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Bispecific Fc gamma receptor engaging molecules directed against the conserved viral M2 ectodomain protect against influenza A virus infections

Content

Influenza virus infections cause 3 to 5 million cases of severe illness and 250 000 to 500 000 deaths each year. The best way to prevent disease is vaccination. However due to the short immune memory and antigenic drift in the viral hemagglutinin and neuraminidase protein, vaccines need to be administered yearly. Therefore, and as a measure against pandemic influenza outbreaks, antivirals are indispensable in the battle against influenza virus infections. Here, we describe the development of a new antiviral strategy based on the use of bispecific single domain antibodies (VHHs) termed BiFEs (Bispecific Fcg Receptor Engaging molecules), that can simultaneously bind an influenza A virus infected cell and an immune effector cell. The BiFEs were constructed by linking a VHH directed against the conserved ectodomain of the influenza M2 protein (M2e) to a second VHH directed against the mouse Fc gamma receptor I (FcgRI), mouse FcgRIV or human FcgRIIIa protein. BiFEs were recombinantly produced in Pichia pastoris. Using a newly developed cell-based activation assay, we demonstrated the specific and highly selective activation of individual FcgRs in the presence of the BiFEs and influenza A virus-infected cells. In addition, the BiFEs promoted phagocytosis of influenza-infected cells by macrophages. Importantly, BiFEs directed against M2e and mouse FcgRI or –RIV protected BALB/c mice against challenge with influenza X47 (H3N2) virus. These results, together with the ease of production in yeast and the high stability, demonstrate the potential of the BiFEs as a new antiviral treatment option for influenza virus infections.

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