The Influence Of Adeno Associated Virus Vector Receptor (AAVR) And Co-Receptors And Their Mutations On Tropism And Transduction Of Adeno Associated Virus During Gene Therapy: A Review

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Abstract
Gene therapy is an experimental treatment being investigated to correct defective genes that are responsible for disease development. To treat cancer and genetic illnesses, researchers are looking into a variety of gene therapy techniques. Finding a proper vector to transfer DNA into tissues is one of the most difficult aspects of gene therapy. Some gene therapy vectors have issues with infecting both quiescent and dividing cells, provoking an immunological response, lack of indefinite expression, and reproducible high titre. The adeno virus, retrovirus, and recombinant modified adenovirus are top contenders for gene therapy vectors (rAAV). The issues with gene therapy may be resolved by the adeno associated virus (AAV). Hemophilia is a condition which may be benefited by the gene therapy using AAV as vector. Aim of this review is to emphasize on the role of adeno associated virus receptors(AAVR) and co-receptors in tropism and transduction of adeno associated virus(AAV) in the gene therapy of hemophilia In Vitro as well as In Vivo.

Keywords: gene therapy, vectors, tropism, hemophilia

BACKGROUND
Hemophilia is an X-linked genetically inherited coagulation disorder brought on by a deficiency in the coagulation factors of the intrinsic coagulation cascade [1,2]. Hemophilia A is the most common type of haemophilia, affecting one out of every 5000 live male births. It is caused by a mutation in the factor VIII (FVIII) gene, which results in the loss of functional FVIII protein. FVIII is a necessary cofactor for the serine protease factor IX (FIX), which is absent in haemophilia B patients.

Current treatment options and their drawbacks
Currently, the standard treatment for haemophilia is the prophylactic infusion of exogenous coagulation factors made from pooled plasma or recombinant protein. Because FVIII and FIX proteins have short biological half-lives, repeated infusing (2–3 times per week) are necessary to maintain trough levels over 1%, which is the minimum efficiency level for preventing the incidence of spontaneous bleeding. Anti-drug antibodies, also known as inhibitors, are a common side effect of factor replacement therapy [3]. As a result, patients are no longer responsive to factor replacement and require bypassing drugs, which are frequently costly, have brief biological half-lives, and are less successful in maintaining hemostasis over the long term than FVIII or FIX.

Patients with inhibitors can also be put on an immunological tolerance induction (ITI) strategy, which requires periodic infusions of super physiological doses of coagulation factor until inhibitors are diminished or abolished and factor replacement therapy can resume [4,5]. Since about 2/3rds of people with haemophilia A benefit from inhibitors, immune tolerance induction (ITI) is frequently stopped in patients with haemophilia B because of allergy and nephrotic syndrome [6]. Given the high lifetime costs, frequent infusions, and considerable health effects, there is a need for new, cost-effective haemophilia medications with decreased risk and improved function.

Gene therapy can be very beneficial in the treatment of monogenic illnesses like haemophilia because it replaces a disease-causing gene that is either absent or produced as a nonfunctional protein with a functional copy. The initial challenge of poor delivery of the therapeutic genetic carrier into targeted cells and tissues was overcome by the use of viral vectors generated from mammalian viruses that have gradually evolved to convey their genomic cargo into cells and tissues. In these vectors, which contain little wild-type viral sequences, the therapeutic gene cassette replaces the virulent, replicative.
and structural viral genes. In experimental and clinical trials throughout the years, hepatic in vivo gene transfer utilising adeno-associated viral (AAV) vectors has shown the most effectiveness, with numerous phases 3 trials for haemophilia A and B.

The cellular and host tropism of viruses is one of the most essential and notable properties of viruses [7]. For their survival as parasitic creatures, viruses must compromise with the number of positive and negative components present in target cells. They do not reproduce at all if there is no suitable interaction with cells. Viral tropism can thus be assessed at each phase of the replication process, from entry into cells to progeny production from cells. The two primary types of viral tropism are receptor-dependent and independent tropisms. Viral replication is prevented from occurring inside of the cell or on the cellular membrane via a receptor-dependent viral entrance step and (receptor-independent post-entry replication steps).

Tropism is the ability of a virus to infect a specific subset of cells within the host. The presence of virus receptors on the cell surface of a host cell affects the tropism of many viruses. The interactions of adeno-associated virus (AAV) with certain surface glycans and a proteinaceous receptor dictate AAV entrance. The adeno-associated virus receptor (AAVR) (also known as KIAA0319L) is a critical cellular receptor that allows vectors from various AAV serotypes to be transduced.

Adeno-associated virus (AAV) vectors are currently the most promising choices for virus-based gene therapy due to their broad organ tropism, non-pathogenic origin, and immunogenicity [8]. They have been licensed in Europe for the treatment of lipoprotein lipase deficiency and have been successfully utilised in clinical trials to treat genetic disorders such as haemophilia B2 [9]. Although the fundamentals of AAV cellular entrance are still unclear, efforts are being made to produce AAV variants with unique and biomedically valuable cell tropisms to enable for successful systemic delivery [8,10]. Particularly, it is unclear which polypeptide receptor(s) are required for AAV entry following cell adhesion. It has become increasingly obvious that attachment to potential cell surface receptors is the first step for effective transduction, despite the fact that the precise mechanism of tissue-tropism of AAV serotype vectors in vivo is still uncertain. Additionally, it has become evident that most AAV serotype vectors first facilitate attachment by adhering to different cell membrane glycans, which act as main ligands. Similar to AAV2, it is likely necessary for AAV serotype vectors to attach to supplementary membrane receptors known as co-receptors in order to enter cells. Hence the precise role of AAVR and co-receptors in tropism and transduction of AAV needs to be explored.

The first human cell line that was incapable of being infected by wild-type AAV2 or transduced by recombinant AAV2 vectors was reported by Ponnazhagan et al., suggesting that AAV2 invasion in human cells is receptor-mediated [11]. A study speculated that the cellular receptors for AAV2 might be a 150-kDa protein that is found in membranes, however they provided no evidence to support this assertion. [12]. Heparan sulphate proteoglycan (HSPG) was found to be the cell receptor for AAV2 by Summerford and Samulski [13]. Every cell from across the species barrier, with the exception of the initial human cell type reported by a study, express HSPG, which explains the broad tropism of AAV2 [11].

Despite the fact that clinical efficacy was not the main objective, a phase I clinical trial for prospective cystic fibrosis gene therapy failed to show clinical effectiveness while proving the safety of recombinant AAV2 vectors in humans. AAV2 vectors failed to effectively convert these cells because Duan et al. showed that HSPG is primarily expressed on the baso-lateral edge derived from human airway epithelial cells rather than the apical surface [14][15]. Additionally, it was found that heparan sulphate proteoglycan is insufficient for viral entry into cells despite being required for AAV2 to adhere to cellular membranes.

The very first intracellular co-receptor for adenovirus 2 is the human fibroblast growth factor receptor 1 which was discovered by Qing et al. [16]. Summerford et al found αVβ5 as another AAV2 co-receptor at the same time [17]. These studies provided a better understanding of the mechanism underpinning AAV2 binding and entrance into target cells. Chen et colleagues isolated AAV sequences from diverse organs in children, primarily tonsils, and found that only 7% among those "Adeno associated virus 2-like" sequences were identical to the wild-type by 98%. [18] and these viruses were unable to link to the cell surface receptor because they lacked the heparan sulphate proteoglycan binding site. These results demonstrated that outside proliferation of AAV2 in culture led to the usage of heparan sulphate proteoglycan as a receptor. AAV2, on the other hand, appears to use a variety of putative cellular receptors. Indeed, in mouse brain and retinal tissues, recombinant AAV2 vectors lacking the HSPG binding region have been demonstrated to have efficient and broad transduction [19,20]. Similar to this, it has been discovered that AAV2 uses several cellular co-receptors in addition to FGFR1 and V5, including CD9, laminin receptor (LamR), hepatocyte growth factor receptor (HGFR), and 51 integrin [21-24], a putative integrin for AAV9 [25]; FGFR1 for AAV2 [16] and AAV3 [26]; platelet-derived growth factor receptor (PDGFR) for AAV5 [27]; epidermal growth factor receptor (EGFR) for AAV6 [28]; and laminin receptor (LamR) for AAV2, AAV3, AAV8, and AAV9 [23].

There are no in vitro or in vivo Indian studies which focus on the influence of AAVR receptor and its gene mutations on the gene therapy of hemophilia.

Future Research perspectives

An experimental study on the role of adeno-associated virus receptor (AAVR) in tropism of AAV in animal models as well as cell lines may be helpful in establishing the role of adeno-associated virus receptors (AAVR) and co-receptors in tropism and transduction of adeno-associated virus (AAV) in the gene therapy of hemophilia In Vitro as well as In Vivo.
Expected outcome from such study
● AAVR has been described as a protein that may quickly endocytose from the cell membrane and go to the trans-Golgi network.
● Direct AAVR binding to AAV2 particles, as well as the possibility that anti-AAVR antibodies can successfully prevent AAV2 infections. Additionally, a variety of mammalian cell types become extremely resistant to AAV2 invasion when AAVR is genetically eliminated.
● All AAV serotypes that have been investigated, AAVR may behave as a vital host factor.
● The strong resistance of AAVR -/- mice to AAV infection may reveal the significance of AAVR for in situ gene delivery.
● Collectively, we may arrive at a conclusion whether AAVR is an ubiquitous receptor implicated in AAV infection.
● The efficiency of Adeno - associated viral mediated gene therapy may be improved by mutations of the AAVR and its co-receptors, which may offer additional therapeutic gene targets.

Significance of the study
The attempts to characterise the function of AAVR and co-receptors with the various AAV serotypes have important implications for their application in human gene therapy. All upcoming research, both basic and clinical, is undoubtedly going to rely heavily on a thorough understanding of AAVR mutations and their effects on viral tropism. Adeno-associated virus (AAV) is controlled by the factors and methods of cell entry and attachment in its use as a gene therapy vector. Despite possible consequences for cell and tissue tropism, a systematic evaluation of how various AAV serotypes interact with their proteinaceous receptor AAVR (KIAA0319L) to establish transduction has yet to be done. Future uses and treatments utilizing this viral vector technology can be improved by defining the molecular determinants of the infectious route. Our findings might point to common sense approaches to and worries about AAV-mediated gene therapy.

An examination of AAVR expression and variants, for instance, may be helpful in identifying the causes and coming up with potential solutions in clinical cases with subpar AAV gene delivery efficacy in studies. AAV might be employed in gene substitution therapies, according to new research that links polymorphisms in AAVR with a neurological phenotype that is detrimental to some human disorders. The outcomes of our research can be utilised to assess and forecast whether patient-specific differences in AAVR may have an impact on the effectiveness of AAV infection.

CONCLUSION
In conclusion, the AAV2-AAVR complex's atomic structure adds to our understanding of the molecular mechanism underlying AAV cell entrance. By identifying specific engineerable candidate residues, the precise virus-receptor interactions identified in this study may aid in the design and optimization of AAV vectors, resulting in particles with improved efficacy and a reduced immune response for gene therapy. The work may point to potential therapeutic targets for the genes AAVR and co-receptors.

REFERENCES
