7.341 Peptides as Biological Signaling Molecules and Novel Drugs

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All living cells possess the machinery for peptide synthesis, secretion, and posttranslational modifications, which together generate enormous structural and functional peptide diversity. Peptides are broadly used as signal molecules for intercellular communication in prokaryotes, plants, fungi, and animals. Peptide signals in animals include vast numbers of peptide hormones, growth factors and neuropeptides. Some of the best known examples are enkephalins (which help us sense pain), somatotropin (which helps us grow), and insulin and glucagon (both of which regulate our blood glucose levels). In plants, peptide signals such as CLAVATA3 play important roles in development. Peptides are also used as components of host defense systems. What determines the functional specificity of each peptide? How do these small polymers of amino acids survive hostile protein-digesting enzymes? How are peptides able to communicate with specific peptide receptors or interacting proteins for proper function? In this course, we will learn about the molecular bases of peptide signaling. In addition, peptides are promising novel therapeutic agents. For example, antimicrobial peptides (AMPs) have broad spectrum antimicrobial activity against bacteria, viruses, and fungi and are found among all classes of life. The ability of these natural molecules to kill multidrug-resistant microorganisms has gained considerable attention and clinical interest, since multidrug-resistant microorganisms have developed resistance to multiple antimicrobial agents and are difficult to treat with available antibiotics. One of the most notorious multidrug-resistant microorganisms are MRSA, deadly strains of methicillin-resistant *Staphylococcus aureus*. Infections with these pathogenic bacteria are untreatable with known antibiotics like gentamicin, streptomycin and kanamycin**.** Some antimicrobial peptides can kill methicillin-resistant *S. aureus* strains, making these peptides promising future drugs. In this class, we will discuss AMPs, their biological functions, mechanisms of action, and applicability as therapeutic agents. Students will learn about various human defense peptides, such as defensins, and about plant peptides involved in symbiosis, such as nodule-specific cysteine-rich peptides. We will consider techniques to detect, quantify and modify peptides. We will also discuss experimental methods such as high-performance liquid chromatography (HPLC) and liquid chromatography coupled with mass spectroscopy (LC-MS) used for quantification of peptides and other small molecules. We will focus on the primary research literature, and students will learn how to read and critique research papers. Additionally, we will visit Cubist Pharmaceuticals, a pharmaceutical company based in Lexington, MA, which is developing peptides as drugs for various pathological conditions, such as complicated urinary tract infections.