Review Article

Modification in Gene Expression of CCR5 Co-Receptor and Down Regulation of Virion Molecule with Primary Human T- cell in HIV Infection

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Abstract:

About 1 2% of population in western European white people are resistant to hiv-1 infection due to modified gene of ccr5 receptor molecule. Modification of ccr5 receptor gene blocks the virion molecule to enter into the host cell. Mutations gene lead to slow progress rate of infection and low expression of cd4 + T cell. The hypothesis of researcher is that the modified allogeneic transplant with modified M303/M303 gene in ccr5 leads to resistant for HIV and AIDS patient. Deletion of gene in ccr5 receptor develops the ability of resistant with HIV-1. Down regulation of ccr5 receptor with macrophages T cell reduce the immune response and lead to slow progressive rate of infection. Different gene-editing methods are involved in ccr5 gene editing such as TALEN, ZFN, and CRISP/Cas. Mutant gene transplant in ccr5 receptor prevent the further exposure of dangerous retrovirus. As comparison of heterogeneous and homogenous .The heterogeneous analogues has more resistance as compare to homogenous genetic order. Chemokine and inflammatory mediator are the less active in heterogeneous. The homozygous mutation in ccr5 gene (ccr5Δ32) base pair deletion induces non-functional ccr5 receptor and heterogonous mutation has resistant of HIV 1 and slow progressive effect.

Keywords: Modification, CCR5 co-receptor, Downregulation, CD4+ cell, Mutation, Deletion, Heterozygotes, Chemokine

Introduction:

Ccr5 is chemokine receptor co- receptor which facilitate or HIV entry into CD4 + t -cell and also interact with various hematopoietic cell which induce the loss of CD4+ cell and progression of severity of HIV complication [1]. CD4+, ccr5 and cxcr4 are not only the receptor it has unique feature on the level of the physiological system which has roll in in in signaling transduction in host cell. Expression of ccr5 receptor with host cell involved

in entry of genome material into the host cell molecules which influence the stability of infection and rate of disease progress. CBR5 has Mabs transfecting unit it which has ability to non-reactivity with T-cell from (Δ32/ Δ32) individual [2]. Expression of loci in ccr5 receptor Δ32 heterozygotes has low level of expression in individual host which decrease the expressions of ccr5 as compared to the normal heterozygotes. Variability in expression of individual to individual difference from each other ccr5 receptor genetic coding material. Interaction of the membrane of host and expression of ccr5 on T-cell which macrophages tropic hiv-1 infection of PBMC macrophages tropic hiv-1. Anti ccr5 MABS inhibited the infection of macrophage tropic but doesn't with T-cell tropic. The chemokine receptor migrate tissue which different expression of ccr5 molecule for different immune response has different primary genome of ccr3, exotoxin receptor are responsible for progress of infection. In HIV -1 RANTES, MIP-1a, and MIP-1b has ability suppressed. The expression of macrophage tropic as well as ccr5 receptor genome the individual defective ccr5 expression has low progressive rate of hiv-1 infection [1, 2]. The coding of ccr5 sequence in zinc finger protein (ZNF) induces the resistant to HIV infection. Modification ZFN and nucleus gene editing of ccr5 receptor radius the susceptibility of generate cytokine production and entry of co- receptor c-c chemokine receptor 5 (ccr5Δ32). Mutation in ccr5 expression of homozygous 32 base pair deletion in ccr5 result the disable receptor for further function. Long term of ccr5 Δ32 heterozygotes is effective to reduce the ccr5 Δ32 effective zinc finger protein (ZFB) domains has ability to modulate the gene expression by fusion to well character transcriptional activation and separation domain. The domain catalytic enzyme FokI involve in zinc finger nucleus at the site of human genome. The coding of ccr5 receptor involved in the mutation in genome of CD4 + cell. Mutation in the coding and gene editing induce the low affinity to bounding with CD4 + and macrophages response in body [3]. Mutation of The ccr5 Δ 32 cause relative resistant in white people. Gene of heterozygote phenotype was deleted which induce the resistant to HIV 1. The deletion of chemokine such as RANTES, MIP-1a, MIP-1b which inhibit the entry cell membrane. The RANTES, MIP-1a, MIP-1b are resistant of HIV -1 due to reduce of expression of ccr5, ccr3 receptor [4].Down-regulation of ccr5 responses throughout the cell membrane to entry into the cell due to chemokine, RANTES, macrophage inflammatory protein. B-chemokine inhibit M-tropic HIV 1 infection by blocking the pathway of interaction with homozygous (ccr5Δ32/ccr5Δ32) genotype down regulation of ccr5 receptor could be advantage of antiviral therapy approach of HIV infection.(1%-2%) population of Western European are resistant to HIV 1 infections due to modification and mutation of gene in ccr5 receptor expression molecule . Ccr5 undergoes down regulation due to deletion coding of genetic order. Hammerhead ribosome has specifically ccr5 mRNA interact with ccr5 and reduce genetic expression of ccr5 co-receptor [5]. Most of the

Indian population has HIV-1 infection predominantly by subtype isolated which does not undergo down regulation of ccr5. The virion protein Nef and soluble gp120 protein induced the down regulation of co receptor which utilization phenotype specific manner [6]. The micros RNA are most effective tool to down regulation of ccr5 co-receptor. There are three artificial micro RNA (amiRNA) which helps the gene expression. About 95% reduce ccr5 expression with the most effective (amiRNA) combination. Pri-miRNA, siRNA, miRNA processing the primary RNA transcription in nucleus of host cell it form Hairpin structure which express the ccr5 co-receptor [7]. The HIV+Elite and viremic controller (EC/VCs) genetic of host cell have potential of down regulation with interaction of memory T-cell and reduced the other factors such as chemokine's, low down the ccr2 and ccr5 transcription with influence the mRNA. Chromosome 3p21 of host cell genome HLA-B, HLA- alleles are associated with down regulation of viral genome in CD4+ T-cell [8]. The homozygous mutation in ccr5 gene (ccr5Δ32) base pair deletion induces non-functional ccr5 receptor and heterogonous mutation has resistant of HIV 1 and slow progressive effect [9]. The microRNA prolongs miR-103, and miR107 genes are regulate the expression of ccr5 transference of micro RNA 103 micro in MDMs expression which down regulate and inhibit the entry of host cell [10]. The recombination ofTHP-1 cell act as anti-viral while combination with ccr5T4L protein on ccr5 tropic HIV-1 .this combination inhibits the Macrophage conjugation and reduces the cytokines [11]. Mast cell the powerful immune cell which has the ability to generate the various allergic reactions in order to damage the cell. Ccr5 expression on mast cell is unique because of the mast cell develop from mast progenitor (MCP) deletion of ccr5 expression in MCP of mast cell which reduce the chemotactic signals [12]. As comparison of heterogeneous and homogenous .the heterogeneous analogues has more resistance as compare to homogenous genetic order. Chemokine and inflammatory mediator are the less active in heterogeneous.Ccr5 expression of gene Cal-1 has encode a short hairpin down regulation of ccr5 and c-46 which inhibit the entry of host cell. CD4+host cell has transducing encode the genetic which reduce the infection of HIV 1[13]. Sulfated tyrosine molecule of ccr5 amplifier the binding to Mip-1a, MIP-1b, gp120/CD4 complex to enter into the cell which expression the ccr5 and cd4 T cell [14]. The steam cell disrupt the ccr5 gene in human hematopoietic steam/progenitor cell .In engraft NPD/SCID/IL2RYnull with HSC in ZFN (zinc figure nuclease. The polyclonal multi-lineage progress with ccr5 gene dysfunction permanent in human ccr5 gene [15]. Polyclonal multi-lineage interaction with the specific site of ccr5 receptor genetic code to reduce the efficiency of ccr5 receptor long-term interaction leads permanent destruction of ccr5 co-receptor [14, 15]. The two pathways non homologous end joining and error prone pathway a result the deletion of nucleotides in homologous DNA. Modification of mega Tall and TALEN cleavages site AAV, CCR5, and GFP genetic target expression of hematopoietic cell

[16]. Gene modification for gene editing of the zinc finger nucleases domain of enzymeFokI, Cys2His2 zinc figure interaction of specific side of DNA which influences the domain site of homozygous. For 32bp deletion in ccr5 resistant HIV-1 infection [17]. T-tropic is used cxcr4 as co-receptor in progress of disease whereas M-tropic are used for ccr5 as co-receptor on macrophage, monocyte, peripheral blood mono nuclease cell (PBMC). Various gene editing technique are involved in the deletion of gene.

Table: - 1 New GE technologies [18]

Nuclease	Origin	Delivery tool	Advantages	Disadvantages
TALEN	Xanthomonas	AV(Adenovirus)	Each TALE repeat (33–35 amino acids) consist which are involved in editing of nucleotide in human	the binding site starts with a T base:- larger size than ZFN; off-target effect and sequence recognition are required
ZFN	Eukaryotes	AV, AAV, LV (Adenovirus Associated)	Each ZF module (30 amino acids) consists and binds with sequence-specific nucleotides.	off-target effects
CRISPR/Cas	Bacteria	Plasmids	targets multiple sites to produce large gene fragment deletions	It involved in PAM ,off-target effects

CRISPR/Cas: - clustered regularly interspaced palindromic repeats/CRISPR-associated protein 9, LV: - lentivirus, PAM: - protospacer adjacent motifs, TALE: - transcription activator-like effector, TALEN: - transcription activator-like effector nuclease, ZFN: - zinc-finger nuclease)

In ccr5 receptor has existing 32 base pair deletion which leads to non-functional receptor resistant to HIV usually from donor with the ccr5Δ32 genotypes [19]. Hypothesis of gene editing based on allogeneic transplant ccr5 with modified M303/M303 mutation lead to resistant for HIV/AIDS in patient [20].

Conclusion:

Gene editing of ccr5 and cxcr4 co- receptor prevent the further expose of the HIV/AIDS and its complications. Deletion or inserting of gene in ccr5 reduces the progressive infection. Mutation of genetic code in ccr5 leads to inhibit entry of virion molecule and its replication phenomena.

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