Abstract

Vitiligo is a depigmenting skin disorder characterized by circumscribed macules in the skin resulting from the loss of functional melanocytes. It is a complex disorder, involving genetic predisposition and a number of potential precipitating factors such as oxidative stress, autoimmunity and neurochemical factors in its pathogenesis. Oxidative stress causes disruption of cellular redox potential that extends to the endoplasmic reticulum (ER), causing accumulation of misfolded proteins, which activates the unfolded protein response (UPR). Earlier studies have reported dilated ER in the melanocytes at the periphery of vitiligo lesions suggesting involvement of ER stress in vitiligo pathogenesis. In the present study, we have explored the role of selected polymorphisms of genes involved in ER stress, immuno-regulatory mechanisms and melanogenesis; and also examined the role of homocysteine (Hcy) induced ER stress in *in-vitro* cultured normal human melanocytes (NHM). Our population based studies identified proteasome subunit beta 8 (*PSMB8)* rs2071627, methylenetetrahydrofolate reductase *(MTHFR)* rs1801131, X-box binding protein-1 *(XBP1)* rs2269577 and tyrosinase *(TYR)* rs1126809 polymorphisms as genetic susceptibility loci, altered *PSMB8, XBP1, IL17A* expression, and elevated anti-tyrosinase autoantibodies in vitiligo patients of Gujarat population. Further, we observed significantly elevated homocysteine and decreased vitamin B_{12} levels in vitiligo patients. Our *in-vitro* studies in NHM revealed that homocysteine induced oxidative stress, ER stress and activation of UPR signalling further lead to apoptosis. We also observed inhibition of melanogenesis, significant increase in the expression of pro-inflammatory cytokines *IL6, TNFA* and *IFNG* and decreased expression of anti-inflammatory cytokine *IL10* in NHM upon homocysteine treatment. Over all the findings of present study suggest that *PSMB8, MTHFR, XBP1* and *TYR* polymorphisms along with elevated homocysteine levels might cause genetic susceptibility towards vitiligo. Further, homocysteine in addition to other triggering factors might lead to ER stress mediated melanocyte destruction in vitiligo.