How to Cite:
Vijayan, A. K., & Muthukrishnan, A. (2022). p53 Polymorphism in Oral Lichen Planus: A comprehensive review. *International Journal of Health Sciences*, *6*(S5), 7733–7744. https://doi.org/10.53730/ijhs.v6nS5.10441

p53 Polymorphism in Oral Lichen Planus: A comprehensive review

Dr Aswathy K. Vijayan
Reader, Department of Oral Medicine and Radiology, PMS College of Dental Science and Research, Vattapara, Thiruvananthapuram, India
Corresponding author email: aswathykvijayan4@gmail.com

Dr Arvind Muthukrishnan
Professor and Head, Department Of Oral Medicine and Radiology, Saveetha Dental College and Hospital, Saveetha Institute Of Medical and Technical Sciences, Saveetha University, Chennai, India
Email: arvindmuthukrishnan@yahoo.com

Corresponding Author
Dr Aswathy K.Vijayan, Department of Oral Medicine and Radiology, PMS College of Dental Science and Research, Vattapara, Thiruvananthapuram-695028, Kerala
Email: aswathykvijayan4@gmail.com

***Abstract*---**Oral lichen planus (OLP) is a chronic relapsing inflammatory disease. It involves T-lymphocyte aggression targeted to the basal layer of the oral mucosa.p53 plays a central role in the prevention of normal cells from the development of the malignant phenotype. Somatic alterations in p53 cause defects in normal p53 function. Wild type p53 plays an important role in repairable damage of the cell due to cellular stresses. Over-expression, as well as polymorphic variants of Mouse double minute 2(MDM2), have effects on p53 disturbances. In addition, degradation of p53 by E6 protein of high-risk human papillomavirus is also suggested as one of the mechanisms which attenuate p53 responses in oral carcinogenesis. Polymorphisms in *p53* are anticipated to cause measurable disturbance in p53 function. Polymorphism of the codon 72 on exon 4 of the gene *p53* is the first and most commonly known polymorphism of this gene. The presence of p53 has been demonstrated as an early marker of dysplasia in Oral Potentially Malignant Disorders. This review discusses about p53 polymorphism as an early indicator of genetic predisposition to neoplastic transformation in OLP.

***Keywords*---**Oral lichen planus (OLP), gene p53, Polymorphism.

Introduction

Oral lichen planus (OLP) is a relatively common chronic disease of oral mucosa affecting mainly the middle-aged and elderly.[1]Lesions can appear anywhere in the oral cavity but are more common on the buccal mucosa, gingiva and lateral borders of the tongue, almost always in a bilateral fashion.[1,2]The pathogenesis of OLP is not clear.[3]There is strong evidence that the mechanism leading to basal cell damage is a cell-mediated immune process involving T lymphocytes with cytotoxic activity against the epithelial cell.[3,4] The diagnosis of OLP should be based on the modified World Health Organisation(WHO) criteria proposed by Van der Meij and Van der Waal in 2003.[5]OLP has a documented risk for malignant transformation. The reported annual malignant transformation rates vary between 0.4% and 5.6%.[6] Lichenoid dysplasia is the term coined by Krutchkoff and Eisenberg to describe lesions that resemble OLP but are dysplastic.[7] Malignant transformation into oral squamous cell carcinoma (OSCC) is considered one of the most serious complications of OLP. The malignant transformation of OLP is not fully understood.[8]

Molecular markers offer the possibility to identify cases with potentially malignant lesions. These changes can be detected before malignant cells are detectable histologically.[8]Numerous potential markers have been identified and their associations with early detection, progression and prognosis of oral potentially malignant disorders (OPMDs) have also been discussed.[8]Various factors resulting in molecular alterations seem to be involved in the progression of malignant transformation.[9]Currently, there are no prognostic markers to identify which chronic OLP lesions are at a higher risk for malignant transformation.[8,9] Every OLP patient should be monitored carefully to detect early cancer development. To understand the etiopathogenesis of OLP, it is important to recognize the key molecules in it.[10]Molecular alterations in OLP samples might represent useful biomarkers for predicting and monitoring malignant progression. There are molecules which may be ominous predictors of OLP malignant transformation.[11]

P53 Family

P53 gene is a tumour suppressor gene. It is located on the short arm of chromosome 17 (17p13.1) and has 11 exons. The p53 protein is comprised of 393 amino acids. It is divided into five domains with each domain having a different structure and function.[12]The most important role of p53 is to integrate signals emerging from a wide range of cellular stresses due to environmental carcinogen exposure.[13] p53 induces adaptive and protective cellular responses by triggering the transcription of specific genes. This prevents cell proliferation, by inducing growth arrest at the stage of the cell cycle followed by DNA damage or apoptosis if the damage is not repairable. Thus, it preserves the integrity of the genome. These functions of p53 make this protein the “guardian of the genome”.[13,14]

Disturbance in the p53 is a frequent event in cancerous tumours. Somatic mutations with single-base substitutions, followed by loss of heterozygosity(LOH), deletion at the 17p13.1 locus of the *TP53* gene, polymorphisms in the *p53* gene and activated mouse double minute 2(MDM2) are expected to be associated with cancer risk by compromising the normal activities of p53.[15]Together, all of the

above-mentioned mechanisms lead to alterations in p53 responses in the cancer cell(Figure 1).[15,16,17]

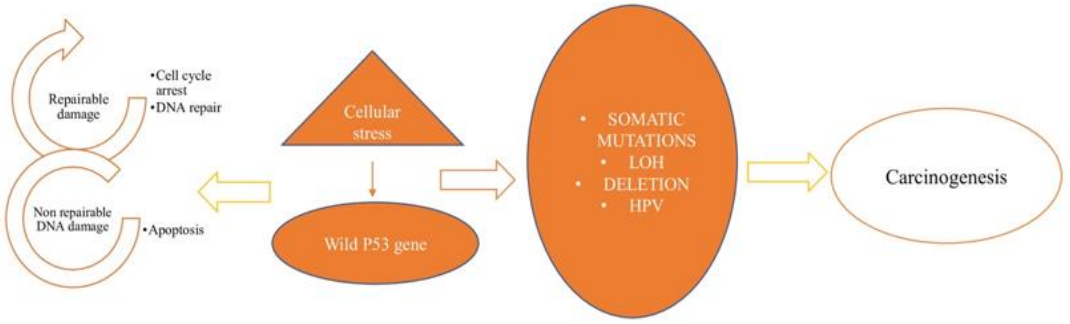

Fig. 1. Mechanisms that lead to alteration in p53 responses

p63 and p73 belong to the p53 family, having roles in embryogenesis and cell differentiation. p63 and p73 exhibit functions similar to p53.They are involved in the removal of damaged cells and induction of apoptosis.p73 can substitute its function to a certain extent when the p53 gene is mutated. There are few studies on the role of p73 in OLP.[18,19] The increased expression of p73 was observed in samples of the dysplastic oral mucosa, irrespective of the degree of dysplasia, compared to normal mucosa. [20] p63 gene encodes proteins with an essential role in the development of oral mucosa, salivary glands, teeth, and skin.[21] Antibodies against p63 and p73 were detected in sera of OLP patients. This gives speculation that there might be a positive correlation with the duration and severity of the disease.[19,21]

Stability control of p53

The expression level of p53 is dependent on a balance between protein production and degradation.[22] The steady-state expression level of the endogenous p53 is maintained at an extremely low level.[23]p53 is rapidly induced at the protein level in response to a variety of cellular stresses such as DNA damage.[24] The proteolytic degradation of p53 was mediated by the physical interaction between p53 and oncogenic Mouse double minute 2(MDM2). MDM2 bound to NH_2-terminal transactivation domain of p53, targeting p53 for proteasome-dependent degradation.[25]This results in inhibition of the transcriptional activity of p53. The induction and activation of p53 in response to cellular stresses have been shown to be largely regulated at the posttranslational level through multiple mechanisms.[22,23] p53 is largely regulated at the protein level through chemical modifications such as phosphorylation and acetylation.[23]

MDM2 and its association with p53

MDM2 is a key negative regulator of p53 activity.[26] The levels of p53 in the normal cell are tightly controlled. MDM2 protein encoded by the mouse double minute 2 gene can ligate the p53 protein through its E3 ubiquitin ligase.[27]The

ubiquitinated p53 can be transferred to the cytoplasm and degraded by proteasomes.[28] Studies have reported that MDM2 transgenic mice expressing higher levels of MDM2 in various tissues, develop spontaneous tumours compared to non-transgenic mice.[29] It has been reported that one intronic polymorphism (T>G) of MDM2 may result in higher MDM2 mRNA and protein levels.[30] However MDM2 polymorphism could not independently modify the risk of polymorphism. Thus, the presence of this polymorphism may attenuate the p53 responses, thus increasing cancer susceptibility.[28,30]

HPV and its association with p53 protein

Human papillomavirus is a small, nonenveloped, double-stranded, circular DNA virus with a diameter of 52–55 nm.[31] The participation of HPV in oral carcinogenesis was first proposed by Syrjanen *et al.* in 1983.[32]The different HPV types are characterized by genotypic variations in the DNA base sequences of E6 and E7. It is these genotypic differences that permit stratification of the virus oncogenic phenotype into high and low-risk types. High risk includes HPV-16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59 and low risk are HPV 6, 11, 42, 43, 44.The molecular mechanisms by which HPVs disrupt key cellular elements responsible for cell cycle regulation and apoptosis have been identified.[33,34]Degradation of p53 by the E6 protein of HR-HPV is also one of the mechanisms by which the normal function of p53 is altered in HPV-associated oral carcinogenesis.[35]The cells that contain damaged DNA enter aberrantly into mitosis, sustain proliferative ability and may eventually contribute to the propagation of structural chromosomal abnormalities in HR-HPV-associated cancer.[36]

Various investigators have reported the prevalence of HPV infection in OLP worldwide.[37]However, results show large variations from low prevalence to high prevalence.[37]Several reports from Asia found high HPV infection in OLP.[38,39]There are various theories explaining the role of HPV in the pathogenesis of OLP and its malignant transformation.[40] OLP is accepted to be a T-cell-mediated inflammatory disease. The HPV seems to act as a cytoplasmic antigen thereby inducing a different host cell protein profile.[40]Various Case-control studies have been done, exploring the possibility of viral involvement in the pathogenesis of OLP is improving.[37,40]

There are large regional and time trend variations in prevalence rates of HPV in OLP.[41]The prevalence of HR-HPV type 16 and 18 infections in OLP varies widely across the different geographical regions of India.[37]The prevalence of high-risk HPV infection in OLP is reported to vary from 0% to 80%.[42] HPV prevalence is higher in Asia and Africa and less in the northern and eastern sides.[38,39,43,44]

Oral lichen planus and P53 Polymorphism

Several sequence variations are present in the p53 gene.[13]The International Agency for Research on Cancer (IARC) TP53 mutation database lists 29 common polymorphisms in the non-coding region of TP53.[45]Most of these variations are intronic and have no cancer-related biological consequences.[46] Polymorphism of the codon 72 on exon 4 of the gene p53 is the first and most commonly known polymorphism of this gene.[46] In this polymorphism arginine (CGC) is converted to

proline (CCC) in the protein sequence. It has been suggested that two alleles of codon 72 have different carcinogenic properties.[47] Dumont et al. reported that tumours containing the Arg form can localise to the mitochondria and release cytochrome c into the cytosol, inducing apoptosis markedly better than those of the pro-form. p53-codon72-Arg is more efficiently translocated to the mitochondria, interacting with proapoptotic proteins such as GRP75 and Hsp60, thereby triggering apoptosis.[48]

p53 protein harbouring the Arg allele was more susceptible to degradation by HPV E6 protein and had a significantly higher frequency of *p53* mutations.[46]Several studies have been done to examine the possible role of p53 codon 72 exon 4 polymorphism in HPV-associated cervical carcinomas in India. Storey et al. reported that a specific p53 allele polymorphism makes women genetically highly susceptible to developing cervical cancer if infected with the high-risk HPV types 16/18. They revealed that a higher prevalence of arginine genotypes makes the p53 highly susceptible to HPV E6- mediated proteolytic degradation in vivo. Caucasian women carried a high frequency of p53-Arg homozygous alleles. They were at risk of developing HPV-induced cervical cancer about seven times more than those with Pro/ Arg heterozygotes. However, the authors reached this conclusion by comparing the prevalence of p53 arginine homozygous alleles between only two study groups i.e. HPV positive cervical cancers and HPV-negative healthy normal controls.[49] Contrary to this Katiyar S et al. have tested this hypothesis in the Indian population by screening the *p53* genotypes in cervical, oral and breast cancer in three categories of subjects including carcinomas positive for high-risk HPV types 16 and 18, carcinomas negative for HPV 16/ 18 and HPV negative healthy control women. The study detected no significant difference in the prevalence of p53-Arg/Pro alleles between HPV-positive and HPV-negative cancer patients or controls.[50]

Moreover, it was also reported that there is a tissue-specific influence of Arg72Pro polymorphism on apoptosis.[51] Hu et al. observed that the Pro form of the p53 gene has significantly higher levels of apoptosis compared to the Arg form in primary lymphocytes.[52]Moreover, the Arg form of the p53 gene was associated with poor apoptosis in head and neck tumours. Such tissue-specific function of this polymorphism may explain why most epidemiological studies remain inconclusive.[51,52]

Three genotypes that were found in codon 72 exon 4 of p53 were G/G, C/C, and G/C. In p53 codon72 polymorphism, the wild-type genotype is (G/G) and the variants are (G/C) and (C/C).[53] This indicates that the homozygous genotype GG may be related to a lower risk of developing OC, while the heterozygous genotype and the homozygous genotype C/C would be related to a higher risk of cancer or OPMD.[53,54] This could be because the Pro72 variant is less efficient in suppressing cell transformation, slower to induce apoptosis, and less efficient at binding and inactivating p73, which is a tumour suppressor protein responsible for apoptosis.[13,53,54]

Several authors reported that the distribution of arginine, proline homozygotes and pro/arg heterozygotes fit the Hardy-Weinberg equilibrium.[55]This is a principle based on both gene and genotype frequencies that remain constant

between generations in a population with infinitely broad interbreeding in which mating occurs randomly, and there is no selection, migration, or mutation.[55]

Studies in OLP have shown some degrees of polymorphism and mutation in the p53 gene, especially in women.[56] In addition, some studies have shown apoptosis in lichen planus due to the expression of p53 protein.[57] Various studies from Iran observed a significant association of Arg72Pro polymorphism with OLP.[58] Further, it was suggested that the association of Arg72Pro polymorphism with OLP was modulated by ethnicity and allelic frequency. There is a clear trend in the distribution of codon 72 polymorphic alleles, and a correlation between the presence of the GG genotype and distance from the Equator. This could be due to ethnic variation or because of the fact that the frequency of the arginine allele increases with distance from the equator.[58]

Pro/Pro genotype was observed with the highest frequency in Oral lichen planus in the Iranian population.[56] Heterozygous genotype (Arg/Pro) exhibited the highest frequency, in the Thailand population.[59] A high rate of mutation in OLP was found in the Iceland population which is an indication of the premalignant nature of this lesion.[60] On the contrary, in a study by Ghapanchi et al. no significant differences were found in the polymorphism of codon 72 of the p53 gene between the OLP and control group.[61]

In nutshell, it can be suggested that patient populations can be stratified and studied by incorporating information on the inherited genetic polymorphisms of the p53 pathway along with the somatic mutations in p53.[55] Genetic polymorphisms either in the p53 gene or in the MDM2 gene or HPV infection can attenuate p53 response that even remained as wild type.[21] Thus, a comprehensive analysis of all the mechanisms by which p53 response is attenuated in oral lichen planus is very essential to improve our understanding of the malignant transformation of OLP. No conclusive study reports are there at present to justify the relevance of the observed imbalance between p53 and the possible malignant transformation of OLP.[62]

Influence of method used for analysis

There is a wide array of assays used for the detection of p53 polymorphism in OLP samples including Polymerase chain reaction (PCR) and Immunohistochemistry (IHC). Several studies have been undertaken to evaluate the malignant potential of OLP by evaluation of p53 mutations with the use of IHC.[57,58]

The wild type of p53 has a short half-life in the normal tissue. The normal or the wild-type p53 has a half-life of 6 to 20 minutes.[63]The normal p53 cannot be detected by immunohistochemistry in such minute quantities. But when the p53 gene is mutated there is excessive production of altered p53 protein. The mutated p53 gene has a long half-life of 6 hours and thus can be detected by immunohistochemical technique.[64]However, it should be pointed out that in IHC evaluation, excessive expression of *p53* protein in OLP might be due to the presence of inflammatory mediators in the connective tissue. There might be no direct relationship with the mutation in the genome, which might be considered

one of the disadvantages of the IHC technique for the evaluation of mutations.[64,65]

The immunopositivity of p53 expression in OLP ranged from 18% to 100%.[66]The expression of p53 protein in the basal layer in oral mucosa may be due to the wild-type protein induced by environmental factors that occur commonly in the oral cavity.[67,68,69]This phenomenon might be protective allowing keratinocytes to repair damaged DNA. OLP cases exhibit p53 expression in suprabasal cells. This is more suggestive of a mutant p53 showing the presence of cells with DNA damage in more superficial layers of the epithelium, rather than cross-reactivity with wild-type.[68,69,70]

Several studies compared IHC and PCR to evaluate whether immunohistochemical staining for p53 can be useful as an early indicator of genetic predisposition to neoplastic transformation in OLP. p53 immunostaining and the single-strand conformational polymorphism (SSCP) technique for *p53* gene mutations were studied by Shifter et al.[57]They found a discrepancy between the two methods, as p53-positive cases did not show mutations, and concluded that p53 immunohistochemical overexpression may imply a physiological and anti-mutagenesis protective response. However, Valente et al observed that immunohistochemical staining for p53 can be useful as an early indicator of genetic predisposition to neoplastic transformation in OLP.[71]

In general, a hypothesis that can be presented in relation to the premalignant nature of OLP is that the proline allele has a lower potential to induce apoptosis compared to arginine.[46]Since degeneration of keratinocytes in lichen planus is a result of apoptosis, despite polymorphism of arginine compared to proline, less apoptosis takes place, which paves the way for excessive proliferation and malignant transformation of lichen planus.[46,59,72]

Conclusion

p53 plays an important role in the regulation of cell fate determination in response to a variety of cellular stresses. P53 codon 72 polymorphism is one of the genetic risk factors for OLP. This polymorphism may be useful as one of the genetic markers for predicting the occurrence of this disease. Dysfunction of p53 such as mutational inactivation allows the abnormal cell growth and finally results in the malignant transformation. Mutant forms of p53 lack their proapoptotic function and display a dominant-negative behaviour toward wild-type p53. Ethnicity has been suggested to be a critical factor in determining the effects of different TP53Arg72Pro polymorphisms or mutations. The same SNP may play different roles in the development of cancer in different ethnic populations. These variations may be due to racial and geographic differences, as well as to a variety of other factors such as the risk of HPV viruses. Therefore, patients with OLP lesions require accurate and constant follow-ups to prevent malignant transformations and diagnose and treat even minor changes in the oral lesions at early stages.

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