Abstract

For three decades, the ongoing HIV pandemic has taken the lives of tens of millions of people. Still, more tens of millions are fighting this incurable disease today. Current failures in combating this global problem are caused mainly by the virus's extreme ability of mutation, its very effective molecular shield which repels the immune system's attacks, and its immense variability. A breakthrough, achieved relatively recently, is the discovery of the so-called broadly neutralizing antibodies against HIV-1, which carry a very efficient and broad neutralizing response. So far, it's not known how to elucidate the production of these antibodies in the infected hosts to quell or altogether eliminate the virus. This work deals with experimental results, which led to both *in vivo* and *in vitro* proof-of-concept of the so-called protein mimetics, the ability to imitate viral surface epitopes, and therefore stimulate an efficient immune response carried by targeted broadly neutralizing antibodies. This effect is mediated by recombinant binding proteins, based on the Myomedin scaffold. This work describes the selection and characterization of these binding proteins mimicking the epitopes of one of the most effective broadly neutralizing antibodies, 10E8. It shows that the binding affinities of selected Myomedin proteins are on the order of tens of nM (MLA158 $K_d = 10{,}8$ nM), that the affinity towards isotype control antibody is orders of magnitude less, and that there's a significant difference in binding between these selected variants and the paternal wild-type myomesin-1 protein. This work describes the selection and expression of these proteins, their purification and basic biophysical characterizations. Blood sera of mice, vaccinated by protein variants selected and characterized in this work, were able to effectively neutralize most HIV-1 pseudoviruses selected from a representative set. The *in silico* computational part of this work tries to explain the structures of the binding proteins, their interactions with the 10E8 antibody, and describes specific interactions which could be the cause of the observed biological effect. Based on knowledge brought by these results, mimicking binders could be further improved, bringing the development of an HIV-1 vaccine one step closer to reality.

(in Czech)