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Several Interdisciplinary of Chemical Biology

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Perspective

Chemical biology is a scientific discipline spanning the fields of chemistry and biology. The discipline involves the application of chemical techniques, analysis, and often small molecules produced through synthetic chemistry, to the study and manipulation of biological systems. In contrast to biochemistry, which involves the study of the chemistry of biomolecules and regulation of biochemical pathways within and between cells, chemical biology deals with chemistry applied to biology (synthesis of biomolecules, simulation of biological systems etc.).

Some forms of chemical biology attempt to answer biological questions by directly probing living systems at the chemical level. In contrast to research using biochemistry, genetics, or molecular biology, where mutagenesis can provide a new version of the organism, cell, or biomolecule of interest, chemical biology probes systems in vitro and in vivo with small molecules that have been designed for a specific purpose or identified on the basis of biochemical or cell-based screening (see chemical genetics).

Chemical biology is one of several interdisciplinary sciences that tend to differ from older, reductionist fields and whose goals are to achieve a description of scientific holism. Chemical biology has scientific, historical and philosophical roots in medicinal chemistry, supramolecular chemistry, bioorganic chemistry, pharmacology, genetics, biochemistry, and metabolic engineering. Chemical biologists work to improve proteomics through the development of enrichment strategies, chemical affinity tags, and new probes. Samples for proteomics often contain many peptide sequences and the sequence of interest may be highly represented or of low abundance, which creates a barrier for their detection. Chemical biology methods can reduce sample complexity by selective enrichment using affinity chromatography. This involves targeting a peptide with a distinguishing feature like a biotin label or a post translational modification. Methods have been developed that include the use of antibodies, lectins to capture glycoproteins, and immobilized metal ions to capture phosphorylated peptides and enzyme substrates to capture select enzymes.

While DNA, RNA and proteins are all encoded at the genetic level, glycans (sugar polymers) are not encoded directly from the genome and fewer tools are available for their study. Glycobiology is therefore an area of active research for chemical biologists. For example, cells can be supplied with synthetic variants of natural sugars to probe their function. Carolyn Bertozzi's research group has developed methods for site-specifically reacting molecules at the surface of cells via synthetic sugars.

Chemical biologists used automated synthesis of diverse small molecule libraries in order to perform high-throughput analysis of biological processes. Such experiments may lead to discovery of small molecules with antibiotic or chemotherapeutic properties. These combinatorial chemistry approaches are identical to those employed in the discipline of pharmacology.

Chemical synthesis of proteins is a valuable tool in chemical biology as it allows for the introduction of non-natural amino acids as well as residue specific incorporation of "posttranslational modifications" such as phosphorylation, glycosylation, acetylation, and even ubiquitination. These capabilities are valuable for chemical biologists as non-natural amino acids can be used to probe and alter the functionality of proteins, while post translational modifications are widely known to regulate the structure and activity of proteins. Although strictly biological techniques have been developed to achieve these ends, the chemical synthesis of peptides often has a lower technical and practical barrier to obtaining small amounts of the desired protein.

In order to make protein-sized polypeptide chains via the small peptide fragments made by synthesis, chemical biologists use the process of native chemical ligation. Native chemical ligation involves the coupling of a C-terminal thioester and an N-terminal cysteine residue, ultimately resulting in formation of a "native" amide bond. Other strategies that have been used for the ligation of peptide fragments using the acyl transfer chemistry first introduced with native chemical ligation include expressed protein ligation, sulfurization/desulfurization techniques, and use of removable thiol auxiliaries. Expressed protein ligation allows for the biotechnological installation of a C-terminal thioester using inteins, thereby allowing the appendage of a synthetic N-terminal peptide to the recombinantly-produced C-terminal portion. Both sulfurization/desulfurization techniques and the use of removable thiol auxiliaries involve the installation of a synthetic thiol moiety to carry out the standard native chemical ligation chemistry, followed by removal of the auxiliary/thiol.

Chemical biologists often study the functions of biological macromolecules using fluorescence techniques. The advantage of fluorescence versus other techniques resides in its high sensitivity, non-invasiveness, safe detection, and ability to modulate the fluorescence signal. Fluorescent techniques have been used assess a number of protein dynamics including protein tracking, conformational changes, protein–protein interactions, protein synthesis and turnover, and enzyme activity, among others. Three general approaches for measuring protein net redistribution and diffusion are single-particle tracking, correlation spectroscopy and photomarking methods. In single-particle tracking, the individual molecule must be both bright and sparse enough to be tracked from one video to the other. Correlation spectroscopy analyzes the intensity fluctuations resulting from migration of fluorescent objects into and out of a small volume at the focus of a laser. In photomarking, a fluorescent protein can be dequenched in a subcellular area with the use of intense local illumination and the fate of the marked molecule can be imaged directly. Michalet and coworkers used quantum dots for single-particle tracking using biotin-quantum dots in Hela cells.

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