ANTIVIRALS

Identifying adenoviral receptors

PATHFINDER

Lack of understanding of the mechanisms utilized by adenoviruses to infect cells has hampered the development of effective antiviral therapies for numerous illnesses. Now, two papers identify human cellular receptors that mediate the binding and infection of specific adenoviruses: these findings may form the basis for future drug development strategies.

In the first paper, Arnberg and colleagues study the species D adenovirus 37 (Ad37), which is largely responsible for epidemic keratoconjunctivitis — a severe ocular disease for which there are currently no antiviral therapies. Using glycan array screening, they found that the receptor-recognizing knob domain of Ad37 bound to a glycan that matched the disialylated glycan present in ganglioside GD1a. Additional studies revealed that the Ad37 receptor was not the GD1a ganglioside itself, but it was instead composed of cell surface glycoproteins containing the GD1a glycan motif.

Next, to demonstrate whether the GD1a glycan could serve as a functional Ad37 receptor, the authors preincubated Ad37 virions with a soluble GD1a glycan or with a GD1a-binding monoclonal antibody. Both treatments efficiently inhibited Ad37 binding and infection of human corneal epithelial cells compared to control.

To further understand the Ad37–GD1a interaction, the authors applied molecular modelling, nuclear magnetic resonance and X-ray crystallography techniques. They found that the two sialic acids of the GD1a glycan docked with two out of three previously described Ad37 sialic acid binding sites and identified key amino acid residues, notably Lys345, with which the glycan was directly interacting. Further analysis revealed that the GD1a glycan–Ad37 knob interaction had high affinity. Importantly, they discovered that the GD1a glycan-contacting residues were conserved in other species D adenoviruses, suggesting that these adenoviruses may also interact with the GD1a glycan.

Meanwhile, Lieber and colleagues focused on species B adenoviruses, which cause respiratory and urinary tract infections in humans. Using Ad3 dodecahedral particles (PtDds — a product of viral replication) or Ad3 virions as probes in competition binding studies in human cell lines, they identified desmoglein 2 (DSG2) — a calcium binding transmembrane glycoprotein and component of the epithelial cell–cell adhesion structure — as a high-affinity receptor for Ad3. Loss-of-function and gain-of-function studies confirmed DSG2 to be crucial for the binding, infection and spread of Ad3, as well as that of other species B adenoviruses — namely Ad7, Ad11 and Ad14.

They next studied the consequences of adenoviral–DSG2 binding following exposure to Ad3 virions or PtDds, using epithelial cancer cell lines. Pathways involved in epithelial to mesenchymal transition were found to be activated, leading to transient intercellular junction opening, which increased access to proteins located there, including CD46, ERBB2 (also known as HER2/neu) and epidermal growth factor receptor (EGFR). Interestingly, pre-incubation of cancer cell lines with PtDds increased the cytotoxicity of trastuzumab (Herceptin; Genentech/Roche) and cetuximab (Erbitux; Imclone Systems/Bristol-Myers Squibb/Merck Serono) — both drugs are monoclonal antibodies that bind to ERBB2 and EGFR, respectively. Furthermore, intravenous injection of PtDds 12 hours before trastuzumab treatment eliminated tumours in a mouse breast cancer model.

Together, these studies are likely to contribute to the design and delivery of novel antiviral therapies for various infections and may also have important implications for cancer therapy.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPERS Nilsson, E. C. *et al.* The GD1a glycan is a cellular receptor for adenoviruses causing epidemic keratoconjunctivitis. *Nature Med.* **17**, 105–109 (2011) | Wang, H. *et al.* Desmoglein 2 is a receptor for adenovirus serotypes 3, 7, 11 and 14. *Nature Med.* **17**, 96–104 (2011)