Editorial

Herpesvirus Vectors in Gene Therapy

Herpes simplex virus type 1 (HSV-1) is a common human virus, best known as the causative agent of recurrent labial herpes (cold sores) [1]. The unique properties of HSV-1 have increasingly been exploited in vector design, particularly for therapy of the central nervous system diseases.

HSV has natural properties useful for a therapy vector: the latent, life-long infections in the nervous system with long-term gene expression, the episomal non-integrating DNA genome and the numerous dispensable genes allowing cloning of large transgenes and their regulatory sequences [2]. Numerous clinical phase I-III studies using HSV vectors are in progress on therapy of gliomas and other malignancies and of other, mainly neurological, disorders, including pain [3, 4].

The HSV vectors can be genomic, nonreplicating or replicative vectors, or HSV amplicons. HSV amplicons are vectors harboring only minimal amount of virally derived sequences, suitable for delivery of up to 150 kbp of foreign DNA [5]. The use of HSV amplicon vectors has further been improved by the development of HSV-adeno-associated virus (AAV) hybrid vectors, aiming at long-term transgene expression. The wild type HSV, and also the HSV vectors, can evoke both innate and adaptive immune responses in the host organism [6]. The host responses can limit the vector persistence and duration of the transgene expression, but may occasionally also be advantageous in therapy of certain diseases. The current special issue introduces to the reader the different types and uses of HSV vectors, as well as the host responses which may affect the performance of these vectors.

In this issue, *Tsitoura and Epstein* provide an expert overview of the HSV amplicon vectors and the host responses. They discuss the challenges in overcoming the amplicon silencing in the host, as well as the roles of certain HSV genes in counteracting the host responses. The review by *de Oliveira and Fraefel* introduces the HSV/AAV hybrid vectors, and illustrates also the biology of AAV and AAV vectors. The relevant helper viruses and HSV vectors are discussed, and new hybrid virus vectors are presented, such as HSV/Epstein-Barr virus and HSV/retrovirus hybrids. The overview by *Cassady and Parker* elucidates the use of HSV in tumor killing. They present the conditionally replicating HSV vectors for brain tumor therapy. In their paper, various approaches are illustrated for enhancement of tumor killing by HSV, such as combination of HSV virotherapy with other therapeutic modalities, or the tumor-specific targeting of HSV vectors. The authors discuss strategies to facilitate replication of HSV vectors in malignant cells without restoration of neurovirulence. In an extensive review, *Manservigi et al*. elucidate the design and applications of recombinant HSV vectors, with an emphasis on the genomic HSV vectors. They present the key issues of the HSV life cycle relevant to the vector development and introduce the different types of HSV vectors. The applications of HSV vectors are described in therapy of chronic diseases of the nervous system, in cancer therapy and also in vaccine vector design. The targeting strategies and means of imaging of HSV vectors are illustrated, and the authors also discuss the host responses and other factors compromizing the HSV vector efficacy. New perspectives for HSV-mediated tumor therapy are discussed, including the exploitation of microRNAs.

This special issue of The Open Virology Journal presents state-of-the-art reviews by experts of the HSV vector field, covering the different types and uses of HSV vectors and elucidating the central questions such as vector design and targeting, silencing of the transgenes and other effects of the host responses. Hopefully this special issue is useful for the readership; for those interested in applications of HSV and for those considering the choice of viral vector for their particular gene therapy purpose.

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