Biochemistry

Peptide Chemistry

Applications of Membrane-Interacting Peptides

Cell membranes can be difficult to move molecules across, which is especially true for large biologics like antibodies. While some peptides are capable of easily crossing the membrane, they can be difficult to work with due to their size and short half-life. The lab of **Bill Wimley** uses directed screening methods to engineer peptides with useful, membrane-interacting properties. These have advantages over other membrane-interacting peptides, including resistance to degradation, increased half-life, and smaller size (12-15 amino acids instead of normal 30-40 amino acids peptides). The lab's considerable expertise has allowed them to generate an array of peptides with different uses centering on their membrane-related characteristics.

Antimicrobial Peptides

Antimicrobial peptides are used by would-be host organisms to fend of invading microbes. These molecules work by permeableizing the bacterial membrane. These Defensin peptides are relatively large and can have complex internal bonds that make them difficult to manufacture commercially for use as an exogenous antibiotic treatment. The Wimley Lab is working to make peptides with the same properties that are easier to work with. Through directed screening, they have identified antibiotic peptides that are useful against a variety of pathogenic organisms. Interestingly, the most current iteration of these peptides are highly resilient against even quickly-evolving bacteria like *Pseudomonas* developing resistance. This makes them highly attractive in an era when antibiotic resistance is becoming an increasing problem, and the pipeline for new antibiotics is relatively narrow.

Antiviral Peptides

Enveloped viruses like *influenza* are also vulnerable to membrane-penetrating peptides. Unlike antimicrobial peptides, which can have some bacterial-specific activity due to the different lipids bacteria use in their membranes, anti-viral peptides can (in theory) affect host cells in addition to the virus, as enveloped viruses derive their envelopes from the host cell membrane. Despite this challenge, the Wimley Lab has managed to develop a suite of peptides that appear to have specific anti-viral activity with minimal toxicity to host cells.

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Antiviral Peptides (cont.)

These peptides are active against a variety of enveloped viruses, including *Lassa* and *Influenza*. Currently, there are very few specifically antiviral therapies, and these peptides present a potent potential treatment option against viral diseases.

Membrane Penetrating Peptides

The labs antimicrobial and antiviral peptides rely on the ability of the molecules to form pores in the membranes and envelopes of their targets. Pore formation is not the only useful form of peptide-membrane interaction. Peptides that are able to easily cross the cell membrane can deliver cargo into the cell that otherwise would not be able to pass the lipid bilayer. The lab has developed three classes of short peptides that are able to enter into the cell. The first have a highly positive net charge and enter the cell by a currently-unknown mechanism. These molecules are capable of delivering large biologic payloads (like antibodies) into the cell, making them highly useful in developing therapeutics that target previously inaccessible, internal cellular targets. The second is capable of spontaneously crossing the cell membrane, meaning there is no active transport by the cell. While large biologics like antibodies cannot serve as cargo for these peptides, smaller molecules can. The third is able to form pores in response to a change in pH, potentially taking advantage of the drop in pH that happens after things are internalized by the cell. These peptides offer three different, dynamic ways to bring molecules into the cell.

Membrane-Interacting Peptides Expressed by Ebola

In collaboration with the lab of **Bob Garry,** the lab studies a naturally-occurring membrane-associated peptide: The delta peptide of the *Ebola* virus. This peptide is highly conserved, expressed in large quantities, and its sequence suggests that it may interact with membranes. Using a variety of model systems, this peptide has been shown to be a pore-forming peptide that may contribute to the pathogenesis of *Ebola*, specifically the gastrointestinal symptoms associated with morbidity and mortality, in addition to high levels of disease transmission. Working with a local biotech, the labs are developing potentially diagnostic and therapeutic antibodies against this highly conserved and pathogenically important viral membrane-targeting peptide.

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