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Title: Galectin-3 as a regulator of γ -herpesvirus specific CD8 + T cell immunity and the utility of single domain antibodies

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Abstract: The study was planned to gain insights into the molecular mechanisms and pathways involved in differentiating CD8 + T cells during γ -herpesvirus infection. These viruses are species-specific and hence are studied in a specific host. Murine herpesvirus 68 serve as one of the most accessible model system. CD8 + T cells are critically involved in controlling intracellular infections such as those caused by viruses. A comprehensive transcriptomic analysis of γ -herpesvirus (MHV68)-specific TCR transnuclear (TCR-TN) CD8 + T cells, that were obtained somatic cell nuclear transfer (SCNT) approach, was performed. These cells are considered as physiologically relevant population because of their method of generation that requires no transgenesis. We observed differential expression of several thousand transcripts in γ -HV expanded CD8 + T cells as compared to their naïve counterparts encompassing various pathways and forming different networks. Activated cells highly upregulated galectin-3, a member protein of galectin family. We therefore explored the role of galectin-3 in influencing anti-MHV68 immunity and demonstrated its recruitment intracellularly at immunological synapse (IS) during CD8 + T cell activation. By virtue of its presence at the IS, galectin-3 constrained T cell activation, proliferation and functionality. The localization of galectin-3 to IS was evident both in the naïve and memory CD8 + T cells responding through their TCRs or the coreceptors suggesting for its role as an intrinsic negative regulator. Accordingly, animals lacking galectin-3 signal because of gene knockout mounted a stronger MHV68-specific CD8 + T cell response to the majority viral epitopes displayed by different MHC haplotypes. The enhanced effector CD8 + T cell response led to a better viral control. This study therefore established galectin-3 as a potential intracellular target in γ -herpesvirus specific CD8 + T cells whose function could be disrupted to enhance antiviral immunity. Then we explored the possibility of using single domain antibodies (sdAbs) as intrabodies to disrupt galectin-3 interaction intracellularly. Intrabodies can be efficiently selected from phage display libraries of sdAbs. The genetic information encoded in differentiated camelid B cells is used to generate these libraries. We generated such a library that consisted of more than 20 million clones and biopanned sdAbs not only against galectin- 3 but also against other antigens and some of these tcould have a translational value. The expression of such sdAbs was demonstrated intracellularly. Additionally, sdAbs against the components of snake venom were selected from the phage display libraries and their efficacy in neutralizing the toxicological effects was demonstrated using in vitro assays as well as in vivo zebrafish model. Our data showed that sdAbs can serve as a potent anti-toxin to manage envenoming by snake bites.


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