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Commentary

Role of Endoplasmic Reticulum Stress in Vitiligo Pathogenesis

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DESCRIPTION

Vitiligo, one of the most common pigmentory disorders, usually starts in childhood or young adulthood and the clinical manifestation begins before 20 years of age in 50% of cases, while in 25% of cases, the onset is before the age of 14 years. Our previous study revealed that 21.93% of Gujarat vitiligo patients exhibited positive family history and 13.68% of patients had at least one affected first-degree relative. Large scale epidemiological studies have reported that about 15%-20% of patients has one or more relatives with vitiligo and similar concordance has been observed in identical twins. Though the exact mechanism underlying the loss of melanocyte in vitiligo is not clear, the advanced research in the past few years has added significantly to understand the disease pathology. Several theories have been put forward to explain the etiology of the disease such as oxidative stress, autoimmune, neurochemical and genetic hypotheses. Studies have revealed that vitiligo is a complex, multifactorial and polygenic disorder. The complex genetics of vitiligo involves multiple susceptibility loci, incomplete penetrance and genetic heterogeneity with gene-gene and gene-environment interactions. It has been reported that out of the total risk of vitiligo, 20% attributes to environmental factors, 57% to common genetic variants, and 23% to rare genetic variants.

Proteasome Subunit Beta 8 (PSMB8) and Transporter Associated with Antigen Processing 1 (TAP1)

Generation of antigenic peptides and their transport across the Endoplasmic Reticulum (ER) membrane for assembly with Major Histocompatibility Complex (MHC) class I molecules are essential steps in antigen presentation to cytotoxic T lymphocytes. Proteasome Subunit Beta 8 (PSMB8) and Transporter associated with Antigen Processing 1 (TAP1) have been reported to be associated with several autoimmune diseases including vitiligo. The PSMB8, often referred to as LMP7, encodes for Interferon-Gamma (IFN-γ) inducible subunit of immune proteasome, i.e. β5i involved in the degradation of ubiquitined intracellular proteins into peptides that are especially suited for presentation by MHC class I molecules. Whereas, TAP1 encodes the subunit of an IFN-γ inducible heterodimer, which binds with peptides cleaved by the proteasome and transports them to be loaded into nascent MHC class I molecules for its presentation to CD8+ T cells. The Genome-Wide Association Study (GWAS) in generalized vitiligo patients revealed that the association of TAP1-PSMB8 might have derived from linkage disequilibrium with major primary signals in the MHC class I and class II regions.

Methylenetetrahydrofolate Reductase (MTHFR)

Several studies have reported increased homocysteine and reduced vitamin B12 and folic acid levels in vitiligo patients. Methylene Tetrahydrofolate Reductase (MTHFR) is an essential regulatory enzyme involved in the conversion of homocysteine to methionine. It catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The human *MTHFR* gene is located at chromosome 1p363 and consists of 11 exons and 10 introns. Polymorphisms of *MTHFR*, i.e. exon 4 C/T and exon 7 A/C result in decreased activity of MTHFR enzyme and affect homocysteine levels. These two polymorphisms of *MTHFR* were reported to be associated with several diseases including vitiligo.

X-box Binding Protein 1 (XBP1)

X-box binding protein-1 is a transcription factor, encoded by the *XBP1* gene located on chromosome 22. The XBP1 regulates the expression of genes necessary for the proper functioning of the immune system and in the cellular stress response. XBP1 is involved in the downstream of Inositol Requiring Enzyme-1 (IRE1) activation in the Unfolded Protein Response (UPR) mechanism. Apart from its known role in UPR, XBP1 is also involved in the regulation of plasma cell differentiation and immunity. IRE1 oligomerizes and activates its ribonuclease domain through auto-phosphorylation. Activated IRE1 leads to the non-canonical splicing of a 26-nucleotide sequence from ubiquitously expressed XBP1 mRNA (unspliced). Removal of this intron causes a frameshift in the XBP1 mRNA coding

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sequence resulting in the translation of a 376 amino acid polypeptide i.e. spliced XBP1 (sXBP1) isoform rather than the 261 amino acid polypeptide, unspliced XBP1 (uXBP1) isoform.

The sXBP1 is an active transcription factor that up regulates target genes *via* the ER Stress-Responsive Element (ERSE) region. XBP1-116 G/C polymorphism is located in the promoter of the *XBP1* gene affecting its promoter activity. XBP1-116 G/C promoter polymorphism was found to be associated with diabetes, inflammatory bowel disease and bipolar disorder.

Interleukin-17A (IL17A)

IL-17A is a disulfide-linked homodimeric pro-inflammatory cytokine produced by Th17 cells, which form a distinct subset of the CD4+ T-cell lineage. It plays a major role in psoriasis and over recent years, has garnered interest of many researchers due to its association with several autoimmune disorders. The involvement of Th17 cells has also been reported in autoimmune skin inflammatory disorders such as psoriasis and atopic dermatitis. A previous study has reported that elevated IL17 levels in lesional skin and serum of vitiligo patients. Another study showed a positive correlation between serum IL-17A levels and the extent of the depigmentation patch area in vitiligo, suggesting that Th17 cells are involved in the progression of vitiligo. Interestingly, it was found that IL17A can stimulate the keratinocytes and fibroblasts to secrete TNF-α. The *IL17A* gene is located on chromosome 6, spanning a region of 4252 bp.

Tyrosinase (TYR)

Tyrosinase is present inside the melanosomes and it is a key enzyme involved in melanogenesis. The enzyme is mainly involved in two distinct reactions of melanin synthesis:

- The hydroxylation of a mono-phenol and,
- The conversion of an o-diphenol to the corresponding o-quinone. The o-quinone undergoes several reactions to eventually form melanin pigment. Interestingly, tyrosinase is also identified as a principal autoantigen in vitiligo.

CONCLUSION

Currently, more than 50 vitiligo susceptibility loci have been identified in Caucasian population. Nevertheless, several vitiligo susceptibility loci in the genes involved in immunoregulation (*CTLA4, NLRP1, MYG1, ICAM1, HLA*), cytokines (*TNFA, TNFB, IL4, IFNG, IL1B, IL1RN*) and redox homeostasis (*SOD, CAT, GPX1, G6PD*) have been identified as susceptibility loci for vitiligo in Gujarat population. Genetic polymorphisms might influence gene expression or protein function and thereby predispose individuals to deregulation of the normal homeostasis leading to the onset of the disease. Based on the literature study, role of the following genes polymorphisms has been explored in the present study.