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Mini Review

Host range of zoonotic hepatitis E viruses

Albrecht Gröner*

PathoGuard Consult, 64342 Seeheim-Jugenheim, Germany

*Author for correspondence:
Email: info@patho-guard.com

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Abstract

Based on a proposed classification, the family *Hepeviridae* is divided into two genera: *Orthohepevirus* and *Piscihepevirus*. The genus *Orthohepevirus*, divided into seven species, contains the fast majority of HEV strains identified so far: *Orthohepevirus* A, B, C and D. Within *Orthohepevirus* A genotype HEV-1 and HEV-2 infect only humans; for genotype HEV-3 and HEV-4 the predominant host species are pig, wild boar, rabbit, deer, mongoose and human. Genotype HEV-5 and HEV-6 infect wild boar and genotype 7 and 8 camel. *Orthohepevirus* B infect chicken, *Orthohepevirus* C infect rat and ferrets and *Orthohepevirus* D infect bat. In this review article epidemiological aspects of HEV due to crossing species barriers based on infectivity studies are assessed.

Background

Hepatitis E virus (HEV) is a small (approximately 27-34 nm in diameter), non-enveloped virus with a positive sense, single-stranded RNA genome. HEV is, however, a quasi-enveloped virus with a lipid layer when collected from cell culture or from blood. In faeces, the lipid layer is removed by the bile [1,2].

HEV is a major cause of acute clinical hepatitis among humans throughout the world. Acute hepatitis E in humans in developing countries is caused by the HEV genotypes 1 (HEV-1; occurrence mainly in Asia) and 2 (HEV-2; occurrence mainly in Africa and Mexico) with a host range restricted to humans [3]. These genotypes are transmitted primarily by the faecal/oral route (primarily by contaminated water). The human associated as well as zoonotic genotypes of HEV are grouped into the species *Orthohepevirus A*, which includes a total of 8 genotypes, originating mostly from pig, wild boar, rabbit, and camel species. *Orthohepevirus B* consists of avian hepatitis E virus species, whereas *Orthohepevirus C* viruses were isolated from rodents (rats, voles, and shrew) and carnivores (such as ferrets, mink and foxes). HEV from bats are classed in the species *Orthohepevirus D* and fish-related HEV belongs to genus *Piscihepevirus* [4] (compare Table 1).

Interspecies Infection of HEV

Autochthonous HEV infections in industrialized countries have been identified over the last years triggered primarily by food borne infections caused by HEV genotypes 3 and 4. Pigs and wild boars been recognized as main reservoir for these genotypes. Besides pigs, wild boars, rabbits, deer and mongoose, some further animal species are reported to be infected by HEV, frequently by further HEV genotypes.

Transmission of HEV from animals to humans are reported frequently, primarily via swine and wild boar [11-14], especially by undercook pork [15-21]. As, besides suidae, further animals, such as rabbits, cows, bison, deer, hare, goat, sheep and equines as well as camel [4,22-29] are infected by *Orthohepevirus A*, the interspecies transmission of HEV should be studied carefully in order to define risk mitigating strategies to avoid, or at least minimize, the transmission of HEV to humans from other sources than pork. Prevalence and partly incidence of HEV in naturally infected animals were also reported: e.g., for rabbits [30], deer [28,31-33], mink and ferrets [34-35], rodents (rats, mice, voles, squirrel) [36-38], wild and domestic carnivores (racoons, racoon dogs, dogs and cats) [36] and zoo animals including non-human primates [40-42].

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Family	Genus	Species	Genotype	Host
Hepeviridae	*Orthohepevirus*	*Orthohepevirus A*	1	human
			2	human
			3	human, pig, wild boar, deer, hare, mongoose, monkey (Macaca sp.), rabbit, equines, goat, sheep, bottlenose dolphin
			4	human, pig, wild boar, rhesus monkey, cow, sheep, goat, yak
			5	wild boar
			6	wild boar
			7	dromedary camel, human
			8	Bactrian camel
		Orthohepevirus B		chicken
		Orthohepevirus C	C1	rat, greater bandicoot rat, Asian musk shrew
			C2	ferret, mink
			currently unclassified	field mice, vole dwarf hamster krestel fox
		Orthohepevirus D		bat
		Currently unclassified		moose, bison egret
	Piscihepevirus	*Piscihepevirus A*		Cutthroat trout
Classification based on published data [4-10].				

Table 1: Classification of Hepeviruses.

In contrast to naturally occurring interspecies transmissions of HEV, experimental transmission studies are performed under defined conditions as standardized test animals, inoculum and inoculation route, and follow-up for infection markers. Such experimental infectivity studies provide information of the infectious dose of the experimental host and, if the experimental animal is suitable regarding sensitivity to HEV infection and clinical markers, a small animal model as an alternative to pigs (and non-human primates) may be an appropriate basis for vaccine development and antiviral drug testing.

Therefore, studies were performed to infect laboratory animals as rabbits, mice and rats with a human pathogenic HEV variant, commonly from infected pigs or wild boars. A study covering the above-mentioned parameters was performed employing a liver suspension from a wild boar with a known HEV RNA concentration and for some further studies HEV from bile and faeces with a known HEV RNA concentration [43]. This material was inoculated in rabbits, Wistar rats and mice demonstrating a very effective transmission to European rabbits, limited transmission to rats and no transmission to mice (diverse mouse strains) as shown in Table 2.

Animal model	Inoculation	Results		
		Number of animals inoculated	Number of animals infected	
			HEV infection detected	Clinical symptoms
Rabbit*				
immunized	Liver homogenate: 7.3 x 10^6 copies of HEV gt 3 (i.v.)	3	Very low number of HEV RNA detected in faeces#. Slight booster of antibody response§	no clinical symptoms detected
positive control		2	Seroconversion and HEV RNA in faeces	
negative control	PBS	2	No HEV infection markers and no clinical symptoms detected	
Wistar rats				
naïve	Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (i.v.)	8‡	Seroconversion detected in 2 animals. Very low number of HEV RNA detected in faeces in another animal as well as in the contact animals	no clinical symptoms detected

Immunosuppressive treatment[†]	Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (concurrently i.v. and orally)	8	No HEV infection markers and no clinical symptoms detected
negative control	PBS	12[‡]	No HEV infection markers and no clinical symptoms detected
Mice			
Wild-type C57BL/6	Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (concurrently i.v. and orally)	2	No HEV infection markers and no clinical symptoms detected
$CD4^{-/-}$ mice	Faeces suspension: 2.8 x 105 copies of HEV gt 3 (concurrently i.v. and orally)	2	
$CD8^{-/-}$ mice	PBS	2	
$IFNAR^{-/-}$ mice	Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (orally)	3	No HEV infection markers and no clinical symptoms detected
	Liver homogenate: 1.8 x 10^6 copies of HEV gt 3 (i.v.)	3	
	PBS	2[‖]	
BALB/c nude (nu/nu	Liver homogenate: 5.8 x 10^5 copies of HEV gt 3 (i.v.)	4[‡]	No HEV infection markers and no clinical symptoms detected
	Faeces suspension: 8.8 x 10^4 copies of HEV gt 3 (i.v.)	4[‡]	
	bile: 2.3 x 10^5 copies of HEV gt 3 (i.v.)	4[‡]	
	PBS	4	

[*]Results from 2 independent experiments compiled; [#]vaccinated with rat HEV capsid protein; [§]vaccinated with HEV gt 3 capsid protein; [†]pretreatment with dexamethasone (0.15 mg/kg Voren Suspension®, Boehringer Ingelheim; subcutaneously); [‡]plus one additional rat co-habited (contact exposure control); [‡]8 naïve animals and 4 immunosuppressed animals; [‖]1 control animal per group

Table 2: Sensitivity of animal models for hepatitis E virus genotype 3.

The data reported by Schlosser et al. [43] demonstrated that rabbits are sensitive for HEV-3 isolated from a wild boar: The virus was detected in faeces of naïve rabbit after being infected and seroconverted; however, HEV RNA could not be detected in serum samples. In one of two rabbits HEV RNA was detected also in the liver and gall bladder at necropsy (the naïve rabbits were the positive control animals (non-vaccinated animals) in this study employing two different vaccines, either rat HEV capsid protein or HEV-3 capsid protein. Further studies with a larger number of animals have to confirm the tendency that the rat HEV capsid containing vaccine does not protect rabbits as effectively as HEV-3 capsid protein when challenged with infectious HEV-3. In Wistar rats no clinical symptoms were observed and only in a small number of inoculated animals the markers of HEV infection (HEV RNA in faeces or seroconversion) could be detected. Immunosuppression by dexamethasone had no impact on improved susceptibility of rats to a HEV infection. Wild-type and immunodeficient (interferon-alpha/beta receptor-, CD4- and CD8- negative and BALB/c nude mice) mice were resistant to HEV infection.

These data are in line with published data demonstrating a high sensitivity of rabbits to HEV infection. However, the rabbits showed minimal clinical symptoms. For rats, divergent results are published [44-46] and mice are considered to be resistant to HEV infection [47]; however, for Balb/c nude mice different results were reported [48]. Table 3 compiles results from experimental infectivity studies using *Orthohepevirus A* genotype 3 and 4.

Animal species inoculated	Result	Author
Chimpanzee	HEV RNA in faeces; seroconversion	Meng et al. [49] Yu et al. [50]
Rhesus macaque	HEV RNA in faeces; seroconversion	Meng et al. [49]
Cynomolgus macaque	HEV RNA in faeces and serum; seroconversion	Liu et al. [51]
Wild boar	HEV RNA in faeces and serum; seroconversion	Schlosser et al. [52]
Domestic pig	HEV RNA in faeces; seroconversion	Thiry et al. [53]
Rabbit	HEV RNA in faeces; seroconversion	Han et al. [44] Chen et al. [45] Han et al. [46]
Rat (Wistar rat)	not susceptible for HEV-1, -3, -4 but for rat HEV (*Orthohepevirus C)*	Li et al. [54]
	Limited susceptibility to HEV-3	Schlosser et al. [43]
Mouse		
C57BL/6 mice	Not susceptible no HEV infection markers detected	Li et al. [55,47]
C57BL/6, IFNAR-/- CD4-/- CD8-/- SPF Balb/c nude (female)	not susceptible no HEV infection markers detected	Schlosser et al. [43]
SPF Balb/c nude (male)	HEV RNA in faeces and serum; seroconversion	Huang et al. [48]
Mongolian gerbil	HEV RNA in faeces; seroconversion	Liu et al. [56]

Table 3: Experimental HEV infectivity studies (Orthohepevirus A – HEV-3 and HEV-4).

Conclusion

The risk of zoonotic HEV infection of humans is virtually restricted to *Orthohepevirus A* genotypes 3 and 4 and food-borne transmission of HEV, primarily due to consumption of undercooked meat, appears to be a major route [57,58]. Primarily immunocompromised patients may also be infected by the rat HEV (*Orthohepevirus C*, HEV–C1) [59-61] but also by camel HEV (*Orthohepevirus A*, HEV-7) [62]. Epidemiological surveillance in a wide range of animals such as rabbits, hare, deer, wild boar, pigs and rodents should be performed to assess the risk of HEV transmission to humans. These studies should also include animal manure applications and runoff contaminating surface water as well as irrigation causing concomitant contamination of products such as vegetables, berries and shellfish [57]. Risk mitigation strategies to avoid or minimize the infection of humans is improved hygiene, avoiding rodent droppings and preparing food properly (heating) or inactivate HEV contamination otherwise.

Cross-species transmission studies can assess the increased risk of HEV contamination in the environment and define the most appropriate small animal model for vaccine and antiviral drug development.

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