

Although non-human primates, marmosets in particular, are strongly responsive to MOG, leading to MS-like pathology and MS-like disease, they do not develop the disease spontaneously. This is also the case for our closest living relatives, the hominoid primates (e.g. chimpanzee, bonobo, gorilla, orangutan). If EBV-infection in genetically prone individuals would be the cause of MS, then it is difficult to envisage why the disease manifests only in humans and not in chimpanzees, which are 98% genetically identical to us and are infected with an EBV-like virus, called EBVcmp (Ehlers et al., 2010). We posited therefore that MS may instead be caused by a uniquely human set of pathogenic events that cause instability of axon–myelin units. Stability of the unit involves interaction of myelin-associated glycoprotein (MAG) with the gangliosides GD1a and GT1b (Panel C), which are expressed on the axon membrane (Yang et al., 1996; Pan et al., 2005) (Panel B). MAG is a sialic acid-binding lectin (SIGLEC) with high specificity for N-acetylneuraminic acid (Neu5Ac) (Collins et al., 1997). The seminal work of Varki et al. reveals a genetic defect in humans that does not occur in hominoid primates, namely of the CMP-N-acetylneuraminic acid hydroxylase (CMAH), which is the rate-limiting enzyme in generating N-glycolylneuraminic acid (Neu5Gc) in cells of non-human mammalian species (Varki, 2001, 2017). Neu5Gc is therefore a foreign antigen for humans. The dietary intake of Neu5Gc-rich food, such as the red meat from livestock (cow, pig, sheep, goat) (Wang, 2009), induces Neu5Gc incorporation in the glycocalyx of body tissues (Tangvoranuntakul et al., 2003) and in gut microbiota (Taylor et al., 2010). The latter can elicit the production of anti-Neu5Gc antibodies (Taylor et al., 2010). Reaction of the anti-Neu5Gc antibodies with incorporated Neu5Gc can elicit "low-burning inflammation" in tissues (Samraj, 2015). As in hominoid primates, Neu5Gc is recognized as a self-associated molecular pattern (SAMP) and these antibodies are not formed. It is currently unclear whether dietary Neu5Gc is also incorporated in the brain. The rapid postnatal growth of the human brain places an exceptionally high demand on building blocks, including sialic acids, for the generation of gangliosides (Wang, 2009). It is tempting to speculate, but unproven, that the consumption of Neu5Gc-rich food, such as meat and dairy products, during childhood induces Neu5Gc incorporation in brain gangliosides, which can hinder MAG binding (Collins et al., 2000). Intriguingly, it was found that common marmosets share the genetic CMAH deficiency with humans, which is a remarkable case of parallel evolution, and could therefore serve as a useful animal model to test the dietary cause of MS (Springer et al., 2014). This means that marmoset EAE provides the ideal preclinical model for testing a dietary cause of MS.

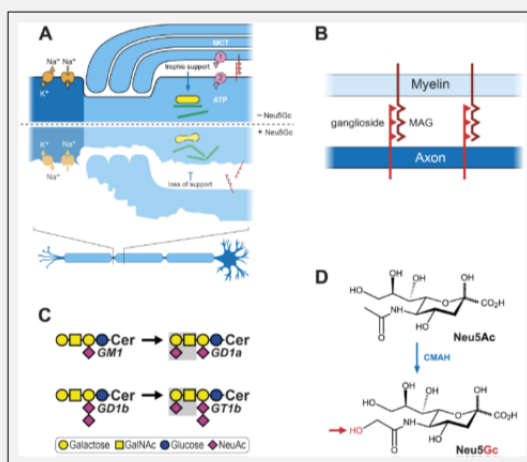


Figure from (t Hart, 2016b)