THE INTEGRATION AND CONTROL OF METABOLISM pdf

1: Chapter 22 : Integration and Hormonal Regulation of Mammalian Metabolism

Metabolic control: Design of metabolic pathways. Regulatory enzymes fine control (allosteric, substrate/product feed-back and feed-forward controls, covalent modification) and coarse control (induction and repression of enzyme synthesis).

Control of Carbohydrate Metabolism; the "Phosphofructokinase-Fructose bisphosphate phosphatase Couple". Blood sugar, or glucose, is the major source of energy for many tissues. Blood cells and the brain are normally completely dependent upon blood sugar. Their metabolism is locked to this substrate and they have no reserve carbohydrate. Glycogen stores are not found in these tissues. And, while skeletal muscle can cover much of its energy requirement through oxidation of fats, hard working muscle uses carbohydrates. Muscle tissue can, in fact, take up so much glucose from the circulation that hypoglycemia and loss of consciousness results. We can get an overview of regulation of carbohydrate by studying hepatic metabolism. We find all of the hormone and enzyme functions that control carbohydrate metabolism there. The major control points in glycolysis and gluconeogenesis are the enzymes which catalyze the reactions between fructosephosphate and fructose-1,6-bisphosphate. Phosphofructokinase-1 PFK-1 and fructose bisphosphate phosphatase are regulated by allosteric "feedback" mechanisms and by hormones. They are regulated by common signal substances. However, these have opposite effects on these two enzymes and, therefore, upon metabolism. Let us look at PFK-1 first. The PFK-1 step is the slowest in glucose metabolism glycolysis. It is, therefore, very well suited as THE primary controlling point in this process. PFK-1 is sensitive to the physiological concentrations of these nucleotides and its activity increases as AMP levels increase. PFK-1 is also sensitive to citrate which is released from the mitochondria to the cytosol when the liver uses fatty acids. This occurs between meals and is a part of the "fatty acids spare carbohydrate" business. Both PFK-1 and fructose-1,6-bisphosphate phosphatase are regulated by another of those "fructose-diphosphate" things. A hormone sensitive kinase, phosphofructokinase-2, produces the 2,6 bisphosphate from fructosephosphate. This kinase is subject to cyclic AMP-stimulated phosphorylation. The phosphorylated form has phosphatase activity, not kinase activity. The phosphorylated form uses fructose-2,6-bisphosphate as its substrate, thus reversing the effects of the non-phosphorylated PFK Fructose-2,6-bisphosphatase controls carbohydrate metabolism by regulating the activities of PFK-1 and fructose bisphosphate phosphatase. Hormones that increase the rate of glycolysis increase the level of fructose-2,6-bisphosphate. Hormones that phosphorylate PFK-2 reduce the levels of fructose-2,6-bisphosphate and favor gluconeogenesis. The liver is sensitive to several hormones that increase cyclic AMP. These are glucagon, adrenalin and noradrenalin. These inhibit glycolysis by reducing the concentrations of an activator of PFK-1 fructose-2,6-bisphosphate. The same hormones stimulate gluconeogenesis by removing an inhibitor of the key enzyme by inhibiting the action of an inhibitor. Thus, insulin activates glycolysis by increasing the activity of PFK-2 and synthesis of fructose-2,6-bisphosphate. This is coordinated with inhibition of gluconeogenesis at the fructose bisphosphate phosphatase step by the same signaling substance. In summary, it is fructose-2,6-bisphosphate levels that are a major regulator of carbohydrate metabolism. This is a control substance synthesized in answer to stress or hunger and geared towards stabilizing blood glucose levels. The constant adjustment in the rates of PFK-1 and fructose bisphosphate phosphatase lead to fluctuations in the concentrations of metabolites before and after these reaction steps. In most tissues, hexokinase is responsible for the initial reaction in glycolysis, phosphorylation of glucose and formation of GP. Hexokinase is inhibited by physiological concentrations of this intermediate. This markedly inhibits hexokinase activity and reduces uptake of glucose to most cells. In most tissues there follows a control point which was explained earlier in respect to "the carbohydrate-sparing effect of fatty acids". If there is an acetyl-CoA excess in mitochondria, this will "turn off" conversion of pyruvate to acetyl-CoA. A "backup" in glycolysis results, turning off glucose metabolism. Hepatic energy metabolism quite generalized and most of the possible metabolic pathways operate in the liver. However, some significant differences are found. The major glucose-phosphorylating enzyme in the liver is glucokinase. This enzyme is not product-inhibited and the glucokinase reaction proceeds rapidly even when PFK-1 is overwhelmed with

substrate. This ensures uptake and storage of sugar in the liver after meals. The liver has several means of storing glucose. It can be stored as glycogen to be used to rapidly stabilize blood sugar levels in postprandial periods and during exercise. Glucose in excess of that required for energy metabolism and glycogen storage is converted to fatty acids and triglycerides. These are then sent out into the circulation as VLDL for transport to and storage in adipose tissue. Excessively high blood sugar levels lead to increased blood triglycerides through this mechanism. Hepatic carbohydrate metabolism is strongly influenced by insulin and glucagon. These hormones stabilize blood sugar levels through regulation of glycolysis and gluconeogenesis. Insulin acts at three major points: Glucagon and adrenalin activate glucose formation and release from the liver to stabilize blood glucose between meals and under physical work. The latter through the PFK-2 - fructose-2,6-bisphosphatase system. Metabolic Control is Organ Specific Differing enzymatic makeup gives differing metabolic patterns. The mechanisms of metabolic integration would be much easier to understand if they were common for our various organs. Unfortunately for ease of understanding, not function this is not the case. All of our cells are equipped with the same genetic information. In spite of this, the various cell types express or suppress differing genes. Tissues differ, therefore, in their enzymatic makeup, in their hormone responsiveness and the possibilities for transport of various substances over cell membranes. There are countless examples of differing enzymatic activities in our various tissues. I will pinpoint just a few examples here. We can use hepatic metabolism as a "reference", since the liver carries out most of the steps in carbohydrate and lipid metabolism. Here we have both active glycolysis and gluconeogenesis, deamination of amino acids and ureogenesis and lipid synthesis. In spite of the fact that skeletal muscle uses much of the glucose we consume or produce daily, muscle does not carry out gluconeogenesis, cannot dephosphorylate GP and, therefore, cannot generate glucose and stabilize blood sugar levels. Muscle lacks receptors for glucagon and does not react to the increases in glucagon levels seen postprandial. The relatively large glycogen reserves in skeletal muscle cannot be mobilized to buffer blood sugar but are important for energy metabolism in muscle. These are activated through the adrenergic nervous system and adrenalin. The energy stored as muscle glycogen can only be utilized in the muscle cells where it is found. However, if it is used in anaerobic metabolism that is, from glycogen to pyruvate and lactate the lactic acid formed can be transported to other tissues. Both the heart and kidneys use quantities of lactate produced in other tissues. Unlike the liver, skeletal muscle lacks fatty acid synthetase and cannot synthesize fatty acids and triglycerides. In spite of this, the initial step in fatty acid synthesis, acetyl-CoA carboxylase, is active and is subject to control by AMP-kinase. Energy metabolism in the brain is normally based wholly on glucose. The brain has no glycogen reserve. Glucose, which the brain is normally completely dependent upon, must come from the circulation. If blood glucose levels fall below 2. The so-called blood-brain-barrier prevents uptake of fatty acids into the brain. These can partially replace glucose as they are transported over the plasma membrane into the brain. One can ask "why can those energy-rich ketone bodies only replace about half of the glucose requirement in the brain"? These form the barrier across which fatty acids cannot cross. There, the lactate serves as the substrate for aerobic metabolism and energy winning. The glia cells appear to be partially dependent upon anaerobic metabolism for which and ketone bodies are not substrate. A similar system is found in the testes, where Sertoli cells form a barrier between the circulation and germ cells. Sertoli cells produce lactate and send it to germ cell where it is used in energy metabolism. Blood cells lack mitochondria and, therefore, are unable to fully oxidize glucose, their only energy substrate. These cells also produce lactate which is largely taken up by the kidneys and used as a substrate both for energy metabolism and by gluconeogenesis. Metabolic cooperation between cells and the various organs is is the key to healthy survival. Working together is essential even though individual cells just might not know this! And the big question is, what is the master key? All energy-requiring bodily functions use ATP as the direct energy source. AMP kinase increases energy metabolism by increasing glucose uptake by working muscles and through activating fatty acid metabolism. It inhibits fatty acid synthesis, transfer of high-energy phosphate groups from phosphocreatine, inhibits cholesterol synthesis, DNA translation and apoptosis, or programmed cell death. Thus, the balance between the adenine nucleotides catalyzed by adenylate kinase is tightly coupled to mitochondrial energy production as well as anaerobic carbohydrate metabolism. Work at lower levels which continues over time uses

mitochondrial oxidation of fatty acids to generate ATP. Research conducted during the past five years or so has revealed that the AMPK system is far more complex than previously thought.

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2: Integration of Metabolism

Drs Naa Adamafio, Laud Okine, and Jonathan Adjimani teach the various aspects of the integration and control of metabolism at the University of Ghana. They obtained their PhD degrees in biochemistry from Monash University, Australia, the University of Surrey, UK, and Utah State University, USA, respectively.

Fully understanding the complex process of the integration and control of metabolism in cellular organisms requires knowledge in several fundamental concepts. Drawing on nearly two decades of innovative studies, Doctors Naa Adamafio, Laud Okine, and Jonathan Adjimani specifically target the intricacies of metabolism and provide a comprehensive approach to the subject. The text is divided into three essential areas of study: Fundamentals of metabolic control-dealing with the basic concepts of metabolic control and the role played by regulatory enzymes Control of cellular metabolism-including the regulation of the metabolism of major biomolecules, such as carbohydrates, lipids, and compounds containing nitrogen The integration of metabolism-observing the methods in which various metabolic pathways within and between tissues and organs are integrated Whether you are an undergraduate student in biochemistry, a medical student in your preclinical years, or a teacher in the subject area, Integration and Control of Metabolism is a valuable medical resource. Understanding the way in which nutrients are metabolised, and hence the principles of biochemistry, is essential for understanding the scientific basis of what we would call a healthy diet. Extensively revised and updated to reflect current knowledge of nutritional and dietary requirements, Introduction to Nutrition and Metabolism, Fifth Edition presents an accessible text on the basic principles of nutrition and metabolism and the biochemistry needed for comprehending the science of nutrition. This full-color text explores the need for food and the uses to which that food is put in the body, as well as the interactions between health and diet. It describes the metabolic pathways and the biochemical basis of their nutritional and physiological importance. Topics covered include chemical reactions and catalysis by enzymes; the role of ATP; digestion and absorption of carbohydrates, fats, and proteins; issues associated with being overweight; problems of malnutrition; and vitamin and mineral requirements and functions. This new edition contains significantly expanded information on a variety of subjects including appetite control, hormone action, and integration and control of metabolism. The fifth edition also includes a list of key points at the end of each chapter. This text explains the conclusions of the experts who have deliberated on nutritional requirements, diet, and health, as well as the scientific basis for the conclusions they have reached. It also provides a foundation of scientific knowledge for the interpretation and evaluation of future advances in nutrition and health sciences. The accompanying CD-ROM contains new interactive tutorial exercises, PowerPoint presentations for each chapter, self-assessment quizzes, simulations of laboratory experiments, and a nutrient analysis program. Biochemistry and Oral Biology presents a unique exposition of biochemistry suitable for dental students. It discusses the structural basis of metabolism and the general principles of nutrition. It addresses the soft tissues, hard tissues, and the biology of the mouth. Some of the topics covered in the book are the free radical production; scope of biochemistry; characteristics of atoms; structure and properties of water; molecular building materials; ionization of proteins; affinity chromatography of proteins; structural organization of globular proteins; classification of enzymes; and biochemically important sugar derivatives. The naturally occurring fatty acids are fully covered. The nucleic acid components are discussed in detail. The text describes in depth the energy equivalents of different nutrients. The physiological effects of dietary fiber vitamin D deficiency are completely presented. A chapter is devoted to the alternative methods of fluoride administration and description of vitamins. The book can provide useful information to dental students, and researchers. Complex and unexplained phenomena tend to foster unorthodox perspectives. This publication is an example, as is a prior publication that emphasized the concept that intermediary metabolism might play a significant and determining role in hepatocyte proliferation and 1 tumorigenesis. Formulation of this hypothesis was based on an attempt to clarify several poorly understood phenomena; including the observations: Fatty acid and glucose metabolism are tightly linked in a we- established and profoundly inportant interplay. This connection, together with the fact that peroxisome proliferator-induced hepatocyte proliferation and carcinogenesis reflects

inhibition of mitochondrial carnitine palmitoyltransferase-I and fatty acid oxidation, suggested the possibility that regulation of fatty acid metabolism could prove to be a pivotal determinant in the control of cell growth. In , the year in which the paper cited above was published, insight into the importance of growth factors and signal transduction pathways in cell cycle regulation was increasing rapidly, but metabolic and energetic aspects of cell proliferation had attracted relatively little attention. Despite this, the concept seemed inescapable that the two seemingly distinct and unrelated determinants â€" signal transduction and metabolism â€" were integrally linked. B C Currell Language:

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And yet, feedback and feed-forward control mechanisms on the enzymatic level, central nuclear control of protein synthesis and hormonal messaging and signaling all play a part in the integration of metabolism which those of us who are healthy manage so well.

Blood sugar, glucose, is not an "inert and gentle" component of our diet. Chronic high blood levels of glucose lead to protein denaturing and the development of blindness, neuropathy and the kidney damage seen in diabetes. High blood sugar levels lead to increased circulating triglycerides and are responsible for development of cardiovascular disease. Again, integration of metabolism and control by hormones and metabolites, normally prevent these adverse effects of sugar. Let us look at the integration process. We often speak of "body energy", of being energetic or exhausted. What do we really mean by this. What drives our bodies? The energy obtained by "burning" food must first be captured as "high energy" phosphate bonds in adenosinetriphosphate ATP before it can be utilized. Energy to perform "work" comes from splitting off phosphate groups from ATP. This splitting of high-energy phosphate bonds is discussed here just click. The point to remember now is that ATP has a rapid turnover rate. On fact all of the ATP in working skeletal muscles can be used and regenerated in just a few minutes. Amazingly, ATP concentrations are quite stable in spite of this extremely rapid turnover. ATP levels are maintained through several processes: ATP has two "high-energy" phosphate groups. Splitting off both high-energy groups in one step yields AMP and inorganic pyrophosphate ppi. The conversion is very rapid in muscle and liver. The data below are from skeletal muscle. However, through the action of adenylate kinase, adenosine monophosphate AMP levels increase markedly in the working situation. There is a 4-fold rise in AMP levels in this example of a work situation. AMP is an active intracellular signal substance. We shall see that this "normal" AMP is coupled to a kinase which controls, among other things, uptake and metabolism of fatty acids. AMP is also an activator of glycogen mobilization and, therefore, sugar metabolism. Most of our body tissues contain phosphocreatine at concentrations approximately three times that of ATP. Phosphocreatine is a reserve source of high-energy phosphate. While the creatine phosphokinase reaction is the most rapid ATP-yielding reaction we possess, the amount of ATP which is produced is quite small. Under extreme work sprinting, for example the phosphocreatine reserves are used up in about seconds. However, "seconds do count" in sport. During those few seconds muscles can and do work with "explosive force". Olympic sprinters are very large, very muscular persons, not the thin and light runners I used to imagine. They are capable of running meters almost without breathing. While phosphocreatine is important for maximal performance, other sources of energy production must come into play after the first 30 seconds of a sprint. Most of us must have other sources of energy-yielding substrates, even when we run after the bus! In "second place" in the ATP-synthesis race after phosphocreatine comes ATP synthesis coupled to anaerobic metabolism. This is the cytosolic formation of ATP driven by oxidation of glucose or glucosyl groups from glycogen to pyruvate and lactate. Rapid, yes, but how much ATP can we make when the oxidation process is limited to formation of pyruvate and lactate from glucose or glycogen? Only two ATP molecules result for each glucose molecule that is processed. Three ATPs are formed for each glucosyl group that derived from glycogen. The secret here is that anaerobic glycolysis is very rapid. While it is relatively ineffective measured by energy production per glucose molecule consumed, glycolysis does turn out a lot of ATP in a short time. The big and painful disadvantage is that a lot of lactic acid is produced and accumulates in the working muscle. Furthermore, lipids cannot be used as substrates for anaerobic metabolism. Only glucose or glycogen work here. If we press anaerobic glycolysis to the limits, muscles exhaust their stored glycogen and take up so much glucose from the blood that hypoglycemia and CNS malfunction result. You can click here for more information. How do we manage this ATP-balancing? Where does the ATP synthesis take place? The obvious answer is that portion of our cells which is coupled to use of oxygen; to the air we are so very dependent upon. All of our cells, with the important exception of blood cells, contain mitochondria. These organelles mitochondria , probably originally derived from invading bacteria, can completely burn carbohydrates, fats and some amino acids to carbon dioxide and water. It is the

mitochondria that use oxygen and form water while oxidizing our "food". Their actual substrate is acetyl-CoA. All food that can be reduced to 2-carbon fragments can serve as a substrate for mitochondrial ATP production. The combustion process is coupled to reduction of oxygen giving water as a product. The rest of the energy in acetyl-CoA escapes as heat, keeping us nice and warm! While aerobic synthesis of ATP is the most effective way to produce "useable energy", it is a relatively slow process. Please go to the section describing muscle metabolism if you will go through the details of this process Click here. As stated above, acetyl-CoA is the actual substrate for mitochondrial metabolism. Now, overweight has become a major and global threat to our health. Accumulation of fat, especially centrally, is coupled to hypertension, diabetes type 2 and CVD. Unfortunately, things just do not work that way. Our tissues have strong demands as to which substrate they can use. Brain metabolism is completely dependent upon blood glucose as substrate; fatty acids do not cross the blood-brain barrier. Blood cells which do not have mitochondria, are also completely dependent upon anaerobic metabolism and, therefore, blood sugar. Blood sugar levels must also be carefully controlled; too much glucose is toxic and too little leads to CNS disturbances. This kind of control requires hormone regulation of many processes. The main actors here are insulin, glucagon, adrenaline and growth hormone. Many other hormones control appetite and secretion of these "key" hormones. Comprehension of the mechanisms at work is difficult because these enzymatic processes and hormonal control are tightly integrated. Furthermore, our different organs have their own complicated steering systems. What is true for the liver may not be applicable to muscles. An additional factor is the frequent discovery of new hormones and other elements in these so very complicated processes. One thing is sure; new discoveries are altering possibilities for medical treatment of metabolic and endocrinologic imbalances. New approaches to type 2 diabetes, overweight, and cardiovascular diseases are frequently reported in the literature. Turning Metabolism Off and On. Insulin Affects both Glucose and Lipid Metabolism. A good starting point for understanding control of metabolism is a figure recently published in Nature Medicine 10, by R. Barish and Yong-Xu Wang. The authors present information about "cross-talk" between various organs. Here, the signal initiating "cross-talk" is either an increase in blood sugar or fatty acids levels. This can occur either following a meal and uptake from the small intestine or as a result of stimulation of glucose release from the liver. The figure is simplified to aid understanding, but remember, changes in glucagon usually oppose alterations in insulin levels. Thus, gluconeogenesis and glycogenolysis are often initiated by rising glucagon and falling insulin levels. The increased glucose levels stimulate pancreatic secretion of insulin. This has several immediate effects: Increased skeletal muscle glucose uptake. Inhibition of hepatic gluconeogenesis and glycogenolysis and stimulation of glucose uptake in the liver not shown. Inhibition of lipolysis in fat tissue. Muscle tissue and liver do not just take up glucose. They must do something with it. Both tissues have glycogen reserves and these will be filled when glucose is taken up. You can click here for more information about carbohydrate metabolism after meals. If we assume that one sits quietly while eating and continues fairly relaxed thereafter, we would expect that the work level in skeletal muscle would remain fairly constant. What does muscle use as its energy substrate before a meal? What happens after a meal? If insulin stimulates muscular glucose uptake and metabolism, it must also force the tissue to slow down use of fat as an energy substrate. After all, acetyl-CoA, the common substrate for both sugar and fat metabolism is used at a constant rate as long as the work load does not change. I will come back to control of fatty acid use soon but will point out here that insulin inhibits release of fatty acids from fat cells inhibits lipolysis as shown in the figure above.

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4: Regulation of glycolysis and gluconeogenesis (video) | Khan Academy

Fully understanding the complex process of the integration and control of metabolism in cellular organisms requires knowledge in several fundamental concepts. Drawing on nearly two decades of innovative studies, Doctors Naa Adamafio, Laud Okine, and Jonathan Adjimani specifically target the.

Networks - Systems Analysis In our discussions we have considered mostly individual reactions or pathways and not how the various components interacted. But the heart of biochemistry is how the various systems interact to yield a living system. System properties are therefore important. Prologue Networks - telephone, electric grids, roads, airways, train tracks, integrated chips. The biochemicals, cofactors, metals, and enzymes define the parts list. The regulatory circuits and cascades constitute another network. Extracted comments from a 26 Sep 03 Science viewpoint. Leach additions The exhilarating progress of the past decades has brought an unprecedented wealth of quantitative information on living systems, from genomic sequences to protein structures and beyond. But although technical advances make data collection ever easier, investigators are increasingly concerned by their inability to gain a bigger picture. How can this growing mountain of facts be assimilated, and where will the new ideas come from that will help us gain a broader perspective? Everything in a living cell is, of course, connected to everything else, and interactions between macromolecules through multiple noncovalent bonds are the very fabric of life. I have been teaching this sinced the early s. It is therefore an attractive notion that, by taking a top-down view of protein-protein interactions, enzymatic pathways, signaling pathways, and gene regulatory pathways, we will gain a better perspective of how they work. Disciplines such as engineering and the social sciences have used networks to analyze their data for many years. I had visiting lectures by electrical engineering profs in thes for my regulation course. Is this approach useful, and if so, what can it teach us? The answer is already in see MA Savageau, Biochemical systems analysis. Some mathematical properties of the rate law for the component enzymatic reactions. J Theor Biol, Dec ; 25 3: MA Savageau, Biochemical systems analysis. The steady-state solutions for an n-pool system using a power-law approximation. Dynamic solutions using a power-law approximation. J Theor Biol, Feb ; 26 2: The most basic feature of any network is its architecture, which places boundaries on how it acts and how it might have been formed. These three networks will exhibit different global features, even if it is assumed that they contain the same number of nodes and the same number of connections 1. The number of connections per node for both the regular and random networks, for example, will have a roughly normal distribution with an average value that gives a characteristic "scale" to the network. By contrast, the nodes in the third type of network range from a very few highly connected species to a large number of weakly connected species. Characteristically, the number of molecules N with a given number of connections k falls off as a power law: Because N k does not show a characteristic peak value, this type of network is often referred to as "scale free. On the other hand, the extent to which neighbors of a node are themselves connected referred to as its clustering coefficient, or "cliquishness" is almost as large as in a regular network. Scale-free networks are best known in sociology, where they have been shown to represent networks of friends in a population and are sometimes referred to as "small-world networks. A flurry of recently published results really? The interior of a living cell is an aqueous slurry based in large part on multiprotein complexes. Some complexes have been isolated and studied in detail but many more remain uncharted I wonder I doubt this except for wek interactions not what we understand as complexes such as the pyruvate dehydrogenase system , either because they are insoluble or because they depend on fragile, transient liaisons that fall apart as soon as one tries to isolate them. Understanding the nature of these complexes, where they are located, and how they work is crucial for an understanding of the cell. Consequently, investigators have been encouraged to develop fast, high-throughput techniques such as yeast two-hybrid screens and affinity chromatography followed by mass spectrometry to detect which proteins bind to which. Other methods have been devised by which protein associations can also be deduced from genomic data. Unfortunately, each method has its drawbacks and none gives complete or unambiguous data. Side-by-side comparisons of data obtained by different methods show limited reproducibility, and there are serious

concerns that what is examined might be only a subset of the complexes 3. But accuracy can be improved by combining data from different sources, and the results all indicate that protein interaction networks are small-world networks 4 , 5. That is, some proteins serve as hubs for very large numbers of interactions, whereas the others, the majority, act more like simple links and participate in one or a few complexes. Probably the best characterized molecular network that exhibits scale-free properties is that of the interlinked pathways of metabolism. Pathways of enzymatically catalyzed reactions that interconvert the hundreds of small molecules of a cell are very well known and extensively documented. Thirty years ago, Kacser and his colleagues pioneered mathematical methods for the analysis of metabolic networks, representing individual small molecules such as pyruvate or citrate as nodes and the enzyme reactions that interconvert them as connections 6 note the Savageau articles of cited above. These methods allowed them to deduce global features, such as the contributions made by different steps to the overall flux of the pathway, or the way that changing one step would affect the flux through another step at a remote part of the network. This body of work, now known as metabolic control analysis, stands as a pioneering example of how global features can be distilled from a large body of network data 7. Recent graph-theoretic approaches to this same body of information have shown that metabolism also has the properties of a scale-free network. Some molecules, such as pyruvate or coenzyme A, are large hubs, whereas the average molecule undergoes just one or two reactions. The number of catalytic steps required to go from any one compound to any other is surprisingly small, and metabolic networks have a high clustering coefficient, which suggests the presence of local cliques or clusters of connected molecules 8. By itself, the fact that a network has scale-free properties is of limited use to biologists. Power laws occur very widely in nature and can have many different mechanistic origins. If we wish to obtain testable biological insights, we must probe further into the substructure of the network. One way forward is to focus on local clusters or cliques in a network and ask how these are themselves arranged. Can we resolve metabolic networks into hierarchical subsystems of highly interconnected reactions sharing similar functions? Can we relate protein interactions to RNA expression data or to cellular location? Eventually, such a top-down analysis leads us to the same modules and motifs identified in other, more reductionist approaches, as described by Alon 9. There are clearly huge obstacles to overcome before we have a complete understanding of molecular networks. It is technically difficult to identify connections with a high degree of certainty, and harder still to make quantitative measurements of their strength this is really the problem with regulated enzymes that interact with many effectors. Even when the data have been obtained, novel and sophisticated methods are required to understand what they mean. We have a new continent to explore and will need maps at every scale to find our way.

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