OR04

Adeno-associated virus in human liver: natural history and consequences in tumor development

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Adeno-associated virus (AAV) is a defective mono-stranded DNA virus, endemic in human population (35–80%). Recurrent clonal AAV2 insertions are associated with the pathogenesis of rare human hepatocellular carcinoma (HCC) developed on normal liver. This study aimed to characterize the natural history of AAV infection in the liver and its consequence in tumor development. Viral DNA was quantified in tumor and non-tumor liver tissues of 1461 patients and in silico analyses using viral capture data explored viral variants and new clonal insertions. AAV DNA was detected in 21% of the patients, more frequently in the non-tumor counterpart (18%) than in tumor (8%). The full-length viral sequences were reconstructed in 57 patients leading to identify two distinct AAV subtypes: one similar to AAV2, the other hybrid between AAV2 and AAV13 sequences. Episomal viral forms were found in 4% of the non-tumor tissues, frequently associated with viral RNA expression and human herpesvirus type 6 (HHV6), the candidate natural AAV helper virus. In 30 HCC, clonal AAV insertions were recurrently identified in CCNA2, CCNE1, TERT, TNFSF10, KMT2B and GLI1/INHBE. AAV insertion triggered oncogenic overexpression through multiple mechanisms that differ according to the localization of the integration site. Clonal AAV insertions were positively selected during HCC development on non-cirrhotic liver challenging the notion of AAV as a non-pathogenic virus. In conclusion, this is the first large scale study that provides an integrated analysis of wild type AAV infection in the liver with the identification of viral genotypes, molecular forms, helper virus relationship and viral integrations.

OR05

Paracrine delivery of therapeutic biologics for cancer

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A fundamental goal of cancer drug delivery is to achieve sufficient levels within the tumour without leading to high systemic concentrations that might cause off-target toxicities. In situ production of protein-based therapeutics by tumour cells provides an attractive alternative to treatment with repeated high bolus injections, as secretion by the tumour itself could provide high local concentrations that act in a paracrine fashion over an extended duration. For this purpose, we have developed a non-oncolytic adenoviral delivery system that allows for targeting of Ad5 to discrete cell types by redirecting viral tropism to cell surface biomarkers through the use of interchangeable adapters. Furthermore, we recently described the engineering of a protein-based 'shield' that is coated on the Ad5 capsid, which, together with the retargeting adapters, allows for improved tumour specificity and prevention of viral clearance. To test this delivery strategy in vivo, SCID-beige mice bearing orthotopic BT474 xenografts were treated with three doses of either a cancer-specific, non-replicative Ad5 that encodes a secreted anti-HER2 antibody, trastuzumab, in its genome, or with the protein therapeutic itself (Herceptin®). We have employed state-of-the-art whole tumour clearing and imaging with confocal microscopy at high spatial resolution in 3D to assess biodistribution, and large volumetric imaging has revealed that the secreted therapeutic diffuses significantly throughout the tumour leading to a therapeutic effect and delayed tumour outgrowth. Moreover, the systemic concentration of antibody is significantly reduced with viral delivery, suggesting that paracrine delivery may be a promising strategy for delivery of biologics with narrow therapeutic indices.

OR06

Base editor-mediated CD33 engineering to improve safety and efficacy of CD33-targeted cancer therapy

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