citations (*7*), and magnetization plateaus are to be expected as a result. The first of these appears at a value of 1/8 of the saturation magnetization. The required magnetic field of 27 T is quite large but within range of the NMR facility of the Grenoble High Magnetic Field Laboratory. The unique combination of high fields and low temperatures at this facility enabled Kodama *et al.* (*5*) to observe the magnetic superlattice as a dense series of lines in the Cu NMR spectrum at 35 mK. Analysis of the magnetization in the large supercell implied by the high order of the commensurability (1/8) required a numerical solution of the Shastry-Sutherland model.

The spectra could be well fit by the magnetization pattern shown in the figure. One in eight of the dimers is strongly polarized parallel to the external field. But the magnetization pattern is much richer than a simple polarization of 1/8 of the dimers. This more complex pattern can be attributed to the high magnetic polarizability of the singlet ground state of the dimer lattice. As a result, the dilute superlattice of spin triplet dimers is accompanied by a background magnetic polarization. The transition into the superlattice state as the field is increased appears to be first order, which favors an interpretation of it as a crystallization of a dilute bosonic fluid.

Turning our attention back to the quantum ground state, which appears when the kinetic terms dominate, new results on another set of copper salts, $KCuCl_3$ and $TlCuCl_3$, have recently been obtained. Initially, their crystal structure seemed to imply that the dimers formed the rungs of ladders with only weak interladder interactions. However, a detailed mapping of the energy dispersion of the triplet excitations showed a fully three-dimensional network of exchange interactions (*8*).

These salts do not show magnetization plateaus but instead show a continuous rise starting at a threshold magnetization value and ending at the saturation magnetization. The Bose-Einstein condensed state in the intermediate range is characterized by a coherent superposition of the singlet and $S_z = +1$ triplet component on each dimer (*9*). This generates a staggered magnetization transverse to the external field.

The phase in the complex superposition determines the orientation of staggered moments in the *xy*-plane. Elastic neutron-scattering measurements observe a staggered magnetization with long-range ordering with a finite ordering temperature (*10*). Recently, Ruegg *et al.* (*11*) examined the dynamics of the condensate by inelastic neutron scattering and observed a mode with linear dispersion above the threshold magnetization. As shown by Matsumoto *et al.* (*12*), this mode can be nicely interpreted as the well-known collective oscillation (or Goldstone mode) of the Bose-Einstein condensate.

As these recent experiments illustrate, quantum magnetism in a magnetic field offers exemplary systems for exploring the competition between the classical and quantum ground states for interacting bosons—a subject of current research also for the dilute atomic bosonic clouds.

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PERSPECTIVES: CANCER BIOLOGY

A Matter of Dosage

Riccardo Fodde and Ron Smits

Knudson's classic two-hit model of tumorigenesis stipulates that mutation of both alleles of a tumor suppressor gene is needed to trigger tumor formation (*1*). This recessive nature of tumor suppressor genes has been challenged by a growing number of reports (see the table) including recent papers in *Science* and *Nature Genetics* (*2–4*). These studies show that mutation or loss of a single allele may be sufficient to exert a cellular phenotype that leads to tumorigenesis without inactivation of the second allele. This gene-dosage effect is called haploinsufficiency and has been demonstrated by at least two different experimental approaches. Individuals or mice carrying a heterozygous mutation that inactivates only one allele of a tumor suppressor gene exhibit an increased incidence of tumors, a subset of which develop without loss or mutation of the second normal allele (*5*, *6*).

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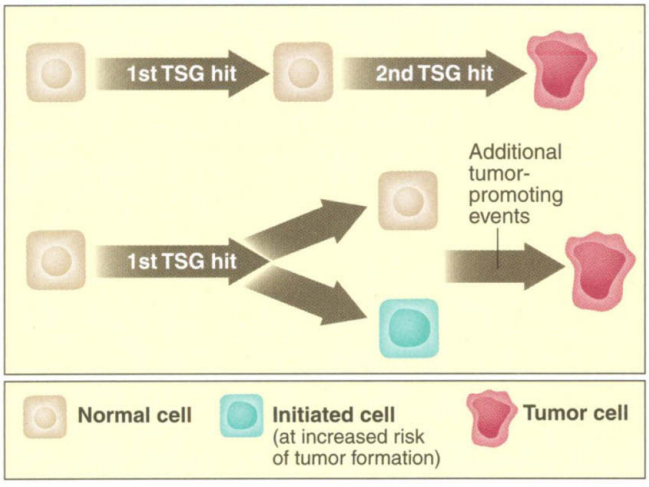
Alternatively, haploinsufficiency can modify cancer risk in humans or mice that either already carry a heterozygous mutation in a separate tumor suppressor gene (known to comply with Knudon's two-hit model) (*7*) or that have been challenged by exposure to radiation or viruses (*8*). Tumors influenced by haploinsufficiency usually have a later age of onset when compared with those caused by inactivation of the second allele (loss of heterozygosity).

Although it is well documented that gene-dosage effects cause developmental defects in model organisms and in certain inherited human diseases, their importance in tumor biology has been overlooked. Morphogen gradients modulate cell proliferation, differentiation, and apoptosis in developing organisms. Exposure to different doses of these diffusible factors is rate-limiting for the determination of cell fate. Likewise, in the presence of a heterozygous loss-of-function mutation in a tumor suppressor gene, fluctuations in gene dosage below tissue-specific thresholds may interfere with the control of fundamental cellular processes (see the table). This results in either the direct triggering of tumorigenesis or modification of the cellular environment so that additional mutations or epigenetic changes in other genes can successfully promote tumor growth (see the figure).

Some tumor suppressor genes are "gatekeepers," that is, they carry out a crucial cellular function that when abrogated leads directly to tumorigenesis. However, there also exists a subset of tumor suppressor genes that are "caretaker" genes involved in DNA repair or chromosomal segregation. Haploinsufficiency at these caretaker genes may result in defective DNA repair and increased genetic instability leading to somatic mutations in other tumor suppressor genes and oncogenes. The recent *Science* and *Nature Genetics* papers (*2–4*) support the notion of DNA repair haploinsufficiency.

Bloom syndrome is a rare recessive disorder characterized by a predisposition to a broad spectrum of tumors. It is caused by loss-of-function mutations in the *BLM* gene, which encodes the DNA repair enzyme recQ helicase. Gruber *et al.* (*2*) genotyped two large series of colorectal cancer patients of Ashkenazi Jewish ancestry and showed that carriers of the BLM^{Ash} founder mutation had a significantly increased risk of developing large-bowel tumors. However, they did not analyze whether the second normal allele was mutated in the colorectal cancers. Thus, they could not discriminate whether the increased colorectal cancer risk was



The two-hit model and the haploinsufficiency model of tumorigenesis. (**Top**) In the two-hit model, both alleles of a tumor suppressor gene (TSG) must be inactivated to trigger tumor formation. (**Bottom**) In the haploinsufficiency model, the gene-dosage defect caused by the expression of only one functional allele contributes to tumor formation either by conferring a selective advantage on the tumor cells (gatekeeper genes) or by causing genetic instability (caretaker genes). Alternatively, haploinsufficiency may not result directly in a specific cellular phenotype. Nevertheless, in both haploinsufficient scenarios, additional tumor-promoting events such as oncogenic mutations, loss of other tumor suppressor genes, or epigenetic changes will be necessary to uncover the haploinsufficiency of the original tumor suppressor gene. (Normal cell, brown; initiated cell at increased risk of tumor formation, blue; tumor cell, pink.)

caused by inactivation of both alleles of the *BLM* gene or by haploinsufficiency. In a related paper, Goss *et al.* (*3*) engineered mice heterozygous for a targeted loss-of-function mutation, Blm^{Cin}, which simulated the BLM^{Ash} founder mutation of the Bloom syndrome patients. These mice exhibited a subtle increase in genomic instability and developed lymphomas earlier than their wild-type littermates exposed to a viral carcinogen; none of the tumors showed inactivation of the second normal allele. To investigate the effect of *Blm* haploinsufficiency on intestinal tumorigenesis, these authors generated compound heterozygous $Apc^{+/-}/Blm^{+/Cin}$ mice and compared their intestinal tumor load with that of $Apc^{+/-}$ mice. A twofold increase in intestinal tumors without loss of the second normal *Blm* allele was observed in these compound heterozygous animals when compared with $Apc^{+/-}$ mice. This finding implies that *Blm* haploinsufficiency is a modifier of intestinal cancer risk. *Blm* haploinsufficiency resembles haploinsufficiency in other DNA-repair genes such as *Fen1* (*9*), which increases tumorigenesis driven by the *Apc* tumor suppressor gene (see the table). Evidence for different degrees of genetic instability in these tumors indicates that haploinsufficiency of these tumor suppressor genes confers a mutator phenotype that may enhance intestinal tumor formation.

A similar effect of haploinsufficiency may operate for tumor suppressor genes such as *p53* (*5*) and *ATM* (*10*). These genes are involved in the cellular response to DNA damage and can induce cell-cycle arrest or apoptosis. Their mutation may result in resistance of cells to apoptosis and expansion of the target cell population, which then undergoes additional mutation. A case in point is ataxia telangiectasia, an autosomal recessive condition caused by mutations in the *ATM* gene, which encodes a serine-threonine kinase involved in the cell's response to DNA double-strand breaks. Loss of ATM activity by truncating or null mutations principally results in lymphoid malignancies in homozygous carriers. In contrast, individuals heterozygous for other types of mutation that interfere with the function of the wild-type allele (missense substitutions, in-frame deletions) have an elevated breast cancer risk. In their *Nature Genetics* paper, Spring and colleagues (*4*) have confirmed this mutation-specific tumor spectrum by generating a new mouse model that carries a dominant-negative targeted mutation in the *Atm* gene. Mice with the targeted mutation spontaneously develop more solid tumors than mice heterozygous for a null *Atm* mutation (*4*). Although the tumor incidence in mice with the dominant-negative mutation cannot entirely be accounted for by haploinsufficiency, it is indicative of dosage-dependent modulation of the corresponding phenotype. Similar correlations between genotype and tumor phenotype have been shown for the *BRCA2* gene: Individuals homozygous for hypomorphic mutations (milder gene defects that encode residual protein activity) develop Fanconi anemia; heterozygous carriers of truncating mutations show increased breast cancer susceptibility (*11*). Such correlations have also been shown for the *p53* gene in mice: $p53^{-/-}$ animals primarily develop lymphomas, whereas $p53^{+/-}$ animals exhibit a broader spectrum of tumors including soft tissue sarcomas, osteosarcomas, and carcinomas of various types (*5*). Notably, *ATM* and *BRCA2* both participate in DNA-damage recognition and response pathways together with other genes like *BRCA1* and *CHEK2* that have been implicated in breast cancer susceptibility (*12*). Dosage variations in the activity of such caretaker pathways may modify cancer risk by increasing genetic instability or by altering the normal DNA damage response.

Tumor suppressor genes come in many flavors. Not only are they involved in a variety of different cellular processes, but they also show differences in tissue-specific protein-dosage thresholds below which they fail to operate normally. This has implications for understanding the molecular and cellular processes underlying tumor initiation and progression, and for identifying new genes that modify an individual's cancer risk. The hallmark of most cancers is chromosomal instability resulting in unbalanced expression of many genes.

TUMOR SUPPRESSOR GENES SHOWN TO BE HAPLOINSUFFICIENT

Genes	Function	Experimental evidence
AML1/CBFA2	Hematopoietic transcription factor	Spontaneous tumor formation in humans (*6*)
Cdh1	Cell-cell adhesion	Tumor formation in combination with $Apc^{+/1638N}$ (*7*)
Dmp1	Cell cycle control	Spontaneous and induced tumor formation in $DMP1^{+/-}$ (*13*)
Lkb1	Kinase of unknown function	Spontaneous tumor formation in $Lkb1^{+/-}$ (*14*)
NF1	Signal transduction	Spontaneous tumor formation in $Nf1^{Lox}$ (*15*)
$p27^{Kip1}$	Cell cycle control	Induced tumor formation (*8*)
Ptch	Signal transduction	Spontaneous tumor formation in $Ptch^{+/-}$ (*16,17*)
Pten	Signal transduction	Tumor formation in combination with TRAMP (*18*)
Atm	Response to DNA damage	Spontaneous tumor formation in $Atm^{+/-}$ (*4*)
Blm	DNA repair	Tumor formation in combination with $Apc^{+/Min}$ Induced tumor formation (*3*)
Fen1	DNA repair	Tumor formation in combination with $Apc^{+/1638N}$ (*9*)
p53	Response to cellular stress	Spontaneous tumor formation in $p53^{+/-}$ (*5*)

This inevitably leads to widespread haploinsufficiency at several gene loci, only a fraction of which provide the nascent tumor cell with some degree of selective advantage. Do tumor suppressor genes exist for which haploinsufficiency is more strongly selected for than complete inactivation? Only accurate and quantitative genome-wide expression profiling by microarray or proteomic analysis will enable such gene-dosage defects to be identified. Analyzing targeted hypomorphic alleles in experimental animals should facilitate the identification of modifier genes, their tissue-specific dosage thresholds, and their interaction with more penetrant tumor suppressor genes and environmental mutagens.

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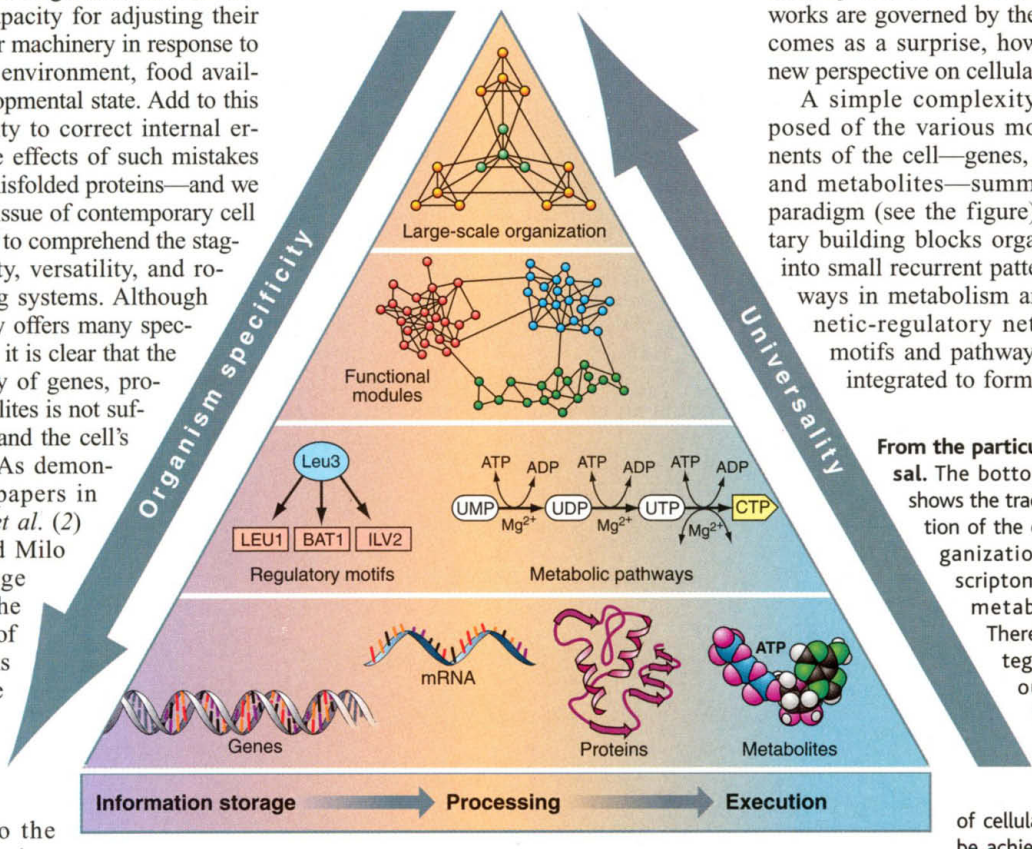
Life's Complexity Pyramid

Zoltán N. Oltvai and Albert-László Barabási

Cells and microorganisms have an impressive capacity for adjusting their intracellular machinery in response to changes in their environment, food availability, and developmental state. Add to this an amazing ability to correct internal errors—battling the effects of such mistakes as mutations or misfolded proteins—and we arrive at a major issue of contemporary cell biology: our need to comprehend the staggering complexity, versatility, and robustness of living systems. Although molecular biology offers many spectacular successes, it is clear that the detailed inventory of genes, proteins, and metabolites is not sufficient to understand the cell's complexity (*1*). As demonstrated by two papers in this issue—Lee *et al.* (*2*) on page 799 and Milo *et al.* (*3*) on page 824—viewing the cell as a network of genes and proteins offers a viable strategy for addressing the complexity of living systems.

According to the basic dogma of molecular biology, DNA is the ultimate depository of biological complexity. Indeed, it is generally accepted that information storage, information processing, and the execution of various cellular programs reside in distinct levels of organization: the cell's genome, transcriptome, proteome, and metabolome. However, the distinctness of these organizational levels has recently come under fire. For example, although long-term information is stored almost exclusively in the genome, the proteome is crucial for short-term information storage (*4, 5*) and transcription factor–controlled information retrieval is strongly influenced by the state of the metabolome. This integration of different organizational levels increasingly forces us to view cellular functions as distributed among groups of heterogeneous components that all interact within large networks (*6, 7*). There is clear evidence for the existence of such cellular networks: For example, the proteome organizes itself into a protein interaction network and metabolites are interconverted through an intricate metabolic web (*7*). The finding that the structures of these networks are governed by the same principles comes as a surprise, however, offering a new perspective on cellular organization.

A simple complexity pyramid composed of the various molecular components of the cell—genes, RNAs, proteins, and metabolites—summarizes this new paradigm (see the figure). These elementary building blocks organize themselves into small recurrent patterns, called pathways in metabolism and motifs in genetic-regulatory networks. In turn, motifs and pathways are seamlessly integrated to form functional mod-



From the particular to the universal. The bottom of the pyramid shows the traditional representation of the cell's functional organization: genome, transcriptome, proteome, and metabolome (level 1). There is remarkable integration of the various layers both at the regulatory and the structural level. Insights into the logic of cellular organization can be achieved when we view the cell as a complex network in which the components are connected by functional links. At the lowest level, these components form genetic-regulatory motifs or metabolic pathways (level 2), which in turn are the building blocks of functional modules (level 3). These modules are nested, generating a scale-free hierarchical architecture (level 4). Although the individual components are unique to a given organism, the topologic properties of cellular networks share surprising similarities with those of natural and social networks. This suggests that universal organizing principles apply to all networks, from the cell to the World Wide Web.

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