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James Mahony
McMaster University, USA

Single domain antibodies as carriers for antiviral therapeutic proteins

Background: The majority of therapeutic proteins in clinical use today are monoclonal antibodies that target a variety of host cell receptors blocking downstream signalling while others target virus receptors or viral surface proteins blocking infection. Recently a number of antibody-based therapeutics comprising proteins or peptides fused with an Fc receptor have been developed and several have received regulatory approval. More recently, single domain antibodies especially monomeric Fc (mfc) fusion proteins have been developed that offer improved tissue penetration and extended half-life. The objective of this study was to employ mfc domains as a stable scaffold to create novel therapeutic proteins that inhibit respiratory viruses.

Methods: Peptide epitope mapping and GST pull-down assays were used to identify essential binding domains on key viral proteins including influenza virus replicase subunits (PA, PB1, or PB2) and RSV phosphoprotein (RSVP). Peptide mimetics were synthesized by FMOC solid phase synthesis. Peptides alone or peptide fusion proteins employing either a maltose binding protein (MBP) or an mfc scaffold were engineered to contain a HIS tag and a tat nuclear localization signal (NLS). These were tested for antiviral activity using shell vial culture and direct IF staining using commercially available anti-influenza and RSV antibodies.

Results: We first developed peptide mimetic inhibitors (10-20 mer) that block type III secretion (T3S) in C. trachomatis and showed that these prevent infection of host cells. We next developed peptide mimetics that target the Influenza and Respiratory syncytial virus (RSV) replicase/polymerase complex. These peptides inhibited virus replication at concentrations between 10-50 μM. These PB1, PB2 or RSV-P peptides were attached to either a bacterial scaffold protein (MBP) or human serum albumin (HSA) and had antiviral activities in the 5-10 μM range. Influenza PB1 and PB2 peptides and RSV-P peptides expressed as mfc-fusion proteins (His-mfc-NLS-peptide) had extended half-lives (>30 hr) and excellent antiviral activity.

Conclusion: We previously developed peptide mimetics that block essential protein-protein interactions of the C. trachomatis bacterial type III secretion system and prevented host cell infection. We have now extended this approach and developed peptides that block the assembly of the replicase complex of either Influenza or RSV and inhibit virus replication. We have used single antibody domains (mfc) as scaffold proteins to both increase the half-life of these antiviral peptides and allow for the scaled up production of these therapeutic proteins in either yeast or *E. coli*.

Biography

James mahony is a professor and Assistant dean at Medical sciences program at MC Master University USA. His major research interest is the characterization of proteins of the type III secretion system of the obligate intracellular bacterial pathogens C. trachomatis and C. pneumoniae with the goal being to develop small molecule and peptidomimetic inhibitors of this secretion system. Additional research projects include the development of peptide inhibitors for influenza and human meta pneumo virus RNA polymerase, elucidation of how coronaviruses interfere with the innate immune response in myeloid dendritic cells, identification of host cell proteins controlling West Nile virus infection, and development of improved diagnostic tests for potentially pandemic influenza viruses.

mahonyj@mcmaster.ca