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How did I get here?

Adenovirus-host interactions for vector
development

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Academic dissertation

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Abstract

Adenoviruses (AdVs) have been developed as vectors for gene therapy, vaccines, and oncolytic applications, owing to their transduction efficiency, broad tropism, and well-established production platforms. Still, clinical translation is limited due to insufficient targeting and complex interactions with host factors. A detailed understanding of AdV-host interactions is needed for the rational design of next-generation vectors. This thesis explores AdV-host interactions in the context of vector development.

Human adenoviruses (HAdVs) are genetically divided into seven species (A-G), where species D is the largest and most diverse. The low seroprevalence of species D HAdVs has made them interesting as gene delivery platforms. In the first study, we identified a new chimeric HAdV-D virus, HAdV-20-42-42. HAdV-20-42-42 was vectorised and we demonstrated that it used the coxsackievirus and adenovirus receptor (CAR) and CD46 for attachment. We also demonstrated the vector's ability to induce a T cell response in mouse splenocytes. The ability to use dual receptors and activate adaptive immunity highlights the potential of species D HAdV as versatile gene delivery platforms.

In the second study, we generated four distinct A549 knockout models by targeting known HAdV receptors, resulting in cells deficient in CAR, CD46, DSG2, or sialic acid. Upon infection with HAdVs, we identified CD46 as the primary entry receptor for a majority of species D HAdVs. We used SPR analysis to demonstrate that binding to CD46 was mediated primarily by the HAdV hexon protein, suggesting the possibility for an interaction with high avidity. Together, these findings provide mechanistic insight into the molecular basis underlying the broad cellular tropism of species D HAdVs.

Given the central role of skeletal muscle as a target tissue for vaccine vectors, we wanted to explore whether HAdV transduction of these cells could be improved. Previously, the endogenous peptide lactoferricin (Lfcin) has been recognised to enhance HAdV-C5 infection in epithelial cells. In the third study, we investigated whether Lfcin could also enhance HAdV-C5 infection in human skeletal muscle cells. We found that Lfcin enhanced infection in a dose-dependent manner, but at very high concentrations it promoted viral particle clustering, which correlated with reduced enhancement. Addition of Lfcin during the early stages of infection markedly improved viral entry and transduction in both proliferating myoblasts and terminally differentiated myotubes. In addition, Lfcin reduced serum-mediated neutralisation of HAdV-C5. These findings demonstrate how endogenous host factors can modulate HAdV infectivity, influence biodistribution, and counter neutralising antibodies.

These studies provide additional insights into HAdV-host interactions by exploring determinants of HAdV tropism, and can be used for the development of safer, more targeted, and more effective AdV-based vectors.

Keywords: Adenovirus, vectors, receptors, attachment factors, CD46, lactoferrin, lactoferricin

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