Capsid protein functions of enteric human adenoviruses

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i sal E04, byggnad 6A, fredagen den 18 maj 2018, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.
Fakultetsopponent: Professor Stefan Schwartz,
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Abstract
Human adenoviruses (HAdVs) cause respiratory illnesses, epidemic conjunctivitis and infantile gastroenteritis. HAdV types 40 and 41 cause enteric infections in infants worldwide. HAdVs use various receptors for attachment onto different host cells. Coxsackievirus and adenovirus receptor, CD46, sialic acid, coagulation factors IX and X, lactoferrin and heparan sulfate are some receptors and molecules which the hexon and fiber proteins (components of the capsid) bind for direct or indirect cellular attachment. The penton base protein (another component of the capsid) is responsible for the internalization of the virus into the host cell. An arginine-glycine-aspartic acid amino acid motif is present in most but not all adenovirus penton base proteins and mediates interaction with $\alpha_v$ integrins, resulting in internalization.

The enteric HAdVs are unique since they do not have this arginine-glycine-aspartic acid motif on their penton base. Using a library of hamster cells expressing specific human integrins, along with recombinant soluble penton base from HAdV type 41 and commercially available soluble laminins, we identified laminin-binding integrins as co-receptors for entry and infection of human intestinal HT-29 cells by the enteric HAdVs.

HAdV types 40, 41 and 52 are the only three HAdVs that have two different fiber proteins, one long and one short. By performing cell binding and infection experiments, we have found that the receptor for the short fiber of HAdV-52 is sialic acid-containing glycans and the long fiber receptor is CAR although most of the binding was dependent on sialic acid-containing glycans. We also observed that the short fiber of HAdV type 40 interacts with soluble heparin or cell surface heparan sulfate. Further investigation pointed out that the specific sulfate groups on heparin/heparan sulfate (sulfated glycosaminoglycans) are important for this binding. Also, we identified that the interaction and utilization of these glycosaminoglycans as receptors is dependent on exposure to low pH. We also studied the potential mechanism behind the symptoms caused by these enteric HAdVs in enteroendocrine cells called enterochromaffin cells. We could show that the short fiber and the hexon of HAdV type 41 stimulated release of serotonin from the enterochromaffin cells, which can be a cause of vomiting and diarrhea.

These studies have given us insight into the role of enteric HAdV capsid proteins as ligands to hitherto unidentified receptors and co-receptors. We also show that these molecules play important functions in the virus’ infectious cycle and probably also in their disease mechanism of host cells.

Keywords
Adenovirus, gastroenteritis, capsid proteins, receptor, integrins, heparan sulfate, sialic acid, serotonin