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A 'Nobel' Look at Metabolism

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Metabolism has recently been in the spotlight because of technical advances in metabolite measurement; however, it is not a new topic in the Nobel Prize's history. Emerging evidence suggests that metabolism is more complex than was previously believed. Retrospective analysis of the Nobel Prize-winning metabolic discoveries may inspire future studies.

Metabolism (from the Greek word 'metabolē', meaning 'change') is the sum of all life-sustaining chemical reactions within living organisms. An organism, as an open system, requires metabolism to exchange matter and energy with its surroundings. In thermodynamic terms, metabolism maintains order and minimum entropy (the degree of disorder) in organisms [1]. In his book *What is Life?*, the physicist Erwin Schrödinger proposed that organisms feed on negative entropy to make use of order in nutrients [2]. Nutrients can be classified into two groups based on the quantity needed in the human diet: (i) macronutrients (carbohydrates, lipids, proteins, and water), required in relatively large amounts; and (ii) micronutrients (vitamins and minerals), consumed in smaller amounts [3]. According to the metabolic basis for these nutrients, the Nobel Prize-winning breakthroughs in metabolism can be roughly categorized into four groups spanning approximately 100 years of research (Table 1).

The Nobel Prize (hereafter prize) is arguably the world's most coveted scientific honor. At least 24 prizes have been awarded for work related to metabolism: 10 times to 15 laureates in Chemistry and 14 times to 28 laureates in Physiology or Medicine (Figure 1) [4]. For the general public, insights into metabolism have substantially added to the knowledge of life science. In this report, I summarize the metabolic discoveries in the Nobel Prize's history.

Carbohydrates

Among macronutrients, carbohydrates are the body's main source of energy. Sugar, a type of carbohydrate, is common in nearly all processed foods [3,5]. In 1902, the second prize in Chemistry was awarded for Emil Fischer's pioneering work on sugar and purine syntheses. Further investigations on the compositions and structure of carbohydrates, including sugar, partially earned Norman Haworth the prize in 1937. Thirty-three years later, Luis Leloir received the prize for his leading discovery of sugar nucleotides. The achievements of these eminent scientists serve as the structural underpinning for carbohydrate synthesis (Figure 1, no. 1, 11, 19). Moreover, for his landmark work addressing how the oxygen supply to muscles in the circulatory system is tightly regulated, August Krogh was awarded the prize in 1920, paving the way for in-depth studies of the metabolic mechanisms of carbohydrates (Figure 1, no. 2) [4].

Two years later, research on the oxygen consumption-related conversions between carbohydrates and lactic acids that contribute to heat production in muscle was recognized with a prize (Figure 1, no. 3). Another critical conversion involving carbohydrates is fermentation. Thousands of years ago, people discovered how to ferment sugar into alcohol to preserve food and prepare beverages including beer and wine. Therefore, it is not surprising that the elucidation of the fermentation process and fermentative enzymes was awarded the prize in 1929. The prize-winning Krebs cycle, also known as the tricarboxylic acid cycle, delineated how glucose, a simple sugar, is broken down through a set of key chemical reactions. The discovery of the Krebs cycle came from the efforts of Hans Krebs and two other laureates, Fritz Lipmann, who discovered coenzyme A, and Albert Szent-Györgyi, who characterized the catalysis of fumaric acids [4,6]. Together, these studies establish our fundamental understanding of the nature of carbohydrate catabolism (Figure 1, no. 6, 10, 15).

Metabolism consists of two types of reactions: catabolism and anabolism. Catabolism involves the breakdown of molecules and the release of energy. Conversely, anabolism refers to the metabolic reactions that construct more complex molecules from simpler units [5]. Glycogen is the primary storage form of carbohydrates in mammals for reserving energy. The course of catalytic conversion of glycogen was depicted in a collaboration by Carl and Gerty Cori. The couple shared the prize in 1947 with Bernardo Houssay, who revealed the pivotal role of the anterior pituitary-derived hormones in carbohydrate metabolism by counteracting and balancing the effects of insulin (Figure 1, no. 14). Insulin is a peptide hormone that regulates blood glucose levels by promoting glycogen deposition in liver and muscles. Given the importance of insulin in treating diabetes, its discovery, and structural identification, as well as the development of its radioimmunoassay, were awarded the prizes (Figure 1, no. 4, 16, 20). It has become apparent that most dietary carbohydrates come from foods of plant origin. The large-scale carbohydrate anabolism in plants occurs generally via photosynthetic carbon assimilation, and the prize in 1961 was awarded to Melvin Calvin for this groundbreaking study (Figure 1, no. 17) [4].

Table 1. Metabolic Research and Laureates in the History of the Nobel Prize [4]

Topic	Year	Category	Laureates	Contributions/discoveries
Carbohydrates	1902	Chemistry	Hermann Emil Fischer	Work on sugar and purine syntheses
	1920	Physiology or Medicine	Schack August Steenberg Krogh	Discovery of the capillary motor regulating mechanism
	1922	Physiology or Medicine	Archibald Vivian Hill and Otto Fritz Meyerhof	Discovery of heat production and the relationship between oxygen consumption and lactic acid metabolism in the muscle
	1923	Physiology or Medicine	Frederick Grant Banting and John James Rickard Macleod	Discovery of insulin
	1929	Chemistry	Arthur Harden and Hans Karl August Simon von Euler-Chelpin	Work on the fermentation of sugar and fermentative enzymes
	1937	Chemistry	Walter Norman Haworth[a] and Paul Karrer	Work on vitamins (C, A, B2), carbohydrates, carotenoids, and flavins
	1947	Physiology or Medicine	Carl Ferdinand Cori, Gerty Theresa Cori, and Bernardo Alberto Houssay	Discovery of metabolic processes of glycogen and sugar
	1953	Physiology or Medicine	Hans Adolf Krebs and Fritz Albert Lipmann	Discovery of the citric acid cycle and coenzyme A
	1958	Chemistry	Frederick Sanger	Work on the structure of insulin
	1961	Chemistry	Melvin Calvin	Work on the CO_2 assimilation in plants
	1970	Chemistry	Luis F. Leloir	Discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates
	1977	Physiology or Medicine	Roger Guillemin, Andrew V. Schally, and Rosalyn Yalow	Discoveries concerning the production and radioimmunoassays of peptide hormones
Vitamins	1928	Chemistry	Adolf Otto Reinhold Windaus[b]	Work on the constitution of the sterols and their connection with the vitamins
	1929	Physiology or Medicine	Christiaan Eijkman and Sir Frederick Gowland Hopkins	Discovery of the antineuritic and growth-stimulating vitamin(s)
	1934	Physiology or Medicine	George Hoyt Whipple, George Richards Minot, and William Parry Murphy	Discoveries concerning liver therapy in cases of anemia
	1937	Physiology or Medicine	Albert von Szent-Györgyi Nagyrápolt	Discoveries in connection with the biological combustion processes, with special reference to vitamin C and the catalysis of fumaric acid
	1937	Chemistry	Walter Norman Haworth[a] and Paul Karrer	Work on vitamins (C, A, B2), carbohydrates, carotenoids, and flavins
	1938	Chemistry	Richard Kuhn	Work on carotenoids and vitamins
	1943	Physiology or Medicine	Henrik Carl Peter Dam and Edward Adelbert Doisy	Discovery of vitamin K and its chemical nature
Lipids	1928	Chemistry	Adolf Otto Reinhold Windaus[b]	Work on the constitution of the sterols and their connection with the vitamins
	1964	Physiology or Medicine	Konrad Bloch and Feodor Lynen	Discoveries concerning the mechanism and regulation of cholesterol and fatty acid metabolism
	1985	Physiology or Medicine	Michael S. Brown and Joseph L. Goldstein	Discoveries concerning the regulation of cholesterol metabolism

Table 1. (continued)

Topic	Year	Category	Laureates	Contributions/discoveries
Proteins, Water, and Minerals	1931	Physiology or Medicine	Otto Heinrich Warburg	Discovery of the nature and mode of action of respiratory enzyme
	1992	Physiology or Medicine	Edmond H. Fischer and Edwin G. Krebs	Discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism
	1997	Chemistry	Paul D. Boyer, John E. Walker, and Jens C. Skou	Work on the enzymatic mechanism underlying the synthesis of ATP
	2003	Chemistry	Peter Agre and Roderick MacKinnon	Discoveries concerning channels in cell membranes

[a]Norman Haworth was awarded the Nobel Prize for his studies with regard to both carbohydrates and vitamins.
[b]Adolf Windaus was awarded the Nobel Prize for his studies with regard to both lipids and vitamins.

Vitamins

Unlike carbohydrates, which are macronutrients, vitamins are essential micronutrients in the diet, albeit in small quantities, that cannot be synthesized by our bodies and the deficiency of which leads to severe diseases [3]. For example, vitamin B1 was found in the husk of rice, with the capacity to protect against beriberi, a chronic illness caused by vitamin B1 deficiency with symptoms including muscular atrophy and paralysis. Further details were subsequently added with respect to how vitamin B1 affects the Krebs cycle through regulation of enzymatic activities and functions [7]. The discovery of vitamin B1, along with the initial work on the growth-stimulating vitamins, was awarded the prize in 1929 (Figure 1, no. 7). Interestingly, the formation of new blood cells was stimulated in dogs fed with liver. Based on this observation, vitamin B12 was determined as a necessary substance for the prize-winning liver therapy in treating patients with red blood cell-deficient pernicious anemia (Figure 1, no. 9). In 1937, the prizes were awarded for the work on vitamin C (Figure 1, no. 10, 11). Historically, the preventive effects of citrus fruits on vitamin C deficiency-induced scurvy were recorded by a Royal Navy surgeon, James Lind, in 1747 [8]. The work regarding vitamins A, B2, and B6 were included in the prize in 1937 and 1938 (Figure 1, no. 11, 12). The most recent prize-winning vitamin is vitamin K. Prompted by the findings that the vitamin K-containing hempseed helped blood coagulation, an approach was developed to treat bleeding (Figure 1, no. 13) [4]. Because of the accumulated knowledge on vitamins, we know that 13 vitamins are required for human health: four fat-soluble vitamins (A, D, E, and K) and nine water-soluble vitamins (C and eight B vitamins).

Lipids

A lipid is a biomolecule that is highly soluble in nonpolar solvents but largely insoluble in polar solvents (e.g., water). Two main subtypes of lipids are sterols (such as cholesterols) and those containing fatty acids, and the related research was awarded three prizes (Figure 1, no. 5, 18, 21). In search of the composition of cholesterols and their closely related sterols, Adolf Windaus demonstrated that ergosterols are effective in treating rickets, a condition that is commonly caused by vitamin D deficiency and results in weak or soft bones [4]. Moreover, the research on the regulation of cholesterol and fatty acid metabolism became a stepping stone toward the first statin drug available to the public, lovastatin, in 1987. Lovastatin is a cholesterol-lowering drug used to reduce cardiovascular disease (CVD), and the birth of life-saving statins can be attributed to these prize-winning studies of lipids [9].

Proteins, Water, and Minerals

Enzymes are mainly globular proteins. Almost all metabolic processes in living cells require enzymatic catalysis to maintain the necessary chemical reaction rates. Cellular respiration is a set of catabolic reactions that converts nutrients into the energy currency ATP [5]. Otto Warburg provided compelling evidence for the nature and mode of the respiratory enzyme hemoglobin. His work and studies on the enzymatic mechanism underlying ATP synthesis were awarded the prize in 1931 and 1997 (Figure 1, no. 8, 23). Another prize-winning enzymatic mechanism related to metabolic regulation is reversible protein phosphorylation (Figure 1, no. 22). Moreover, proteins can assemble in channels in the cell membrane for transporting water and mineral ions, both of which are essential substances for human biochemical processes [4,5] (Figure 1, no. 24). The prize-winning studies on the enzymes and membrane channels opened the gate to understand how the processing and transfer of matter and energy are driven in a cell.

Concluding Remarks

In Alfred Nobel's last will, he stated that the Nobel Prize laureates should have conferred 'the greatest benefits on

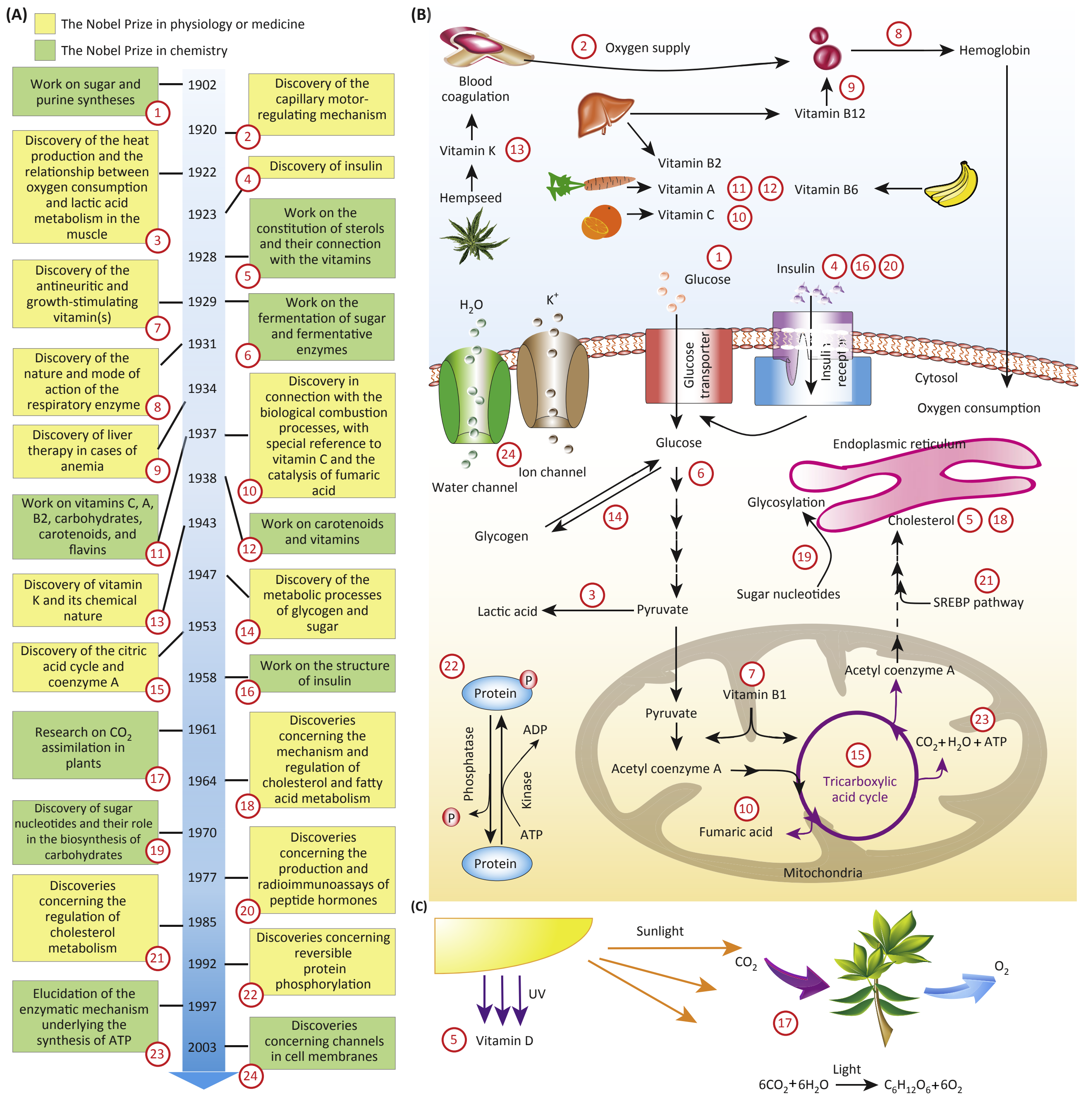

Figure 1. Overview of Metabolism-Related Nobel Prizes. (A) Timeline of the Nobel Prize-winning metabolic research. (B) Schematic presentation of the major discoveries awarded a Nobel Prize in (A) (events with numbers 1–4, 6–16, and 18–24). (C) The Nobel Prizes in Chemistry in 1928 and 1961 were awarded for the studies on UV-induced synthesis of vitamin D [event with number 5 in (A)] and sunlight-driven CO_2 assimilation in plants [event with number 17 in (A)], respectively. Abbreviations: P, phosphate group; SREBP, sterol regulatory element binding protein.

mankind' [10]. Therefore, many studies on carbohydrates and vitamins were awarded at the early years of the prize, when society had relatively insufficient knowledge and availability of food and medicine. The CVD epidemic due to a drastic lifestyle change refocused research efforts to target cholesterols as an anti-CVD strategy. The post-genomic era has also seen several advances in the research of proteins, including metabolic enzymes and membrane channels [4]. While the prize-winning studies were performed in diverse animal models, we now know that the biochemistry of metabolism has been highly conserved across species during evolution [11].

Metabolism has evolved a complex network of signaling pathways that is rewired to meet considerably different metabolic requirements of unhealthy cells to normal cells [12,13]. Targeting the metabolic dependencies of abnormal cells will be a promising therapy in clinical settings [14]. Moreover, the discovery of novel metabolites, along with technological and conceptual advances in metabolomics and isotope tracing, will illuminate the mechanisms underlying metabolic diseases [15]. Although metabolic research has not been awarded the prize in the past 15 years, I believe that in the future, the Nobel Prize will reward scientists in the field of metabolism who address a true unmet medical need for new treatments for serious metabolic diseases, such as diabetes and inborn errors of metabolism.

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Spotlight

Firing Up Glycolysis: BCG Vaccination Effects on Type 1 Diabetes Mellitus

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In addition to the impact of Bacillus Calmette–Guerin (BCG) vaccination on antimicrobial host defence, a novel study reveals beneficial effects on glycaemic control in patients with long-standing type 1 diabetes mellitus (T1DM). These effects are ascribed to an accelerated glucose consumption in immune cells due to increased glycolysis and reduced oxidative phosphorylation.

BCG is one of the oldest vaccines in use, and still the only one available for the prevention of TB. Interestingly, however, aside from the effect on its target infection, a growing body of evidence also points to heterologous protective 'nonspecific effects' (NSE) of BCG against other infections [1]. Broad immunological effects have been proposed to mediate the nonspecific protective effects of BCG, including activation of a heterologous T cell response [2] and/or epigenetic and functional reprogramming of innate immune cells, such as monocytes and macrophages, a process called 'trained immunity' [3]. Interestingly, induction of trained immunity is accompanied by robust changes in the cellular metabolism of myeloid cells, including a strong increase in glycolysis [4].

In addition to the impact of BCG vaccination on antimicrobial host defences, an increasing number of studies also report effects on allergic and autoimmune disease. An interesting novel study published in June 2018 in *NPJ Vaccines* by Kühtreiber *et al*. adds to this body of evidence by revealing potent effects of BCG vaccination on glycaemic control of patients with T1DM and an average disease duration of 19 years [5]. The authors undertook the difficult but important task of performing a prospective long-term trial assessing the effects of BCG vaccination on the regulation of glucose metabolism. Although no improvements in diabetes-associated parameters were observed directly after vaccination with BCG, a robust reduction in HbA_{1c} levels of almost 10% after 3 years and up to 18% 4 years after receiving the BCG vaccine was reported. No effects were observed on β cell regeneration