Novel Chemokine-Based Immunotoxins for Potent and Selective Targeting of Cytomegalovirus Infected Cells

Immunotoxins as antiviral therapeutics are largely unexplored but have promising prospective due to their high selectivity potential and their unparalleled efficiency. One recent example targeted the virus-encoded G protein-coupled receptor US28 as a strategy for specific and efficient treatment of human cytomegalovirus (HCMV) infections. US28 is expressed on virus-infected cells and scavenge chemokines by rapid internalization. The chemokine-based fusion-toxin protein (FTP) consisted of a variant (F49A) of CX3CL1 specifically targeting US28 linked to the catalytic domain of Pseudomonas exotoxin A (PE). Here, we systematically seek to improve F49A-FTP by modifications in its three structural domains; we generated variants with (1) altered chemokine sequence (K14A, F49L, and F49E), (2) shortened and elongated linker region, and (3) modified toxin domain. Only F49L-FTP displayed higher selectivity in its binding to US28 versus CX3CR1, the endogenous receptor for CX3CL1, but this was not matched by a more selective killing of US28-expressing cells. A longer linker and different toxin variants decreased US28 affinity and selective killing. Thereby, F49A-FTP represents the best candidate for HCMV treatment. Many viruses encode internalizing receptors suggesting that not only HCMV but also, for instance, Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus may be targeted by FTPs.