Anti-hyperglucosylated adhesin of non-typeable *Haemophilus influenzae* antibodies cross reacting with glucopeptides of NogoR and OMGp myelin proteins

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Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). It is accepted that an autoimmune mechanism is involved in the pathogenesis. However, etiology remains still unclear. A combination of genetic and environmental factors can contribute to this complex disease. Bacterial and/or viral infections are more and more accepted to be involved in triggering immune response and therefore disease onset. A molecular mimicry mechanism between bacterial and myelin proteins could explain the aberrant immune response leading to non-self-recognition of self-epitopes in myelin proteins. Possibly, bacterial infections could promote aberrant modifications of CNS myelin proteins causing disruption of self-tolerance. In the case of MS our group has been investigating for more than 15 years the involvement of *N*-glucosylation of asparagines (N-Glc). Recently, we have shown that the hyperglucosylated protein HMW1ct($Glc_{7,8,9}$), expressed by non-Typeable Haemophilus influenzae (NTHi), recognizes specific antibodies in MS patient sera and these antibodies cross-react with structure-based designed N-Glc beta-turn synthetic antigenic probes termed CSF114(N-Glc). By a bioinformatic approach, peptides of myelin-related proteins i.e., FAN (Factor associated with neutral sphingomyelinase activation), OMGp (Oligodendrocyte Myelin Glycoprotein), and NogoR (Nogo Receptor) were selected because of structural and sequon homology with CSF114(N-Glc). Considering that N-Glc peptides [N^{641}(Glc)]FAN(635−655), [N^{179}(Glc)]NogoR(173−191), and [N^{192}(Glc)]OMGp(186−204) recognised anti-CSF114(Glc) antibodies, we present herein that these sequences recognise also anti-hyperglucosylated adhesin antibodies. Interestingly, monoglucosylated peptides [N^{179}(Glc)]NogoR(173−191) and [N^{192}(Glc)]OMGp(186−204) were demonstrated to inhibit anti-hyperglucosylated adhesin antibodies (IC_{50}= $2.7\cdot10^{-7}$M and $1.0\cdot10^{-6}$M respetively), despite the protein bears up to nine N(Glc) minimal epitopes. This first example of short monoglucosylated peptides of NogoR and OMGp (involved in CNS regeneration) is in agreement with molecular mimicry between bacterial and myelin proteins. Moreover, the aberrant glucosylation motif fundamental for antibody recognition, further supports the hypothesis of NTHi bacterial infection stimulating and perpetuating autoimmune response in Multiple Sclerosis.