Title

Loss of Cell Surface aGal during Catarrhine Evolution: Possible Implications for the Evolution of Resistance to Viral Infections and for Oligocene Lineage Divergence

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Abstract

The divergence of the two superfamilies belonging to the Infraorder Catarrhini –Cercopithecoidea (Old World monkeys) and Hominoidea (apes, including humans) – is generally assumed to have occurred during the Oligocene, between 38 and 20 million years ago. Genetic studies indicate that this time period was one of active genetic evolution under strong purifying selection for catarrhine primates. This includes selective pressures on the glycoprotein galactosyltransferase 1 (*GGTA1*) gene and subsequent inactivation “clocked” at approximately 28 ma, possibly prior to the Cercopithecoidea/Hominoidea split. The *GGTA1* gene codes for an *a*1,3 galactosyltransferase (GT) enzyme that synthesizes a terminal disaccharide, *a*galactosyl (*a*Gal), found on glycoproteins and glycolipids on the surface of cells in the tissues of most mammals. Currently, catarrhines are the only mammals studied for the terminal *a*Gal residue that do not express this sugar on their cell surfaces. The proposed elective advantage of this mutation for catarrhines is the ability to produce anti-Gal antibodies, which may be an effective immune component in neutralizing *a*Gal-expressing pathogens, as certain helminthes, many bacteria, including those found in primate guts, and some viruses derived from *GGTA1* positive species express *a*Gal on their surfaces. However, many viruses are known to utilize host cell carbohydrates in various ways such as binding receptors or attachment proteins, making these moieties “hot spots” for selective evolution. Cell surface *a*Gal may have predisposed ancestral catarrhines to pathogens and toxins that could utilize the terminal sugar moieties on host cells as binding sites or in other capacities during infection. I found that, in fact, the presence or absence of cell surface *a*Gal affects the course of certain viral infections. Infections of paired cell lines with differential expression of GT showed that Sindbis viruses (SINV) preferentially replicate in *a*Gal-positive cells, whereas herpes simplex viruses type 1 and type 2 (HSV-1 and HSV-2) preferentially grow in cells lacking *a*Gal. In both cases, differences in infection levels resulted from the ability of the virus to successfully initiate infection. This points to a role for *a*Gal in the early stages of viral infections. I also showed that GT knockout mice infected with HSV-2 had higher viral load and greater pathology compared to WT B6 mice that naturally express *a*Gal. The increased susceptibility of KO mice to HSV-2 was not due to an immune component as differences in viral load and pathology were even more evident in immunocompromised mice. This clearly indicates that *a*Gal expression in cells or animal hosts can affect the course of viral infections. I was not able to further confirm differences in susceptibility to

HSV 1 and 2 using mouse backcrosses (KO x WT). Unknown genetic factors, that are independent of *a*Gal expression, may be introduced during the crosses that need to be further investigated. Infections of KO and WT mice with other herpes viruses did not yield definitive data and require further studies with suitable reagents. The mechanism by which GT-dependent differential susceptibility to viruses operates still remains to be deciphered. However, it is clear that susceptibility to certain viral infections is tied to the presence or absence of *a*Gal on the surface of host cells. Overall, these results have implications for the evolution of resistance to viral infections in catarrhines. Pathogens exert great selective pressure on their hosts, and it is possible that a pathogen, able to exploit *a*Gal, could have helped shape primate lineage evolution during the Oligocene.

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