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MINIREVIEWS

Role of histo-blood group antigens in primate enteric calicivirus infections

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Abstract

Human noroviruses (NoV) are associated with large proportion of non-bacterial diarrhea outbreaks together with > 50% of food-associated diarrheas. The function of histo-blood group antigens (HBGAs) in pathogenesis of virus infection was implicated. Until recently however, due to lack of a robust animal and *in vitro* models of human NoV infection, only the partial knowledge concerning the virus pathogenesis (receptor, co-receptor and target cell) and absence of viable vaccine candidates were the frequently referenced attributes of this acute diarrheal illness. Recently, a novel group of enteric caliciviruses (CV) of rhesus macaque host origin was discovered and described. The new genus within the family Caliciviridae was identified: Rhesus Enteric CV, *i.e.*, "Recovirus" (ReCV). ReCVs are genetically and biologically close relatives of human NoVs, exhibit similar genetic and biological features and are capable of being propagated in cell culture. ReCVs cause symptomatic disease (diarrhea and fever) in experimentally inoculated macaques. Formulation and evaluation of efficient NoV vaccine might take several years. As suggested by recent studies, inhibition of HBGAs or HBGA-based antivirals could meanwhile be exploited as vaccine alternatives. The purpose of this minireview is to provide the guidance in respect to newly available primate model of enteric CV infection and its similarities with human NoV in utilizing the HBGAs as potential virus co-receptors to indirectly address the unresolved questions of NoV pathogenesis and immunity.

Key words: Calicivirus; Norovirus; Recovirus; Rhesus macaque; Macaca mulatta; Enteric infection

Core tip: To inform academic community and clinical practice, this short review summarizes existing hypothesis and evidence regarding the relationship between histo-blood group antigens and propensity of enteric caliciviruses to cause infection in primate species.

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INTRODUCTION

Identification of the ABO blood groups was pioneered in 1900's, independently, by Landsteiner[1] and Jansky[2]. In the 1970's, it was described that ABO antigens are associated with sugar moieties, specifically, with N-acetylgalactosamine (type A) and galactose (type B)[3]. Glycoproteins expressed on human red blood cells (RBC) represent A, B and H antigens with H functioning as the precursor for the A, B and O epitopes. It was demonstrated that histo-blood group antigens (HBGAs) including ABO and/or Lewis play a role in pathogenesis of certain infectious diseases including human norovirus (NoV) and *Helicobacter pylori*. The *ABO* genes are in humans positioned on chromosome 9[4,5]. According to molecular comparison of chromosome 9 with genomic DNA of other primate

species, analogous loci are present in rhesus macaque's (Macaca mulatta) chromosome 15[6]. Complex polymorphisms of human HBGA relationships concerning the secretor, *Lewis* and *ABO* gene families including their phenotypic (fucosyl- and glycosyl-transferase mediated) characteristics were extensively reviewed elsewhere[7]. Briefly, these genetic polymorphisms directly determine susceptibility or resistance to HBGA-recognizing pathogens including several groups of enteric caliciviruses (CVs).

Enteric CVs and human NoVs in particular are worldwide annually responsible for significant morbidity and mortality in young children[8]. In the Unites States alone, approximately 23 million cases of acute diarrhea are attributed to NoV infections each year[9,10]. No robust animal or cell culture model existed until recently to mimic the complex NoV genetics and pathogenesis including the host HBGA interactions with the virus. With discovery and characterization of human NoV's close relatives "rhesus enteric caliciviruses (ReCV)" the prototype of which is Tulane virus (TV), such studies became feasible[11-15]. As recent studies indicate that ReCVs can infect humans, likely by utilizing the primate HBGAs as co-receptors for virus entry[13,16], it is of interest to continue to elucidate the role of these molecules in enteric calicivirus infections.

CALICIVIRUS HOST-SPECIFIC RECEPTOR RECOGNITION PATTERNS

Recent *in vitro* experiments with synthetic glycoconjugates with relevance as CV receptors have revealed at least three distinct patterns of virus recognition[17]. While human NoV, ReCV/TV and bovine NoV all utilize HBGAs; other CVs such as feline CV and porcine sapovirus utilize sialic acid *via* N- and O-linked glycoproteins, respectively; and murine NoV uses sialic acid in a strain-dependent manner[17,18]. These distinct patterns of receptor recognition in different hosts have profound implications in virus pathogenesis, as for example porcine sapovirus-compatible O-linked glycoproteins are expressed alongside enteric goblet cells as well as in organs including liver, heart and cerebrum[17].

RELATIONSHIP BETWEEN PRIMATE HBGAs AND ENTERIC CVs

The ABO and Lewis blood groups were described in human and non-human primates (NHP). The specific antigens of these blood groups have been implicated in human NoV and ReCV infections as the virus attachment factors[13,19-21]. First study that suggested such interactions was based on results generated with anti-A/B antibody-mediated hemagglutination inhibition assays[22]. The anti-A and anti-B antibodies are also linked with transplantation immunity. These antibodies are triggered during the early life by exposure to environmental antigenic stimuli including those induced by common viruses. Hence, immunity induced by these stimuli is referred to as "communal immunity". The RBCs of 13 different species were tested for their capacity to bind with NoV antigens but only the human and chimpanzee cells showed reactivity[22]. This is consistent with notion that only humans and anthropoid apes but not other primate species express ABH antigens on their RBCs[23,24]. Non-anthropoid primates including rhesus monkeys secrete HBGAs into mucosal fluids[24,25]. Such an inherent difference between the rhesus and homo species is thought to be due to evolutionary pressures that asserted themselves during last 5 millions years to alleles encoding the blood groups[5]. From these and other studies, evidence suggests that *ABO* gene polymorphism in primates was generated more through the process of convergent evolution[26]. Notwithstanding, there still are shared features between the human and NHP blood group antigens including the capability of human HBGAs to recognize ReCVs and capability of rhesus HBGAs to recognize human NoVs[13]. Saliva analysis can be used to determine the specificity of ABO antigens in rhesus macaques and other monkey species.

CONSIDERATIONS FOR PRE-CLINICAL STUDIES WITH PATHOGENS THAT UTILIZE HBGAs

All primates including humans, apes and monkeys are secreting HBGAs into mucosal fluids-depending on their secretor phenotype. Since biomedical research with anthropoid apes is due to understandable ethical constraints severely restricted, bulk of the pre-clinical research is currently conducted with other animal models, from which the best available human-like alternative is rhesus macaque (Macaca mulatta). Knowledge about the individual animal HBGAs is therefore required. An assumption that HBGA profile of randomly selected group of research macaques will reflect the free-ranging population is inaccurate due to selective importation and breeding in captivity of animals from different parts of the world. As most of the captive research rhesus macaques in the United States are of Indian origin, they predominantly belong to HBGA type B, oppose to free-ranging macaques from South-East Asia and China that possess more polymorphic distribution of their HBGAs with significant proportions of type A, B, AB and O[13,24].

HBGA phenotyping of 500 rhesus monkeys of the Tulane colony revealed majority of animals being type B. Although this result is consistent with some historical studies conducted in 1970's[27], results conducted with free-ranging macaques in Thailand showed more polymorphic distribution[24]. Unpublished results conducted by our group at Tulane indicate differences between the Indian *vs* Chinese origin rhesus macaques: The Chinese macaques appear to have more human-like distribution (14% type A, 65% B, 11% O and 10% AB) than Indian macaques (97%

type B) (Farkas T personal communication).

An important distinction between the rhesus and human enteric caliciviruses is the capability of rhesus caliciviruses to be propagated *in vitro*[10]. A hypothesis that both rhesus and human enteric caliciviruses utilize HBGAs as the *in vivo* cell entry receptors/co-receptors could therefore be addressed with HBGA-defined, experimentally challenged macaques. Consideration would have to be given to a pre-screening stage of experiment when animals, free of virus-specific antibodies and defined in respect to their ABO and Lewis blood groups, are identified from the larger pool of candidates.

ARE HBGAs PRIMARY OR SECONDARY DETERMINANTS OF ENTERIC CV INFECTION IN PRIMATES?

It was proposed that human NoVs bind with carbohydrate moieties of the ABH and Lewis antigens when these are secreted into biological fluids and that such binding is associated with productive infection and illness[27-29]. In fact, inhibition of HBGA binding was suggested as an antiviral strategy for treatment of NoV infection[30]. Secretor or non-secretor phenotype depends on complex polymorphisms of *ABO, FUT2* and *FUT3* loci[7,21]. Few recent studies however, demonstrated that not only secretors but also non-secretors might get infected, suggesting that no strong correlation exists between the NoV infections and HBGA specificities of their hosts[31,32]. Another study with NoV virus-like particles also suggested that binding of NoV antigens to intestinal epithelial cells takes place regardless of HBGA expression on the surface of these cells[33]. An explanation that not all of these studies did take into account the HBGA binding properties of NoVs involved[21] seems unsatisfactory, not fully addressing the controversy. In order to corroborate the link between susceptibility to enteric calicivirus infection and its host ABO/Lewis phenotype, a challenge experiment with a well-defined NHP surrogate of NoV infection might need to be considered.

As enteric calicivirus infections were demonstrated in ABO type B (secretor) macaques of the Tulane colony regardless of their Lewis antigen characteristics, studies with type A and O macaques could provide further clues regarding the susceptibility or resistance of a particular phenotype to infection. In addition, retrospective HBGA analysis of recently reported Bangladeshi patients, infected with rhesus enteric calicivirus (TV strain), should also be informative[16].

Latest structural analysis of GI human NoVs revealed critical extension of the P domain loop region that appears to be responsible for binding of the GI.7 NoV with non-secretor HBGAs[34]. The "extended P domain loop" is not present on other GI NoVs that are known to bind with secretor HBGAs. These findings are for the first time directly addressing the controversies in respect to relationship between human NoV infectivity and its host HBGA properties. Nevertheless, these remarkable structural analysis data will need to be corroborated by epidemiological investigations and experiments with illness-prone models of human NoV infection. Because of its human-like characteristics, ReCV/TV model might be the one suitable for such purpose.

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