Assignment

What are natural products? How these compounds are different from primary metabolites? Explain their classes and biosynthesis. Also their role in antibiotic discovery

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Natural Products

A natural product is a chemical compound or substance produced by a living organism—that is, found in nature. In the broadest sense, natural products include any substance produced by life.[4][5] Natural products can also be prepared by chemical synthesis (both semi synthesis and total synthesis) and have played a central role in the development of the field of organic chemistry by providing challenging synthetic targets. The term natural product has also been extended for commercial purposes to refer to cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients. Within the field of organic chemistry, the definition of natural products is usually restricted to organic compounds isolated from natural sources that are produced by the pathways of primary or secondary metabolism. Within the field of medicinal chemistry, the definition is often further restricted to secondary metabolites. Secondary metabolites are not essential for survival, but nevertheless provide organisms that produce them an evolutionary advantage. Many secondary metabolites are cytotoxic and have been selected and optimized through evolution for use as "chemical warfare" agents against prey, predators, and competing organisms.

Natural sources may lead to basic research on potential bioactive components for commercial development as lead compounds in drug discovery. Although natural products have inspired numerous drugs, drug development from natural sources has received declining attention in the 21st century by pharmaceutical companies, partly due to unreliable access and supply, intellectual property, cost, and profit concerns, seasonal or environmental variability of composition, and loss of sources due to rising extinction rates.

How these compounds are different from primary metabolites.

Natural products are often divided into two major classes, the primary and secondary metabolites. Primary metabolites have an intrinsic function that is essential to the survival of the organism that produces them. Secondary metabolites in contrast have an extrinsic function that mainly affects other organisms. Secondary metabolites are not essential to survival but do increase the competitiveness of the organism within its environment. Because of their ability to modulate biochemical and signal transduction pathways, some secondary metabolites have useful medicinal properties. Natural products especially within the field of organic chemistry are often defined as primary and secondary metabolites. A more restrictive definition limiting natural products to secondary metabolites is commonly used within the fields of medicinal chemistry and pharmacognosy.

Classes

The broadest definition of natural product is anything that is produced by life, and includes the likes of biotic materials (e.g. wood, silk), bio-based materials (e.g. bio plastics, cornstarch), bodily fluids (e.g. milk, plant exudates), and other natural materials (e.g. soil, coal). A more restrictive definition of a natural product is an organic compound that is synthesized by a living organism. The remainder of this article restricts itself to this more narrow definition.

Natural products may be classified according to their biological function, biosynthetic pathway, or source. One estimate of the number of natural product molecules is about 326,000. The natural products have two main classes.

Primary metabolites

Primary metabolites as defined by Kossel are components of basic metabolic pathways that are required for life. They are associated with essential cellular functions such as nutrient assimilation, energy production, and growth/development. They have a wide species distribution that spans many phyla and frequently more than one kingdom. Primary metabolites include carbohydrates, lipids, amino acids, and nucleic acids which are the basic building blocks of life.

Primary metabolites that are involved with energy production include respiratory and photosynthetic enzymes. Enzymes in turn are composed of amino acids and often non-peptidic cofactors that are essential for enzyme function.[19] The basic structure of cells and of organisms are also composed of primary metabolites. These include cell membranes (e.g. phospholipids), cell walls (e.g. peptidoglycan, chitin), and cytoskeletons (proteins).

Primary metabolite enzymatic cofactors include members of the vitamin B family. Vitamin B1 as thiamine diphosphate is a coenzyme for pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase, and transketolase which are all involved in carbohydrate metabolism. Vitamin B2 (riboflavin) is a constituent of FMN and FAD which are necessary for many redox reactions. Vitamin B3 (nicotinic acid or niacin), synthesized from tryptophan is a component of the coenzymes NAD^+ and $NADP^+$ which in turn are required for electron transport in the Krebs cycle, oxidative phosphorylation, as well as many other redox reactions. Vitamin B5 (pantothenic acid) is a constituent of coenzyme A, a basic component of carbohydrate and amino acid metabolism as well as the biosynthesis of fatty acids and polyketides. Vitamin B6 (pyridoxol, pyridoxal, and pyridoxamine) as pyridoxal 5′-phosphate is a cofactor for many enzymes especially transaminases involve in amino acid metabolism. Vitamin B12 (cobalamins) contains a corrin ring similar in structure to porphyrin and is an essential coenzyme for the catabolism of fatty acids as well for the biosynthesis of methionine.

DNA and RNA which store and transmit genetic information are composed of nucleic acid primary metabolites. First messengers are signaling molecules that control metabolism or cellular differentiation. These signaling molecules include hormones and growth factors in turn are composed of peptides, biogenic amines, steroid hormones, auxins, gibberellins etc. These first messengers interact with cellular receptors which are composed of proteins. Cellular receptors in turn activate second messengers are used to relay the extracellular message to intracellular targets. These signaling molecules include the primary metabolites cyclic nucleotides, diacyl glycerol etc.

Secondary metabolites

Secondary metabolites in contrast to primary metabolites are dispensable and not absolutely required for survival. Furthermore, secondary metabolites typically have a narrow species distribution. Secondary metabolites have a broad range of functions. These include pheromones that act as social signaling molecules with other individuals of the same species, communication molecules that attract and activate symbiotic organisms, agents that solubilize and transport nutrients (siderophores etc.), and competitive weapons (repellants, venoms, toxins etc.) that are used against competitors, prey, and predators. For many other secondary metabolites, the function is unknown. One hypothesis is that they confer a competitive advantage to the organism that produces them. An alternative view is that, in analogy to the immune system, these secondary metabolites have no specific function, but having the machinery in place to produce these diverse chemical structures is important and a few secondary metabolites are therefore produced and selected for. General structural classes of secondary metabolites include alkaloids, phenylpropanoids, polyketides, and terpenoids.

Biosynthesis

The biosynthetic pathways leading to the major classes of natural products are described below

- Photosynthesis or gluconeogenesis → monosaccharides → polysaccharides (cellulose, ch itin, glycogen etc.)
- Acetate pathway → fatty acids and polyketides
- Shikimate pathway → aromatic amino acids and phenylpropanoids
- Mevalonate pathway and methyletrythritol phosphate pathway → terpenoids and steroids
- Amino acids → alkaloids
- Carbohydrates

Carbohydrates

Carbohydrates are an essential energy source for most life forms. In addition, polysaccharides formed from simpler carbohydrates are important structural components of many organisms such the cell walls of bacteria and plants.

Carbohydrates are the products of plant photosynthesis and animal gluconeogenesis. Photosynthesis produces initially 3-phosphoglyceraldehyde, a three carbon atom containing sugar (a triose). This triose in turn may be converted into glucose (a six carbon atom containing sugar) or a variety of pentoses (five carbon atom containing sugars) through the Calvin cycle. In animals, the three carbon precursors lactate or glycerol can be converted into pyruvate which in turn can be converted into carbohydrates in the liver.

Fatty acids and polyketides

Through the process of glycolysis sugars are broken down into acetyl-CoA. In an ATP dependent enzymatically catalyzed reaction, acetyl-CoA is carboxylated to form malonyl-CoA. Acetyl-CoA and malonyl-CoA undergo a Claisen condensation with lose of carbon dioxide to form acetoacetyl-CoA. Additional condensation reactions produce successively higher molecular weight poly-β-keto chains which are then converted into other polyketides. The polyketide class of natural products has diverse structures and functions and includes prostaglandins and macrolide antibiotics.

One molecule of acetyl-CoA (the "starter unit") and several molecules malonyl-CoA (the "extender units") are condensed by fatty acid syntheses to produce fatty acids. Fatty acid are essential components of lipid bilayers that form cell membranes as well as fat energy stores in animals.

Role in antibiotics discovery

The development of antibiotics for human chemotherapy is one of the most important medical advances of the twentieth century; the vast majority of antibiotics in clinical use are microbial natural products or their semisynthetic derivatives. Pharmaceutical companies have been unsuccessful in identifying new antibiotics by screening libraries of synthetic compounds, because their chemical collections lack suitable chemical diversity tuned to entry into and retention by bacterial cells. Since natural products possess more of the physiochemical properties required for in vivo activity, there is a growing movement toward a return to these compounds for antibiotic discovery. Traditional screening methods for new antibiotics are plagued by the rediscovery of known compounds; consequently, new strategies are required to find new activity. For example, using medicinal chemistry to revisit discarded or underexplored scaffolds, or screening for adjutants (e.g., inhibitors of resistance enzymes) can breathe new life into old antibiotics. The chemical diversity of antibiotics can also be increased by exploring new sources for antibiotic-producing organisms, by employing synthetic biology approaches using known scaffolds, and by mining genomes for silent or cryptic biosynthetic clusters.