critical component of primary immune response, capable of capturing protein antigens in the oral epithelium and presenting them to specific T cells in the context of MHC II molecules. Specifically, oral mucosal LCs can engage and internalize various pathogens. Since the oral cavity is exposed to many antigens, the LCs have a significant immunological role in the most of the oral lesions. They act as immune mediator cells, tumor cells, vectors of infected cells, and phagocytic cells. Their density and distribution in different oral pathologic conditions may reflect different immunological mechanisms involved the pathology of these diseases. This wide range of functions creates immense scope for further research to ascertain the precise role of LCs in various oral lesions in the coming era. However, several questions still remain unanswered and insights gained from further investigation would have both a wide immunological significance as well as clinical implications.

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