Molecular Markers of Oral Lichen Planus

Type of Manuscript: Review Article
Running Title: Molecular Markers of Oral Lichen Planus- A Review

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Total Number of Words: 3607

***Abstract*: Oral Lichen Planus (OLP) is known to be a chronic inflammatory disease of uncertain etiopathogenesis. Though it is often asymptomatic, a severe form of this will exhibit symptoms such as excessive pain that can disturb daily activities (swallowing, eating, etc.). According to the World Health Organization (WHO), it is potentially precancerous as it is associated with an increased risk of cancer. Lichen Planus can occur independently in the skin or even in the genital, anal, oesophageal, nasal and laryngeal mucosa. At present, prognostic markers are unavailable to help in the detection of lesions that are potentially malignant. This study aims towards identifying any available cellular or molecular markers pertaining towards a better diagnosis of OLP. A proper knowledge on the clinical features, pathogenesis and diagnosis will allow also contribute to a better treatment option.**

***Keywords*: Genetics, Inflammation, Molecular Markers, Oral Lichen Planus, Pathogenesis.**

Introduction

The oral cavity is a vision to an individual's health or at present, any diseases, making it an alert system to the body. The reasoning behind this is because a majority of systemic diseases are accompanied by symptoms displayed in the oral cavity. It is a common occurrence that oral manifestations precedes that of symptoms present in other sites throughout the body. [1]

Originating from a combination of a Greek word "lichen" which means tree moss and a Latin word "planus" which means flat, the name is suggestive of it being a form of flat fungal infection. [2] Lichen planus (LP) broadly is a form of inflammatory disease that affects mucocutaneous structures in the body such as the skin, hair, nails and other mucosal surfaces. [3]

The World Health Organization (WHO) in the year 1978, has defined oral lichen planus as a form of budding precancerous condition. This is in association with the knowledge that it represents a generalized state of a high increase of cancer risk. This common type of inflammation involving the oral mucosa is accompanied by a prevalence rate of 0.5% to 2.2% of the population. [4] The average age group that is affected are 30-60 years, more specifically present in middle-aged women and younger-aged men. With regard to children, OLP is uncommon and if present, it is accompanied with a cutaneous disease. [5]

Even with WHO's description of OLP being a precancerous condition, it's potential of being premalignant is still uncertain. It's ability of transforming into a malignancy is estimated to be in a range of 0.5-2.9% in OLP patients. With regard to diagnosis, no prognostic markers are available to allow a better identification of a high risk progression of this disease. As an alternate option, OLP patients are monitored carefully in order to detect any cancer progression. [4]

Hence, to fully understand the etiopathogenesis of OLP, knowing the major molecules in relation to the disease is of significant importance. Thus, the main aim of this review is to determine specific molecular markers that is related to the etiophathogenesis of OLP, enabling a better prediction of its malignancy.

Epidemiology

In an oral pathology clinic, OLP is described as the most common non-infectious mucosal disease affecting adult patients. [6] More commonly affecting women than men, they exhibit a ratio of 2:1 to 3:1 respectively. [7, 8, 9] The age range that is more prevalent is around 30 to 60 years old. In children, OLP is not a common occurrence unless it is related to a cutaneous disease. [10] In terms of recovery, only 17% of these patients had full recovery [8] but about 39% of OLP patients had remission of their lesions. [11]

Etiology

Genetics (5)

In OLP, familial cases are uncommon. Regarding genetic background, OLP patients are seen to be associated with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1 and DRW9. [18,19,20,21] Among Chinese patients, it was noted that there was an increase in HLA-DR9 and Te 22 antigens.[22]

Dental Materials

During a dental treatment, specifically any conservative procedures, the dental materials that are used are said to act as a triggering factor. Some of the materials include NSAIDs, beta blockers, sulfonylureas and antimalarial. [23,24,25,26]

Habits

Cigarette smoking though not a common association with OLP patients, [27] however specifically in Indian communities, it has been a suggested as an etiological factor. [28] This is also similar to that of betel nut chewing which is more common in OLP patients than those who don't practice this. [29,30,31]

Infectious Agents

Although there is no confirmation, OLP has been said to be associated with bacteria like a Gram-negative anaerobic bacillus and spirochetes. [25] In some studies, it was suggested that *Helicobacter pylori* (HP) is involved in the etiology of OLP. [32,33] However, in the more recent studies, no such evidence was obtained. [34] Similar to that of the candida species, several studies showed it's relation to OLP but other studies showed that it was not significant. [35, 36]

Clinical Features

The main characteristics that OLP exhibits includes orthokeratosis hyperkeratosis, acanthosis, degeneration of basal cells, sub epithelial eosinophilic amorphous band a dense infiltrate of lymphocytes. Having similar characteristics both clinically and histopathologically makes OLP hard to differentiate with that of graft-vs-host (GVH) disease. [37] Clinically, OLP can be divided into six types; which includes, papular, reticular, plaque-like, atrophic, erosive and bullous. [38]

The most common form of OLP is the reticular type. Commonly, it is characterized with bilateral and white hyperkeratotic lines interlacing with each other surrounded by an erythematosus border. [8,9,39] A sub classification of this reticular type includes papular and plaque forms that exhibits a multifocal leukoplakia, varying from smooth regions to irregular and elevated regions. [39]

The second commonly seen OLP is the atrophic form. [8] Symptom wise, it exhibits varying stages of pain and uncomfortability. [9] Clinically, it appears as patches of diffuse and erythematous regions. [39] At instances, it can have a resemblance to two forms of clinical features; which includes the characteristically white striae that is encircled by an area of erythematous origin. [40] Other types of OLP like the bullous form and the bullae can easily rupture as it is commonly observed in the lateral border of both the buccal mucosa or the tongue. [8]

Another form of OLP is the erosive type that is considered to be the most significant. The reason behind this is because the symptomatic lesions are at most common surrounded with a fine radiantly fine keratinized striae showing a network manifestation. [41] The plaque-like type of OLP however will show a whitish homogenous irregularity which is quite same to leukoplakia. This is said to be so as it is associated with the dorsum of the tongue as well as the mucosal surface of the cheek. [40]

Histology

In general, the characteristic histological components of OLP includes; the presence of a dense, band-like chronic infiltrate of lymphocytic origin underneath as well as which is found underneath the basal cell layer, a layer of basal cells that have undergone liquefactive degeneration, the presence of colloid bodies, a layer of rete pegs that exhibits a saw-tooth appearance, acanthosis or epithelial atrophy as well as a characteristic hyperkeratosis or parakeratosis. [42,43,44]

With regard to the colloid bodies, they are formed through the degeneration of both keratinocytes as well as immune-complexes; which is normally placed in the supra-basal epithelial region. [45] The presence of colloid bodies is suggestive that they are of apoptotic keratinocyte origin. This is seen by the appearance of DNA as well as nuclear fragmentation and immunoglobulins; which in this case is specifically IgM. [42,46,47,48,49]

In mentioning hyperkeratinisation, clinically, it appears as Wickham's striae as well as occasionally the area of acanthosis. As the epithelium of this type of disorder is very thin when compared to a normal oral mucosa, it would provide a limited amount of protection when it comes to both mechanical and chemical irritation.[50]

Diagnosis

When a classic skin lesion is present, the clinical aspects that could be viewed provides enough evidence for a right diagnosis. With that in mind, for the purpose of a histopathological study, an oral biopsy is recommended for the confirmation of the suspected diagnosis that was done clinically. The reason behind this is to rule out mainly dysplasia and malignancy. [105] The modified WHO diagnostic criteria for OLP can be seen based on the table 1 below.

Table 1: Modified Diagnostic Criteria for OLP and OLL (2003)

Modified WHO diagnostic criteria of OLP and OLL
Clinical criteria

- Presence of bilateral, more or less symmetrical lesions
- Presence of a lacelike network of slightly raised gray–white lines (reticular pattern)
- Erosive, atrophic, bullous, and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa

In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term ''clinically compatible with'' should be used

Histopathologic criteria

- Presence of a well-defined, band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
- Signs of liquefaction degeneration in the basal cell layer
- Absence of epithelial dysplasia

When the histopathological features are less obvious, the term ''histopathologically compatible with'' should be used

Final diagnosis of OLP or OLL

To achieve a final diagnosis, clinical as well as histopathological criteria should be included

OLP

A diagnosis of OLP requires fulfilment of clinical and histopathologic criteria

OLL

The term OLL will be used in the following conditions:

1. Clinically typical of OLP but histopathologically only compatible with OLP
2. Histopathologically typical of OLP but clinically only compatible with OLP
3. Clinically compatible with OLP and histopathologically compatible with OLP

Data from Ref. [106]

Treatment

When it comes to OLP, no specific treatment can be implemented. Depending on the exhibited symptoms, the extent of clinical effects, the patient's medical history including other factors, then the treatment can be planned out. [51]

Drug Therapy

The administration of drugs for treatment of OLP commonly comprises of both systemic and topical corticosteroids, cyclosporine, tacrolimus, retinoids that are topically applied as well as pimecrolimus.in. These drugs are considered to be the main choices for any OLP treatment plan. [52]

When treating a atrophic and erosive variant of OLP, systemic treatments are more preferred as topical applications have showed failure in its effects. In contrast to this, treating OLP only by systemic corticosteroids shows a decrease in effectiveness compared to either by usage of topical corticosteroids or by the mixture of both methods. [39,51,53,54,55,56]

Non-drug Therapy

One method of therapy that does not involve any usage of drugs is through ultraviolet radiation. This method of irradiation have shown a numerous amounts of success when it comes to treating OLP; proved by a variant of studies that were made. If difficult or multicentric lesions are encountered, carbon dioxide lasers are used. [57,58]

Surgical procedures can also be an option in treating OLP. A surgical procedure known as resection is normally opted for plaques that are isolated or when dealing with lesions of a non-healing nature. This method of action allows for a better quality tissue specimens not only for diagnosis but simultaneously can provide a cure for localised lesions. [59]

Molecular Markers and OLP

A normal oral mucosa undergoes transformation into whether it be a lichen planus or any similar mucosal diseases through a process that involves a multistep complex. This complex involves that of replication of the DNA, division of the cell, death of the cell as well as the adhesion between cells. To better comprehend the molecular mechanisms present in OLP, the involvement of many molecular markers are studied beforehand. [4]

A) Cell Cycle Markers

I. Rad-51

Rad-51 is considered to be of major importance during the recombination of homologous DNA. Not only that, it also plays an important role in repairing damage that is done to the DNA as well as during mitosis and meiosis. [60] This enzyme makes an appearance towards the end of the G1 phase and shows an increase during the S phase and it remains at a constant level throughout the G2 and M phases. When there is a higher level of Rad-51, the chances of DNA damage resistant is also higher. With that in mind, there exist a relation between that of an increase in Rad-51 protein as well as genome instability and tumour progression. [61,62,63] In the past, it was seen that an increase in Rad-51 shows a relation to that of cancer cells originating from OLP. [64] However, its expression is not further studied in relation to that of either OLP or even biopsies of oral cancer samples. [4]

II. Cdk

This group of complex known as cyclin-dependent kinase complexes (Cdks) plays a crucial role during the cell division cycle. One variation known as cyclin-dependent kinase 1 (cdk-1) is known to be a subunit, specifically a catalytic one of the protein kinase complex. It can also be identified as M-phase promoting factor which plays a role in inducing the entry into mitosis. This form of kinase complex controls the transitioning of both G1 phase to S phase as well as of G2 to M phase. Moreover, it is involved in a subgroup of apoptosis programs. [65,66] When it comes to its relation to that of oral

cancer, in recent times, cdk-1 mRNA shows a prominent upregulation which was arising from OLP. [64] With this knowledge, another known fact that the increasing proliferating activity as well as apoptosis further indicates that cdk-1 has the high possibility of acting as a marker for OLP lesions. [4]

III. P53

This nuclear protein; which is the transcription factor p53, shows a response to that of diverse cellular stresses. This response is important when it comes to the regulation of a variety of target genes that functions to cause arrest of the cell cycle, apoptosis, senescence, DNA repair as well as the changing of metabolism. Also dubbed as the guardian of human genome, it is currently being widely investigated in relation to that of cell cycling as well as in the development and progression of cancer. [67,68]

When in relation to that of cancer cells, the alteration of p53 is normally a result of gene mutation. This mutation causes a mutated protein to be expressed as a result of a change in a single amino-acid. [69] In its mutated state, p53 loses its function which results in the uncontrolled proliferation as well as the loss of antiproliferative property (apoptosis & senescence) that further induces cancer development. [67,68,70]

Based on various studies of the expression of p53, there are many proof that shows the increase in p53 expression especially seen in basal and parabasal keratinocytes particularly OLPs that are associated with dysplasia. [71,72,73,74] In contrast to this, the expression of p53 is said to not be related to that of the progression of malignant cells. As there is no association of p53 and apoptosis markers that could be proven, there is a possibility of the fact that its expression is more so related with that of cell cycle and not that of cell apoptosis. However, there is a relation between that of p53 expression and the proliferation marker Ki-67 in OLP. In terms of its investigation, these statements can only be proven through immunohistochemical studies as the method of DNA sequencing cannot be used. [73]

B) Cell Proliferation Markers

I. Topoisomerase II alpha

This type of enzyme functions to alter the DNA's tertiary structure but at the same time not affecting the primary structure which is based upon the nucleotide sequence. This ability of Topoisomerase II alpha is of importance for DNA topology, repair and replication. It is done through the a sequence of breaking and re-joining of the DNA double helix. [75] This cell cycle-related protein is normally present in both normal and neoplastic cells where S, G2 and M phases are involved. In contrast to that, this enzyme is the lowest in G0 and G1 phases. In relation to that of OLP, there were no earlier studies that could be found. [76,77] However, topo II alpha is seen to have an association with that of oral precancerous lesions as well as head and neck carcinomas. It is said to be of high value when it comes to acting as a marker in which the proliferative activity of the particular lesion can be assessed. [78,79,80] With that information, as topo II alpha is involved in such activities, it could be a marker for cell stress which makes it even more of a potential marker for OLP. [4]

II. Cyclin D1

Cyclin D1 is one of the many types of D-type cyclins that acts as a controller of G1 phase progression through rate-limiting. These cyclins are expressed during the G1-S phases of the cell cycle with dependence to that of Cdks. Adding to that, this cyclin also plays a role during cellular proliferation, metabolism, as well as differentiation in cellular level. If there exist an overexpression of cyclin D1, there will be loss of cell cycle control with a higher rate of cell proliferation. [81] In relation to that of cancerous cells, it's overexpression shows a correlation to that of an early onset of cancer or a risk of tumour progression as well as metastases. [82] Till this day, there is only one such finding that provides information on the association of the overexpression of D1 with that of a higher rate of cell proliferation. [71]

III. Ki 67 (Mib-1)

Ki 67 is dubbed as a monoclonal antibody only shows a reaction with that of the nuclear antigen of proliferative cells and not as such with that of quiescent cells. During the late G1, S, G2 as well as M phases, this antibody is normally expressed. However, in contrast to that, the it cannot be detected during the G0 phase. Being labelled as the anti-Ki-67, Mib-1 is another type of monoclonal antibody that possesses a significant usage during paraffin sessions. The expression of Ki-67 in a healthy oral epithelium can normally be discovered at most in the parabasal layer but not in the basal layer. This antibody also plays a role in during tumour pathology in order to evaluate the proliferative action of the neoplastic tissues. [83,84,85] Based on a number of studies that were done, there is presence of an increase in Ki-67 expression seen in OLP when it is contrast to that of a normal oral mucosa. When dealing with an erosive form of OLP, it is seen that Ki-67 exhibits the most rigorous expression. With that in mind, there could be high possibility of Ki-67 being an effective marker for malignant alteration. [86]

IV. Proliferating cell nuclear antigen (PCNA)

PCNA is a nuclear protein that is frequently expressed at high rates during the G1 phase with a maximum during the changeover through S phase and slows a decrease when reaches the G2 phase. Based on that revelation, it is said to be of outmost importance during cell replication as it is available in proliferating cells. Moreover, PCNA also is of importance during the synthesis of DNA repair. [87,88] Based on a number of preceding studies, in oral dysplasia and SCC, there is a significant increase PCNA assertion. When to that of Ki-67, it is said to have a better ability in detecting cell expression even when the cells have long left the cell cycle. The reason behind this is because in nearly all of the cycling cells there exist at the very least two intracellular forms of PCNA; both which are associated with replication and not associated with replication. Another reason to back this statement is also because of the fact that with PCNA having a half time of 20 hours, it has the capability of determining even the expression of cells that have exited the cell cycle. Hence, it is considered to be an even more dependable method of assessing the proliferation activity of cells. [85]

In its atrophic form, PCNA have shown a higher rate of expression when associated with that of OLP lesions; which is similar to that of Ki-67. [74,89,90]

C) APOPTOTIC Markers

I. Bcl-2

When the regulation of apoptosis comes into consideration, Bcl-2 uptakes an important role in doing so. These proteins exhibits effects towards that of the dysfunction of the mitochondria; which in this case involves the alteration of the mitochondrial membrane potential, the passage of the permeability transition pore as well as the liberation of cytochrome c. These consequent events will in turn result in the activation of caspase and later forms the apoptosomes. [91,92] The Bcl-2 family possesses two forms of activity; which includes inhibiting apoptotic activity (Bcl-2, Bcl-X, Bcl-W, Mcl-l, A1) or can be a promoter of cell death instead (Bax, Bad, Bak, Bid, Bik, Blk, Bim, Bcl-X). Overall, Bcl-2 will under normal circumstances inhibit the activation of caspase-3. On the other hand, when Bax in turns blocks the activity of Bcl-2, caspase-3 has the ability to continue with its function. [91]

As there are other caspase markers, only caspase-3 is said to have an involvement with that of the early and specific apoptosis and thus making it a relevant involvement in OLP. [84,93,94,95,96,97] The expression of caspase-3 in OLP is somewhat irregular with it being in a range as less as 10 % to higher than 50% particularly in basal cells. With the reference to several studies on Bcl-2 expression, they will relatively show a weak involvement in OLP keratinocytes. Thus, this further proves the role of apoptosis in OLP. [47,48,94,97,98,99]

D) Cell Adhesion Molecules

CAMs of known as cell adhesion molecules are normally present in the surfaces of mostly all epithelial cells in which they will join together with the extracellular matrix molecules or even the receptors of other cells. These events is necessary for the maintenance of a solid and secure tissue structure. [4]

I. Ck-19

Cytokeratins are normally very specific to that of epithelial cells. [100] The reason behind this is because it is involved in the preservation of the mechanical stability as well as the integrity of the epithelial cells and tissues. Being that cytokeratins are a part of the intermediate filament proteins (IFPs), it acts as an important marker during the differentiation of tissues. With that in mind, it makes of value to the characterization of malignant tumours. [100] The expression of Ck-19 suprabasally have been associated with that of mucosal instability making it a useful marker for cellular atypia; which can be found in potentially pre-malignant lesions in the oral mucosa. [101] Henceforth, in association to that of OLP, the changes in Ck-19 can be useful in relation to evaluating both the inflammation and malignant alteration of the given lesion. [4]

II. E-cadherin

Cadeherins are known to be transmembrane glycoproteins that commonly shows an involvement in the adhesion of calcium-dependent cells. [4] In an average oral epithelium, E-cadherin can be seen in the lower para basal layer as well as the basal cell layer. When a human carcinoma is associated, the expression of E-cadherin is normally lost or even decreased in number. This characteristic that is shown corresponds with the invasive and metastatic nature that these tumours possess. [102,103,104] Coming into the earlier stages of oral carcinogenesis, there is a possibility of an increase in the expression of E-cadherin. With that in in mind, the reduction of E-cadherin especially in dysplastic and SCC lesions, it can act as a molecular marker during cancer development typically in OLP. [4]

Conclusion

In the light of the review, oral lichen planus is still considered to be a chronic variant of lichen planus that needs treatment in the long run and a constant observation. Even with various studies and awareness regarding OLP, there is still at present doubts in relation to this disease. With that in mind, more emphasis should be given to trials and studies in order to determine more clinical features as well as treatments plans that can be implemented for a better form of therapy option.

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