Human hepatitis A virus is united with a host of relations

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The History of HAV

Earliest descriptions of epidemic liver disease, most likely due to hepatitis A virus (HAV), can be found in ancient Chinese literature, and similar observations, often in association with conflict and social disruption, have appeared on many occasions. However, evidence that the infection was of viral etiology was not obtained until human volunteer experiments were conducted during and shortly after World War II. The ability of the virus to infect subhuman primates was demonstrated in 1967 (1), and the first in vitro cell culture was reported in 1979 (2). The virus was finally visualized by electron microscopic examination of stool specimens from human volunteers in 1973 (3). The virus particles were ~30 nm in diameter and resembled picornaviruses morphologically. Subsequent molecular characterization of the RNA genome confirmed that the virus is indeed a member of the picornaviruses; a large family of single-stranded, positive-sense RNA viruses. However, many features of HAV serve to distinguish it from typical picornaviruses, and it has long occupied a phylogenetic relationship on the periphery of the picornavirus family (4). In addition to its unique properties, HAV is unusually highly conserved; for example, there is a single serotype with minimal antigenic variation. The unique properties and apparent phylogenetic isolation have made the evolutionary relationships of HAV to other picornaviruses a puzzle. However, in PNAS, Drexler et al. (5) have dramatically changed this situation with a report of the identification of a plethora of new viruses that are clearly closely related to human HAV but were isolated from a wide range of small mammals.

HAV causes self-limiting infection of the liver and is transmitted by the feco-oral route. There is no evidence of long-term persistence of infection, as is typically associated with hepatotropic viruses that are transmitted parenterally, such as hepatitis B and C viruses. HAV is resistant to high temperature and extremes of pH, and, as a consequence, it

survives well in the environment and can be highly concentrated by filter-feeding molluscs. Consumption of contaminated molluscs has been associated with extensive epidemics of hepatitis A, for example, in China, where many thousands have been hospitalized as a consequence. A chemically inactivated vaccine produced from virus grown in tissue culture has been available for many years. Despite its high cost of manufacture, the vaccine is very effective as a consequence of the lack of antigenic variation

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between HAV isolates and its potent immunogenicity. Interestingly, improvements in hygiene result in lower levels of infection with HAV, and a consequent increase in the nonimmune population. Epidemic outbreaks are therefore more likely with infection occurring later in life, often with more serious clinical sequelae.

Novel Features of HAV

Although the structure and organization of the genome of HAV are typical of the picornavirus family in general, there are many features that distinguish HAV from other family members. Some of the most striking peculiarities include a low G/C ratio and low C_pG levels in the genome sequence and a strong codon bias, particularly in the region coding for the structural proteins (6). Intriguingly this bias is toward rare codons, a seemingly counterproductive selection. The strength of the selection

against frequently used codons is demonstrated by the reversion to the less well-used codons if frequently used ones are introduced into the genome. It has been suggested that the function of this codon bias is to reduce the rate of protein synthesis and allow for more accurate folding. Another distinguishing feature of HAV is that the structural protein virus protein 1 (VP1) is extended at its C terminus with an extra domain as VPX, which is important in the virus assembly process (7). The extra sequence of the VPX is then removed by cellular proteases, a process not seen in other picornaviruses, where the cleavage at this junction is carried out by viral protease. In addition to the three major structural proteins, VP1, VP2, and VP3, picornaviruses have a small internally located protein, VP4, which is derived by cleavage of VP0, a precursor of VP2 and VP4, at a late stage in viral maturation. This protein is typically myristoylated at its N terminus and is thought to be involved in facilitating RNA passage into a host cell during the infection process. However, in HAV, VP4 is of vestigial size and is not myristoylated (8). These specific peculiarities in the structural protein-coding region of HAV are most likely related to the unusual properties of the HAV virion, although the details are obscure. The HAV particle is extremely physically robust, and the recently solved structure (9) gives no hints as to where the reported cellular receptor, T-cell Ig and mucin domain 1 (TIM-1) (10), binds or how the particle can be destabilized to release the genome and initiate infection. In addition, it has recently been reported that the virus is released in a nonlytic manner within exosomes (11) and that these “enveloped” forms are equally as infectious as naked virions. This observation has opened up a new paradigm on the mechanisms of transmission of infection within the infected individual.

Evolutionary Origins of HAV

Until now, this intriguing array of unusual properties has resided in phylogenetic isolation with all isolates of the virus belonging to a single

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serotype and with very limited genomic diversity. Drexler et al. (5) sought to improve our understanding of the origins and relationships of HAV by searching for evidence of related viruses among a geographically and phylogenetically diverse spectrum of small mammals, 209 species in all. The study has been very successful, and it has expanded our knowledge of the true diversity of the HAVs and

provided strong indications of their evolutionary relationships. Although the virus sequences comprised 13 species, there was considerable general conservation and all fitted within a single genus. All of the peculiar features of HAV discussed above are conserved in the newly identified viruses. There was evidence of frequent exchange of virus sequences with patterns that did

not necessarily follow the phylogenetic relationships of the hosts. Intriguingly, the viral phylogeny suggests an ancient origin of HAV within small insectivorous mammals. This finding is particularly interesting because one of the features of the structure of the virus is a striking fold in VP2, which is not seen in other picornaviruses but is found in picorna-like insect viruses (9).

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