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Oral Lichen Planus of The Past, Present and Future: A Scoping Review of the Genetic End of Clinical Presentation and Prognosis

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KEYWORDS

Oral lichen planus, Desmocollin , MMP, Tumour suppressor gene, Caspase, TEGF, Interleukin 2

ABSTRACT:

Introduction: Innate immune mechanisms have acquired the limelight owing to their contribution to the pathogenesis of autoimmune disorders. Another significant concept is that of quantitative thresholds for immune-cell signalling, which states multiple genetic factors of relatively small effect may snowball creating /autoimmune disease activation susceptibility. Lichen planus (LP), a chronic mucocutaneous autoimmune disorder of the stratified squamous epithelium.

Objectives: The genetic basis of the pathogenesis, etiology, clinical manifestation and prognosis demands more clarity.

Methods: A literature search was conducted with keywords such as Oral Lichen Planus, Matrix Metalloproteins 2 (MMP2), Transforming growth factor beta 1(TGFB1), Desmocollin (DCN), Caspase (CASP), Tumor Suppressor Gene (TP53), Tumour Necrosing Factor (TNFα), FAM3B, P53, EGFR and Interleukin 2 (IL2) for peer reviewed articles published in English for OLP.The genetically expressed proteins like MMP, TGFB, DCN,EGFR,TGFR and CASP, predominantly function in the clinical disease manifestation .

Conclusions: The prognosis was attributed to the propensity for malignant transformation was expounded by the dysregulation of TSG, P53 and IL2.

1. Introduction

Adaptive immune system is often at the centre stage in immune based research however, innate immune mechanisms have now acquired the limelight owing to their contribution to the pathogenesis of autoimmune disorders. It is now viewed as being central to the pathogenesis of these disorders. Another significant factor is the concept of quantitative thresholds for immune-cell signalling, which states multiple genetic factors of relatively small effect may snowball creating /autoimmune disease activation susceptibility. Additionally, the surrounding environment and its factors; their interaction with the host are beneficial in unveiling the etiopathogenesis, prevention and management of autoimmune diseases.[1]

Lichen planus (LP), a chronic mucocutaneous autoimmune disorder of the stratified squamous epithelium, affects oral and genital mucous membranes, skin, nails, and scalp.[2] Oral lichen planus (OLP) is the mucosal counterpart and its nomenclature originated from the Greek word “leichen” meaning tree moss and Latin word “planus” meaning flat.[3 To pinpoint and elaborate, an exact etiology is yet unknown. Although many contributing factors are recognised namely; dental materials, drugs, infectious agents (HPV, EBV, HHV, HIV), food allergies, bowel disease, trauma, stress, autoimmunity and malignant neoplasms (Table 1).[4]

2. Objectives

The genetic basis of pathogenesis is two-pronged. Its effect maybe direct (expressed protein and its interaction) or indirect (proteins co-expressing in different conditions). For OLP, 48 genes have been attributed of which 7 have been termed as leader genes (genes with highest strength in expression); namely MMP2, TGFB1, DCN, CASP3, MDM2, TP53 and IL2.[5] MMP2, TGFB1 and DCN are attributed to cellular damage and are hiked in levels OLP. CASP3 and

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MDM2 code for cell cycle and apoptosis. TP53 and IL2 code for potential malignant transformation.[6]

In an article by Zhou Y, Vieira A R, it was reported that -308 G/A polymorphism in TNFα is a potential genetic marker for OLP. Wang et al through their research opined that under-expression of FAM3B was associated with the development and malignancy of OLP and its a potential prognostic biomarker for OLP.[7] Another study by Fangyi et al, attributing genetic mutation to OLP transformation to malignancy found TP53, CELSR1, CASP8, and KMT2D to be most frequently mutated. Additionally, the whole exome sequencing in the study observed TRRAP, OBSCN, LRP2, TENM3 and ASH1L to be mutated.[8]

With these factors in the forefront, this scoping review was initiated with focus on recent findings from genome wide association studies that provide most clarity in terms of OLP disease mechanism implication, novel diagnostic approach and disease progression.

3. Methods

A literature search was conducted with keywords such as Oral Lichen Planus, Matrix Metalloproteins 2 (MMP2), Transforming growth factor beta 1(TGFB1), Desmocollin (DCN), Caspase (CASP), Tumor Suppressor Gene (TP53), Tumour Necrosing Factor (TNFα), FAM3B, P53, EGFR and Interleukin 2 (IL2) for peer reviewed articles published in English for OLP till 30th June 2023 in Medline (PubMed), Ovid, Embase, Scopus, Web of Science, Cochrane search and Google scholar. Articles retrieved from electronic search were manually searched for relative references and cross references. The available articles were then reviewed and assessed for the objective of this research (Image 1).

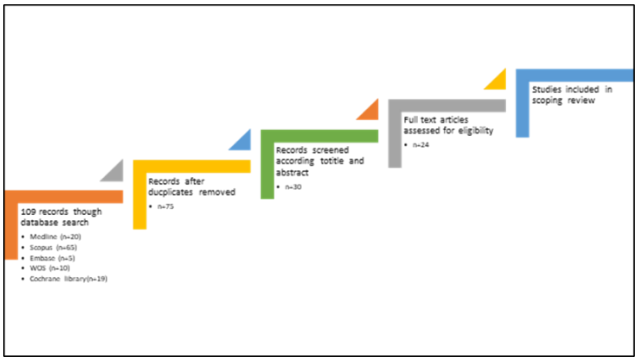

Image 1: Flowchart of search strategy

4. Discussion

Genetic Factors (Table 1 and Table 2)

a.Matrix Metalloproteins (MMPs)

MMPs are a category of zinc-dependent endopeptidases, whose function comprises extracellular matrix and basement membrane digestion. On the basis of substrate specificity, sequence similarity, and domain organization, MMPs are fractionalised as six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs and others. The gelatinases are inclusive of MMP2 and MMP9 proteins.[9] Various studies by Zitka et al, Zhang et al and Paulusová et al have observed altered expression of MMP9 and MMP2 in OLP.[10,11,12] Another study of significance derived a polymorphism at the expression of MMP2 and MMP9 gene; additionally compounding that T allelic substitution resulting in increased transcriptional expression of gelatinase in OLP . Such subjects with nucleotide substitution demonstrated clinical lesions concurrent with that of OLP.[13]

b.Transforming growth factor beta 1(TGFB1)

Transforming growth factor beta 1, is a multifunctional cytokine associated with oncogenesis, immunology and inflammation; it specifically aids in structurally related molecular cell functions namely; differentiation ,proliferation, motility, extracellular matrix production, angiogenesis, apoptosis, and tumorigenesis.[14] In a study by Ghazi et al; all patients with OLP with dysplasia demonstrated TGFB1expression; thereby arriving at the conclusion that chronic inflammation in OLP leads to genetic change whereby the altered expression of TGFB1 induces malignancy.[15] Another study by Danielsson et al. corroborated similar findings of increased TGFB1 expression.[16]

c.Desmocollin

Desmosomes are intermediate filament associated with intercellular junctions playing a major role in cell–cell adhesion, particularly in epithelia. Desmocollin-1 gene and protein expression which codes for desmosomes is altered in the event of dysplasia and in oral squamous cell carcinoma.[17] In a study by Matilla et al. genome bioinformatics demonstrated desmocollin-1; a marker of atrophic OLP at risk of malignancy progression. It was reported that this entity was upregulated during

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dysplasia, thereby decreasing the adhesion among cells. Furthermore, on malignancy development, the expression downregulates and ceases altogether.[18]

d.Tumor Suppressor Gene (TP53)

TP53 is famously known as the gene most frequently mutated in cancer, and its multitude of functions give ample reason for its relevance in cancer development.[19] A recent long standing observational study reported that of 45 OLP subjects, 9 demonstrated TP53 mutation and further malignancy development was noted on follow-up.[20] In another study, of 31 OLP patients, 9 was reported to have TP53 mutation; additionally it was stated that the overall survival declined in patients with positive TP53 protein expression.[21]

e.**Caspase**

Caspase is inflammatory activated in response to pathogenic and endogenous mediators through the formation of inflammatory complexes. They are cysteine-proteases of the interleukin-1bconverting enzyme family, which are required for programmed cell death.[22,23] In a study by Zeng X et al, the upregulation of CASP1 in OLP was reported through intensive and comprehensive bioinformatics analysis which was verified in clinical samples. It was further remarked that the tissue samples demonstrated rise in inflammatory factors (TNF-α, IL-1β, IL-6, and IL-18) and positively correlated with CASP1 demonstrated the upregulation of Caspase in OLP tissues.[24

f.Tumour Necrosing Factor Alpha (TNF-α)

Cytokines contribute immensely to pathogenesis and disease progression of OLP and has been reported so in multiple research publications over the years.[25] The gene polymorphisms of T-helper cell subtype Th1/Th2 cytokines, tumor necrosis factor (TNF)-α, and interleukin-10 (IL-10) have been reported to affect the susceptibility to, and the progression of OLP.[26] Chauhan, et al. further compounded that proinflammatory cytokines are an important factor in understanding the disease burden of OLP and their comorbid factors.[27] In studies by Al-Mohaya MA and Jin X; further evidence was reported in stating that TNF-α polymerism in allele demonstrated a subject to being at higher risk of OLP development and a proportional risk in its malignant transformation.[28]

g.FAM3B

FAM3B is a 235-amino-acid protein belonging to 3 (FAM3) gene criterion. It is encountered in the β-cells of islets and is in tandem with insulin granules pertaining to its amount of expression. Therefore, it can be proportionally regulated through glucose levels. [29] In a study by Wang et al. FAM3B was under-expressed in OLP compared with normal samples and was further significantly downregulated in OSCC compared with OLP. It was thus inferred that under-expression of FAM3B correlated with tumour stage and disease-specific survival (DSS), progression-free interval (PFI) and overall survival(OS) of OSCC patients.[30]

h.P53

p53 also called the “Guardian of genome” is a tumour suppressor protein controlling; cell cycle and apoptosis. In short, it functions to contain the proliferation and thereby prevent cancer. In normal functioning cells, the p53 protein level is low and is unregulated in response to DNA damage, hypoxia, oncogenes and other stress signals. [31] In studies by Mihailovic M et al, Sagari S et al, Bowen AR et al and Sousa FA et al, it was observed that 80% of OLP specimens were positive for p53 staining at the keratinocyte level. The intensity of the staining was corroborative of the type of OLP and the level of inflammation.[32,33,34,35]

i.EGFR

The proto-oncogene epidermal growth factor receptor (EGFR), is a tyrosine kinase growth factor receptor. EGFR gene has been noted to be amplified in various human tumours.[36] In a study by Kumagai et al. a significantly higher level of EGFR expression was in OLP tissues. Additionally, it was of note that the expression was localised to spinous layers of epithelium whereas in normal tissues it is observed in the basal layers.[37] An identical finding was reported by Zhao M et al as well wherein the stronger expression was noted in erosive and ulcerative lesions.[38]

j.IL2

T helper cells 1 (Th1) is predominantly associated with the expression of Interleukin 2 (IL2); in turn associated with cell mediated immunity. In the event of Th2 imbalance as in a dominant response; it often results in cell mediated or autoimmune disorders.[39] In research by

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F.N. Pekiner et al. it was reported that the IL2 levels in serum where curtailed and a simultaneous increase in IL10 response. The inference thus derived was that in the event of Th2 dominant response, OLP was a possible autoimmune disorder.[40]

Conclusion

In this scoping review, the authors ascertained that genetic factors are indeed indicative of clinical inflammatory staging of OLP and its progression to malignancy. This translates as the ability to foresee the prognosis and mitigate the mortality by alternative management protocol. The genetically expressed proteins like MMP, TGFB, DCN and CASP, predominantly function in the clinical manifestation of OLP in the initial stages. The Wickham's striae caused due to increased cell proliferation which was attributed to EGFR and TGFR upregulation. The atrophy and the surrounding areas of erythematous inflammation was explained by the upregulation of CASP, FAM3B, TNFα and DCN. Furthermore, the propensity for malignant transformation was expounded by the dysregulation of TSG, P53 and IL2. The questions raised by the authors at the outset were revealed to be relevant and answered by the findings that a genetic component to the clinical manifestation and prognosis of OLP. These findings were a reaffirmation of Zhong EF et al and Xie at al 8. However, despite the deep-rooted search, the genetic factor initiating the noxious autoimmune inflammatory reaction and resulting in the above cascade of genetic expression changes could not be pin down. A meta-analysis of the above findings was not feasible on contemplating the heterogenicity of the reported researches. The authors suggest a genetic evaluation of long-standing cases for prognosis evaluation at regular intervals; especially in the event of concurrent etiologic factors in the subjects. The evaluation would also be protective against a malignant change.

Conflict of interest

The authors declare no conflict of interest

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Table 1: Etiology of OLP

Sl no:	Etiology	Sub Factors
1	Virus[45]	1. Varicella-Zoster Virus (VZV) 2. Epstein Barr Virus (EBV) 3. Human Herpes Virus (HHV-6 &7) 4. Hepatitis C Virus (HCV) 5. Human Papilloma Virus (HPV)

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2	Systemic Diseases [46,47]	1.Hypertension, 2.Dyslipidemia, 3.Thyroid Dysfunction, 4.Liver Dysfunction 5.Cholecystitis.
3	Autoimmune Disorders[47]	1.Diabetes Mellitus Type I 2.Sjogren's Syndrome 3.Systemic Lupus Erythematosus 4.Multiple Sclerosis, 5.Celiac Disease, 6.Ulcerative Colitis, 7. Hashimoto's Thyroiditis
4	Nutritional Factors[48,49]	1.Vitamin B12, A, E, C, D 2.Haemoglobin 3.Iron 4.Folic Acid
5	Genetic Polymorphisms [13-40]	1.Matrix Metalloproteins (MMP) 2.Transforming Growth Factor Beta 1(TGFB1) 3.Desmocollin (DCN) 4.Tumor Suppressor Gene (TP53) 5.Caspase (CASP) 6.Tumour Necrosing Factor Alpha (TNF-A) 7.FAM3B 8.P53 9.EGFR 10.IL2
6	Psychological Stress [50]	1.Physical 2.Emotional
7	Medications[50]	1.Angiotensin-Converting Enzyme (ACE) Inhibitors 2.Antibiotics 3. Anticonvulsants 4. Antifungals 5. Antimalarials 6. Antipsychotic 7. Antituberculosis Drugs 8.NSAIDS

Table 2: Mechanism of action of the genetic factors

	Factor	Function	Mechanism of action
1	Matrix Metalloproteins[10-13]	Secretes various enzymes like collagenases, gelatinases etc	Dysregulation in the levels of MMP2 causes increased basement membrane degeneration and thus OLP like lesions.[13]
2	Transforming growth factor beta 1[14-16]	Differentiation Proliferation	An inflammation related cytokine, increased expression results in onset and

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		Motility Extracellular matrix production Angiogenesis Apoptosis Tumorigenesis	development of OLP. It induces the alteration of cell functions, increased vascularity and has the propensity to induce malignancy. [42]
3	Desmocollin[17,18]	Cell to cell adhesion	Downregulation in keratinising mucosa leading to inadequate seal between cells and accelerated progression to malignancy[18]
4	Caspase[22-24]	Programme cell death	Extrinsic and intrinsic pathway initiate cleaving of cell substrates leading to cell death.[43]
6	Tumour Suppressor Gene P53[19-21]	1.Controls cell progress in cell cycle and growth 2.Maintains integrity of genome	In OLP patients, when the TP53 is mutated, they result in unchecked growth of cells resulting in malignancy.[20]
8	Tumour Necrosing Factor α [25-27]	1.Stimulate fibroblast growth 2.Diseased cell death at inflammation site	Activation of innate immunity causes the increased expression of TNF α which in turn results in progression of OLP to higher stages.[44]
9	FAM3B[29,30]	Metabolic signalling	This protein is elevated in conditions of elevated T cells and other cells like B cells, Natural Killer cells etc. In OLP, this protein is elevated and is further upregulated in malignancy. Thus, this is a biomarker for OLP progression to malignancy. [30]
10	EGFR[36-38]	Cell proliferation	Binding of the protein to a ligand leads to cell proliferation. In tissues subjected to OLP, elevation demonstrated the increased cell proliferation pertaining to keratinocytes.[36]
11	IL2[39,40]	1.Cell to cell adhesion 2.Cell growth	The protein encoded by this gene is a secreted cytokine vital for the proliferation of T and B lymphocytes. This gene encodes the integrin beta 4 subunit, a receptor for the laminins. This subunit is likely to play a pivotal role in the biology of invasive carcinoma