

## The Current Understanding on Langerhans' Cells and Its Role in Oral Lesions

### Abstract

**Objective:** Description of Langerhans' cells (LCs) as an important antigen-presenting cells responsible for detecting the antigens, recruiting T-cells, and thereby initiating the immune response. An adequate response of the mucosal immune system is essential to protect the mucosa against pathological conditions. Hence, a detailed review was planned about this unique antigen-presenting cell. **Methods:** A literature search of the electronic databases included the MEDLINE, EBSCOHOST, PUBMED, and hand searches of references retrieved were undertaken using the following MeSH terms "Langerhans cells," "LCs in Oral Lichen Planus," "Langerhans cell histiocytosis," "LCs and HIV," "LCs in Periodontitis." **Results:** LCs are present suprabasally in the epithelium of oral mucosa and in the epidermis of the skin. The role played by LCs though not fully elucidated, but several research studies indicate that these cells are involved in the pathogenesis of many oral diseases. In this article, the historical perspective, structure, function, origin, and phenotypic expressions of LCs are discussed in detail. The current understanding on the role of LCs in various oral lesions and its immunological characteristics are discussed. **Conclusion:** LCs act as immune mediator cells, tumor cells, vectors of infected cells, and phagocytic cells. Further studies could bolster the knowledge about the role of Langerhans cells in the immune response of various oral diseases and thereby provide diagnostic tools and help for prognostic evaluation. This review illuminates the pivotal role of Langerhans cells and its immune surveillance as a "Sentinels" of the oral mucosa.

**Keywords:** Langerhans cell histiocytosis, Langerhans' cells, oral diseases, oral lichen planus, periodontitis

### Introduction

Langerhans' cells (LCs) are the prototype non-lymphoid members of the dendritic cell family.<sup>[1]</sup> They are cells of myeloid origin that are known to be involved in immune responses. They are insinuated between keratinocytes but are not attached to them by cell junctions.<sup>[2]</sup> There is an increased population of LCs in the epidermal layer of the skin.<sup>[3]</sup> They contain large granules called Birbeck granules.<sup>[4]</sup>

Under the electron microscope, LCs can certainly be distinguished from keratinocytes by their obvious lack of prekeratin filament bundles.<sup>[5]</sup> Furthermore, their nuclei generally exhibit irregular indentations. Their cytoplasm contains a prominent Golgi complex without much rough endoplasmic reticulum, secondary lysosomes, and moderate numbers of mitochondria. The most distinctive feature of their cytoplasm is the presence of

Birbeck granules, which are abundant in the vicinity of the Golgi complex.<sup>[6]</sup> Most of these are cupped, disk-shaped structures that exhibit a central linear density when cut in certain planes of a section. The central linear density can exhibit a zipper-like pattern of periodic striations that is suggestive of a latticework of intragranular particles. Furthermore, many of these granules have the two-dimensional appearance of a "tennis racket" because of the presence of a vesicular expansion of their limiting membrane at one end of the linear density.<sup>[5]</sup> In contrast to mononuclear phagocytes, LCs lack the capability of phagocytosis as they do not contain lysozyme or  $\alpha$  1-antichymotrypsin known to be present in phagocytes.<sup>[7]</sup> LCs may be induced to express CD4 on their surfaces. This allows for infection by human immunodeficiency virus (HIV) and then LCs transforming into a virus reservoir. Strong chemoattractants that induce migration of LCs include interleukin-1 (IL1)-beta, IL-8, and granulocyte

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**Vidyadevi Chandavarkar, Mithilesh N. Mishra, R. Sangeetha<sup>1</sup>, B. R. Premalatha<sup>2</sup>**

*Department of Oral Pathology, School of Dental Sciences, Sharda University, Greater Noida, Uttar Pradesh, <sup>1</sup>Department of Oral Pathology, Dayananda Sagar College of Dental Sciences, Bengaluru, <sup>2</sup>Department of Oral Pathology and Microbiology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysore, Karnataka, India*

**Submitted :** 03-Jan-2020  
**Revised :** 11-Jun-2020  
**Accepted :** 19-Jun-2020  
**Published :** 26-Nov-2020

**Address for correspondence:**  
Dr. Vidyadevi Chandavarkar,  
21/306, AWHO Society,  
Gurjinder Vihar, Sector Chi,  
Greater Noida 201310, Gautam  
Buddha Nagar, Uttar Pradesh,  
India.  
E-mail: svidyac27@yahoo.co.in

Access this article online

**Website:**  
www.contempclindent.org

**DOI:** 10.4103/ccd.ccd\_4\_20

**Quick Response Code:**



**How to cite this article:** Chandavarkar V, Mishra MN, Sangeetha R, Premalatha BR. The current understanding on langerhans' cells and its role in oral lesions. Contemp Clin Dent 2020;11:211-6.

macrophage-colony-stimulating factor (GM-CSF). LCs produce IL-1-beta and tumor necrosis factor (TNF)-alpha. LCs have not proven to be clonal. These cells are primary antigen-presenting cells and represent the most peripheral extension of the immune system.<sup>[8]</sup> The co-stimulatory proteins present on LCs help to activate helper T-cells to proliferate and differentiate into effector cells. Co-stimulatory proteins release two kinds of signals. Signal 1 is released by MHC protein on the surface of LCs, whereas Signal 2 is released by B7 proteins on LCs recognized by co-receptor protein CD28 on the surface of T-cells. Both signals are required for the activation of T-cells.<sup>[9]</sup>

### Methods

A literature search was conducted using various electronic databases MEDLINE through OVID (1972–2019), and hand searches of references retrieved. The search strategy used was replicated for all electronic databases, was first conducted and up to 2019. The search strategy used the following MESH keywords “Langerhans cells,” “Oral Lichen Planus,” “Langerhans cell histiocytosis,” “HIV,” “Periodontitis.” After the removal of duplicates and unrelated research, 48 publications were reviewed. A literature review of the analysis is dispensed.

### Genesis and homeostasis of Langerhans' cells

The embryonic origin of LCs is from the erythro-myeloid progenitors present in the yolk sac [Figure 1]. They also differentiate from hematopoietic stem cells, which migrate through the fetal liver. Postnatally, the homeostasis of LCs is by transforming growth factor  $\beta$ 1, which plays a key role in the differentiation of LCs from CD34+ hematopoietic progenitor stem cells [Figure 2] 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.<sup>[10,11]</sup> In the epidermis,

LCs are derived from CSF-1 precursors, which also originate from the bone marrow.<sup>[12]</sup> 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. This difference in antigenic load demands different immune responses.<sup>[13,14]</sup>

### Historical background

The LCs were discovered by Paul Langerhans' in 1868, a medical practitioner in Berlin. He made these cells visible by means of gold chloride technique.<sup>[15]</sup> These cells were named as LCs by Sigmund Merkel (1875). However, in 1961 specific structures in the cytoplasm of these cells were detected by Birbeck *et al.* with electron microscopy. These structures were named as Birbeck's granules. These Birbeck granules from then onward served as a distinct marker for LCs and became a morphological hallmark.<sup>[16,17]</sup> The LCs appear as clear cells<sup>[18]</sup> in histology and express CD1a [Table 1].<sup>[19]</sup>

### Oral and maxillofacial Langerhans' cell histiocytosis

In contrast to normal LCs, the cells responsible for this disease are immature cells of Langerhans cell origin. It is an abnormal proliferation of LCs [Table 2].<sup>[20,21]</sup> These “histiocytes” are constituent of lesions occurring in the bone, skin, lymph nodes, spleen, liver, thymus, bone marrow, central nervous system, and gastrointestinal tract. These tumor cells lack the dendritic processes and have round to ovoid, epithelioid morphology. The cytokines produced by these cells include IL-1-beta, IL-3, IL-4, IL-8, TNF-alpha, and GM-CSF. These cytokines perform autocrine as well as paracrine functions in lesion establishment and persistence. These cells have proven to be clonal. These LCs are immature dendritic cells that lack the ability to be functional antigen presenting cells.<sup>[22]</sup> There is a mutation of gene BRAFV600E, which indicates that LC histiocytosis (LCH) is neoplasia. The

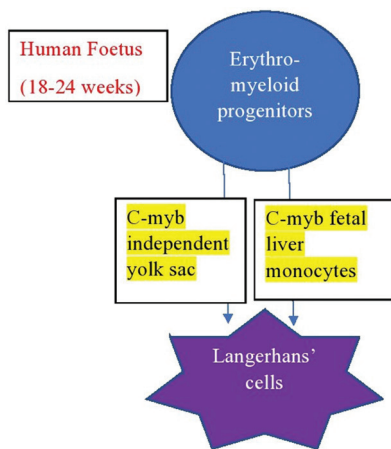


Figure 1: Schematic presentation showing prenatal development of Langerhans' cells from Erythro-myeloid progenitors derived via C-myb independent yolk sac and C-myb fetal liver monocytes

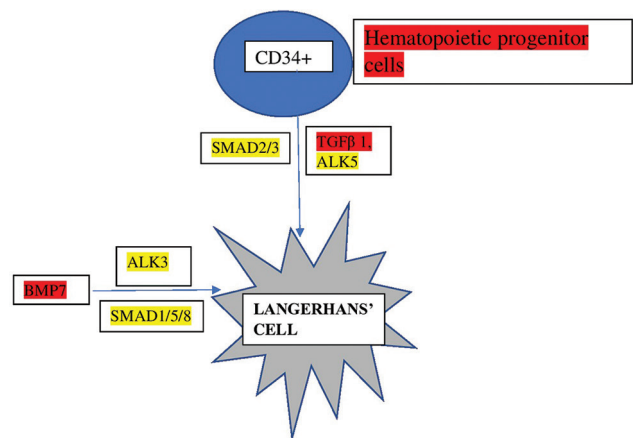


Figure 2: Schematic presentation showing origin and homeostasis of Langerhans' cells derived from CD34+ hematopoietic progenitors by transforming growth factor  $\beta$ 1 and BMP7

immunohistochemical markers for confirmatory diagnosis are CD1a, CD207, CD68, and S100.<sup>[23]</sup> Langerin is a highly sensitive and specific marker for Langerhans cell histiocytosis.<sup>[24]</sup>

In the published literature, there are cases reported in the head-and-neck region involving skull bones and jaws.

Among the oral and maxillofacial LCH patients, >90% of the individuals are younger than 40 years of age with a mean age of 19 years. Unifocal LCH represents about 50% of cases. The site of the lesion is more common in mandible than the maxilla. The posterior regions of the jaws are more frequently affected than the anterior regions. Soft-tissue lesions are more commonly present in gingiva and hard palate. The floor of the mouth, maxillary sinus, and buccal mucosa account for <10% of the lesions. The most common intra-oral presentations are proliferative growth, pain, gingivitis, loose teeth, oral mucosal ulcer, impaired healing, and halitosis. The most common extraoral sites of bony involvement are skull bones.<sup>[21,25]</sup> It is inferred from the above discussion that immature LCs play a key role in the pathogenesis of LCH.<sup>[20-25]</sup>

### Oral lichen planus

Oral lichen planus (OLP) is an auto-immune disease caused by cytotoxic CD8<sup>+</sup> T-cells, in which the basal cells of oral epithelium undergo apoptosis.<sup>[26]</sup> It is a delayed-type hypersensitivity or cell-mediated response to an antigenic stimulus residing within the epithelium.<sup>[27]</sup> LCs are immunologically active and play a role in disease progression.<sup>[28]</sup> Immune-associated (Ia) response-like antigen is a membrane protein known to be a product of the major histocompatibility complex. LCs more frequently expressed Ia-like antigens in the lesional mucosa of OLP patients than in normal oral mucosa [Table 2]. LCs have been alleged to be the target cells involved in the primary immune response; this extended expression of Ia-like antigens may serve as an immune surveillance system. However, the data further demonstrate that lichen planus diseased oral epithelium shows an increase in the expression of Ia-like antigens. This increase is elucidated as an enhanced capacity of LCs to detect and present antigens to epithelial T-lymphocytes.<sup>[29]</sup> Similarly, Ia-bearing LCs are present in the epidermis capable of mediating the immunologic functions of Ia-bearing macrophages. This has important clinical implications with the role of LCs as sensitizing cells in both; contact hypersensitivity and skin graft rejection.<sup>[30]</sup>

According to Farthing *et al.*, in OLP, there is increased expression of HLA-DP/DQ and CD1a/HLA-DR positive LCs, thus indicating that HLA-DP and HLA-DQ expression is upregulated on oral mucosal Langerhans cell (OMLC) in OLP. If this phenotype up-regulation is associated with a functional upregulation, it might account for the increased T-lymphocyte response and hence the clinicopathological

features of the condition.<sup>[19]</sup> A higher number of LCs in dermo-epithelial junctions in OLP and oral lichenoid lesions suggests that they may play a significant role in the adaptive immunity of lichenoid conditions.<sup>[31]</sup> In light of the above discussion, it can be ascertained that LCs increase the antigenic load in lichen planus, lichenoid reactions, and other immunological disorders.<sup>[19,28-31]</sup>

### 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.<sup>[32,33]</sup> They influence the HIV-1 pathogenesis and protective mechanisms 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<sup>+</sup> and CD8<sup>+</sup> 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.<sup>[34,35]</sup> However, it is determined that LCs act as vectors for HIV-1 [Table 2].<sup>[32-35]</sup>

### Noncalcifying epithelial odontogenic tumor

LCs are also found in noncalcifying variant of the calcifying epithelial odontogenic tumor (CEOT). They are present inside tumor epithelial nests.<sup>[36]</sup> While classic CEOT represents a mere 1%–2% of odontogenic neoplasms, Noncalcifying Langerhans Cell rich variant of CEOT is even less common, with only 9 cases reported till date. Most cases have occurred in individuals of Asian descent.<sup>[37]</sup> These cases revealed odontogenic epithelial cells arranged in thin strands or small nests and globules of amyloid materials. Noticeably no calcifications were present in contrast to classical CEOT. They occur predominantly in the anterior and premolar region of the maxilla, whereas classical CEOT occurs in the posterior part of the mandible.

LCs within small odontogenic islands had been confirmed with Anti-Cd1a staining. The pathologic significance of the presence of LCs in CEOT is still unclear. Literature also suggests that the origin of both the odontogenic epithelium and LCs is from oral ectoderm.<sup>[36,37]</sup> These LCs in noncalcifying odontogenic tumors are very close to amyloid globules. Therefore, they may phagocytose and process the amyloid material and then present the processed antigens to T lymphocytes in the regional lymph nodes [Table 2]. Owing to the paucity of this special variant of CEOT, the

**Table 1: Identification and phenotypic expression of Langerhans' cells**

Identification of LCs	Phenotypic expression	Author
Histology	Clear cells	Nanci <sup>[18]</sup>
Histochemistry	Dendritic	Silberberg-Sinakin <i>et al.</i> <sup>[15]</sup>
Ultrastructure	Intracytoplasmic Birbeck granules	Wolff <sup>[6]</sup>
Immunohistochemistry	CD1, CD14, CD23, CD45, CD69, CD74, CD83, HLA-A/B/C, HLA-DR/DP/DQ, S100, MIP-1 $\alpha$ . 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	Barret <i>et al.</i> <sup>[19]</sup>

LCs: Langerhans' cells

**Table 2: Role of Langerhans cells in oral lesions**

Oral lesions	Role of LCs	Author
LCH	Tumor cells	Jaffe <sup>[20]</sup> , Leonidas <i>et al.</i> <sup>[21]</sup> Lombardi <i>et al.</i> <sup>[22]</sup> , Giona <i>et al.</i> <sup>[25]</sup>
Oral lichen planus	Ia like antigen	Lavanya <i>et al.</i> <sup>[26]</sup> , Eversole <sup>[27]</sup> Farthing <i>et al.</i> <sup>[28]</sup> , Sloberg <i>et al.</i> <sup>[29]</sup> , Singl <i>et al.</i> <sup>[30]</sup> , Gueiros <i>et al.</i> <sup>[31]</sup>
HIV infection	Vectors of infected cells	Matsuzawa <i>et al.</i> <sup>[32]</sup> , Stingl <i>et al.</i> <sup>[33]</sup> , Steinman <i>et al.</i> <sup>[34]</sup> , Dezutter-Dambuyant and Schmitt <sup>[35]</sup>
Non-CEOT	Phagocytosis	Wang <i>et al.</i> <sup>[36]</sup>
Diphtheria and chronic hyperplastic candidiasis	Phagocytosis	Ali <i>et al.</i> <sup>[38]</sup>
Oral squamous cell carcinoma	Immune-mediator cell	Barret <i>et al.</i> <sup>[19]</sup> , Rani <i>et al.</i> <sup>[39]</sup> , Daniels <i>et al.</i> <sup>[40]</sup> , Pelliccioli <i>et al.</i> <sup>[42]</sup> , Upadhyay <i>et al.</i> <sup>[43]</sup>
Periodontitis	Functionally altered cell	Barret <i>et al.</i> <sup>[19]</sup> Wilensky <i>et al.</i> <sup>[44]</sup> , Hovav <sup>[45]</sup> , Cirrincione <i>et al.</i> <sup>[46]</sup> , Bodineau <i>et al.</i> <sup>[47]</sup> , Bodineau <i>et al.</i> <sup>[48]</sup>

HIV: Human immunodeficiency virus; LCs: Langerhans' cells, Ia: Immune associated; LCH: Langerhans cell histiocytosis; CEOT: Calcifying epithelial odontogenic tumor

true pathological significance of the presence of LCs in CEOT needs further study.<sup>[36]</sup>

### Oral mucosal infection

LCs lack the capacity for phagocytosis, as they do not contain  $\alpha$ 1-antichymotrypsin.<sup>[7]</sup> It has been believed that LCs lack the capacity for phagocytosis, but the requirement (especially in the oral environment) for an adaptive immune response against bacteria and yeasts would seem to necessitate a phagocytic capacity. Recent studies on murine LC support this conclusion. LC can internalize species of *Cornybacteria* up to 6  $\mu$ m in length and *Staphylococcus aureus*, which is approximately 1  $\mu$ m in diameter (Reis e Sousa *et al.*, 1993). This ability is downregulated after 72 h in culture, suggesting that it is a property retained only while LCs are intraepithelial. In macrophages, phagocytosis is mediated through Fc complement and glycan receptors, but in LCs, it is mediated by glycan receptors only. This may explain why LCs phagocytosis is both slower and less extensive in terms of numbers of particles engulfed compared to macrophages.<sup>[19]</sup> The candidal antigens are also engulfed by process of phagocytosis by LCs. In oral candidiasis, both specific and nonspecific immune reactions are involved. Certain reports have shown that CD1a positive LCs in the epithelia of chronic hyperplastic candidiasis. CD1a positive cells form a network which varies in the location from basal layers to the suprabasal layer.<sup>[38]</sup> Hence

LCs are involved in the phagocytic activity in oral mucosal infections [Table 2].<sup>[19,38]</sup>

### Oral squamous cell carcinoma

LCs are able to present tumor antigens in conjunction with MHC class I molecules [Table 2].

CD1a+ and S 100+ OMLC rise in tumor epithelium of invasive squamous cell carcinomas. In well-differentiated lesions, OMLC occupies the usual suprabasal location, but in anaplastic epithelium, they are scattered randomly. There appears to be no correlation between OMLC density, degree of differentiation, or DNA ploidy status in oral squamous cell carcinoma (OSCC).<sup>[19]</sup> However, a pronounced decrease of LCs in poorly differentiated OSCC has been reported.<sup>[39]</sup>

In view of the fact that OMLC numbers may rise in OSCC, it is interesting that tobacco and alcohol consumption, known predisposing factors for the development of this disease, are also associated with increased OMLC counts. Numbers of CD1a+ OMLC in smokers are raised at sites often affected by squamous cell carcinoma, namely the lip and lateral border of the tongue. Similarly, the density of HLA-DR+ OMLC at the latter site is increased in smokers, whereas smokeless tobacco has the opposite effect.<sup>[40]</sup> Alcohol consumption appears to be less important, at least in terms of OMLC numbers, but may act synergistically with tobacco.<sup>[19]</sup> Few studies have shown nondendritic CD1a positive LCs present in the malignant buccal

mucosa.<sup>[41]</sup> The population of mature dendritic cells is reduced in OSCC as compared to oral epithelial dysplasia. These findings suggest that mature dendritic cells migrate to lymph nodes to present the tumor antigens, thereby activate the immune system. The cytokines secreted by tumor cells limit the maturation of LCs.<sup>[42,43]</sup> Hence, it can be deduced that immature cells are more pronounced in OSCC compared to mature dendritic cells, whereas in epithelial dysplasia mature LCs increase with the severity of grades.<sup>[42,43]</sup>

### Periodontal disease

The OMLC in gingival epithelium responds to the build-up of plaque. With the development of gingival inflammation, there is an increase in ATPase activity. As plaque accumulates, about five times as many CD1a<sup>+</sup> Langerhans cells are seen in clinically inflamed gingiva compared with the numbers in the same patients following periodontal treatment. OMLC in healthy gingiva is less dendritic, more electron-dense, and contains fewer Birbeck granules than those from inflamed sites.<sup>[19]</sup> Dendritic cells hold the immunological cues delivered by pathogen and surrounding medium and thereby cause destructive immunity.<sup>[44,45]</sup> The LCs are altered in HIV-associated periodontitis.<sup>[46]</sup> An increase in the ratios of antigen-presenting cell subsets and, more particularly, matured DC-LAMP<sup>+</sup> dendritic cells were also present in elderly patients of chronic periodontitis.<sup>[47]</sup> However, the number of CD1a<sup>+</sup> LC was significantly decreased in the epithelium and significantly increased in the upper connective tissue of elderly patients.<sup>[48]</sup> LCs are increased in gingivitis compared to periodontitis showing different host responses in both the diseases. Therefore, in periodontal infections, Langerhans' cells are functionally altered [Table 2].<sup>[44-48]</sup>

### Conclusion

In the published literature, it is well documented that LCs play a vital role in presenting antigens to the lymphocytes. Since the oral cavity is exposed to many antigens, the Langerhans cells have a significant immunological role in most of the oral lesions. LCs act as immune mediator cells, tumor cells, vectors of infected cells, and phagocytic cells. This wide range of functions of LCs creates immense scope for further research to ascertain the precise role of LCs in various oral lesions in the coming era.

### Acknowledgments

We would like to thank our mentors for their support and guidance, Dr. K Uma Professor, Dr. Kavita Rao Professor and Head, Dr. Smitha T Professor, Dr. Priya N S Professor, and Dr. Umadevi Professor, VS Dental College, Bangalore, India.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

- Romani N, Clausen BE, Stoitzner P. Langerhans cells and more: Langerin-expressing dendritic cell subsets in the skin. *Immunol Rev* 2010;234:120-41.
- Choi KL, Sauder DN. The role of Langerhans cells and keratinocytes in epidermal immunity. *J Leukoc Biol* 1986;39:343-58.
- Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. *Nat Rev Immunol* 2008;8:935-47.
- Jaitley S, Saraswathi T. Pathophysiology of Langerhans cells. *J Oral Maxillofac Pathol* 2012;16:239-44.
- Cormack DH. *Hans Histology*. 9<sup>th</sup> ed. Philadelphia: Lippincott; 1987. p. 458-62.
- Wolff K. The Langerhans cell. *Curr Probl Dermatol* 1972;4:79-145.
- Stewart JC, Regezi JA, Lloyd RV, McClatchey KD. Immunohistochemical study of idiopathic histiocytosis of the mandible and maxilla. *Oral Surg Oral Med Oral Pathol* 1986;61:48-53.
- Sugaya M, Loré K, Koup RA, Douek DC, Blauvelt A. HIV-infected Langerhans cells preferentially transmit virus to proliferating autologous CD4<sup>+</sup> memory T cells located within Langerhans cell-T cell clusters. *J Immunol* 2004;172:2219-24.
- Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. *Molecular Biology of the Cell*. 4<sup>th</sup> ed. New York: Garland Science; 2002.
- Collin M, Milne P. Langerhans cell origin and regulation. *Curr Opin Hematol* 2016;23:28-35.
- Yasmin N, Bauer T, Modak M, Wagner K, Schuster C, Köffel R, *et al.* Identification of bone morphogenetic protein 7 (BMP7) as an instructive factor for human epidermal Langerhans cell differentiation. *J Exp Med* 2013;210:2597-610.
- Kaplan DH, Li MO, Jenison MC, Shlomchik WD, Flavell RA, Shlomchik MJ. Autocrine/paracrine TGFβ1 is required for the development of epidermal Langerhans cells. *J Exp Med* 2007;204:2545-52.
- Hasséus B, Jontell M, Bergenholtz G, Dahlgren UI. Langerhans cells from human oral epithelium are more effective at stimulating allogeneic T cells *in vitro* than Langerhans cells from skin. *Clin Exp Immunol* 2004;136:483-9.
- van Loon LA, Krieg SR, Davidson CL, Bos JD. Quantification and distribution of lymphocyte subsets and Langerhans cells in normal human oral mucosa and skin. *J Oral Pathol Med* 1989;18:197-201.
- Silberberg-Sinakin I, Baer RL, Thorbecke GJ. Langerhans cells: A review of their nature with emphasis on their immunologic functions. *Prog Allergy* 1978;24:268-94.
- Lampert F. Langerhans cell histiocytosis. Historical perspectives. *Hematol Oncol Clin North Am* 1998;12:213-9.
- Mc Dermott R, Ziylan U, Spehner D, Bausinger H, Lipsker D, Mommaas M, *et al.* Birbeck granules are subdomains of endosomal recycling compartment in human epidermal Langerhans cells, which form where Langerin accumulates. *Mol Biol Cell* 2002;13:317-35.
- Nanci A. *Ten Cate's Oral Histology*. 7<sup>th</sup> ed. St. Louis: Mosby Elsevier; 2008. p. 334-5.
- Barret AW, Cruchley AT, Williams DM. Oral mucosal Langerhans' cell. *Crit Rev Oral Biol Med* 1996;7:36-58.

20. Jaffe R. The histiocytosis. *Clin Lab Med* 1999;19:135-55.
21. Leonidas JC, Guelfguat M, Valderrama E. Langerhans' cell histiocytosis. *Lancet* 2003;361:1293-5.
22. Lombardi T, Hauser C, Budtz-Jørgensen E. Langerhans cells: Structure, function and role in oral pathological conditions. *J Oral Pathol Med* 1993;22:193-202.
23. Nangalia R, Chatterjee RP, Kundu S, Pal M. Langerhans cell histiocytosis in an adult with oral cavity involvement: Posing a diagnostic challenge. *Contemp Clin Dent* 2019;10:154-7.
24. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. *Am J Surg Pathol* 2008;32:615-9.
25. Giona F, Caruso R, Testi AM, Moleti ML, Malagnino F, Martelli M, *et al.* Langerhans' cell histiocytosis in adults: A clinical and therapeutic analysis of 11 patients from a single institution. *Cancer* 1997;80:1786-91.
26. Lavanya N, Jayanthi P, Rao UK, Ranganathan K. Oral lichen planus: An update on pathogenesis and treatment. *J Oral Maxillofac Pathol* 2011;15:127-32.
27. Eversole LR. Immunopathogenesis of oral lichen planus and recurrent aphthous stomatitis. *Semin Cutan Med Surg* 1997;16:284-94.
28. Farthing PM, Matear P, Cruchley AT. The activation of Langerhans cells in oral lichen planus. *J Oral Pathol Med* 1990;19:81-5.
29. Sloberg K, Jonsson R, Jontell M. Assessment of Langerhans' cells in oral lichen planus using monoclonal antibodies. *J Oral Pathol* 1984;13:516-24.
30. Singl G, Katz SI, Clement SL, Green L, Shevach EM. Immunologic function of Ia-bearing epidermal Langerhans cells. *J Immunol* 1978;16:27-30.
31. Gueiros LA, Gondak R, Jorge Júnior J, Coletta RD, Carvalho Ade A, Leão JC, *et al.* Increased number of Langerhans cells in oral lichen planus and oral lichenoid lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;113:661-6.
32. Matsuzawa T, Ogawa Y, Moriishi K, Shimada S, Kawamura T. Immunological function of Langerhans cells in HIV infection. *J Dermatol Sci* 2017;87:159-67.
33. Stingl G, Rappersberger K, Tschachler E, Gartner S, Groh V, Mann DL, *et al.* Langerhans cells in HIV-1 infection. *J Am Acad Dermatol* 1990;22:1210-7.
34. Steinman RM, Granelli-Piperno A, Pope M, Trumppfeller C, Ignatius R, Arrode G, *et al.* The interaction of immunodeficiency viruses with dendritic cells. *Curr Top Microbiol Immunol* 2003;276:1-30.
35. Dezutter-Dambuyant C, Schmitt D. Epidermal Langerhans cells and HIV-1 infection. *Immunol Lett* 1993;39:33-7.
36. Wang YP, Lee JJ, Wang JT, Liu BY, Yu CH, Kuo RC, *et al.* Non-calcifying variant of calcifying epithelial odontogenic tumor with Langerhans cells. *J Oral Pathol Med* 2007;36:436-9.
37. Santosh N, McNamara KK, Kalmar JR, Iwenofu OH. Non-calcifying Langerhans Cell-Rich Variant of Calcifying Epithelial Odontogenic Tumor: A Distinct Entity with Predilection for Anterior Maxilla. *Head Neck Pathol* 2019;13:718-21.
38. Ali A, Rautemaa R, Hietanen J, Beklen A, Kontinen Y. A possible CD1a Langerhans cell-mast cell interaction in chronic hyperplastic candidosis. *J Oral Pathol Med* 2007;36:329-36.
39. Rani SV, Aravindha B, Leena S, Balachander N, Malathi LK, Masthan MK. Role of abnormal Langerhans cells in oral epithelial dysplasia and oral squamous cell carcinoma: A pilot study. *J Nat Sci Biol Med* 2015;6:S128-33.
40. Daniels TE, Chou L, Greenspan JS, Grady DG, Hauck WW, Greene JC, *et al.* Reduction of Langerhans cells in smokeless tobacco-associated oral mucosal lesions. *J Oral Pathol Med* 1992;21:100-4.
41. Mathew JK, Pandian RMK, Gaikwad P, Nadu T, Rabi S. Non-dendritic Langerhans cells: A new entity in normal and malignant buccal mucosa. *Eur. J. Anat.* 2019; 23:383-388.
42. Pelliccioli ACA, Bingle L, Farthing P, Lopes MA, Martins MD, Vargas PA. Immunosurveillance profile of oral squamous cell carcinoma and oral epithelial dysplasia through dendritic and T-cell analysis. *J Oral Pathol Med* 2017;46:928-33.
43. Upadhyay J, Rao NN, Upadhyay RB. A comparative analysis of langerhans cell in oral epithelial dysplasia and oral squamous cell carcinoma using antibody CD-1a. *J Cancer Res Ther* 2012;8:591-7.
44. Wilensky A, Segev H, Mizraji G, Shaul Y, Capucha T, Shacham M, *et al.* Dendritic cells and their role in periodontal disease. *Oral Dis* 2014;20:119-26.
45. Hovav AH. Dendritic cells of the oral mucosa. *Mucosal Immunol* 2014;7:27-37.
46. Cirrincione C, Pimpinelli N, Orlando L, Romagnoli P. Lamina propria dendritic cells express activation markers and contact lymphocytes in chronic periodontitis. *J Periodontol* 2002;73:45-52.
47. Bodineau A, Coulomb B, Tedesco AC, Séguier S. Increase of gingival matured dendritic cells number in elderly patients with chronic periodontitis. *Arch Oral Biol* 2009;54:12-6.
48. Bodineau A, Coulomb B, Folliguet M, Igondjo-Tchen S, Godeau G, Brousse N, *et al.* Do Langerhans cells behave similarly in elderly and younger patients with chronic periodontitis? *Arch Oral Biol* 2007;52:189-94.