GSK3 also phosphorylates substrates in a manner that does not require prephosphorylation ("nonprimed" substrates). These substrates include components of the Wnt signal transduction pathway, such as β-catenin and axin. Interestingly, mutation of Arg^{96} in the phosphate-binding site of GSK3β does not alter phosphorylation of these nonprimed substrates (*7*). Frame and colleagues provide evidence that axin binds to GSK3 at a site distinct from the phosphate-binding site; this binding appears to inhibit GSK3 phosphorylation at Ser^9 in response to insulin (*7*), thereby restricting the effects of insulin to a specific subset of GSK3 substrates. Thus, PKB inhibits GSK3's phosphorylation of primed substrates (such as glycogen synthase, a target of the insulin pathway) without affecting nonprimed substrates (such as β-catenin, a target of the Wnt pathway) (*3*). In this manner, GSK3 is able to selectively regulate primed and nonprimed substrates through phosphorylation, thereby inducing distinct cellular responses.

Is this phenomenon applicable to the differential regulation of signaling pathways by other protein kinases? Mitogen-activated protein kinases (MAPKs) have docking sites (CD and ED domains) that are similar to the Arg^{96} binding site of GSK3 and contribute to substrate specificity (*9*). Whether these docking sites are required for the phosphorylation of a particular subset of substrates but not others requires further investigation. However, the transcription factor Elk-1 contains a targeting domain that is required for phosphorylation by the extracellular signal–regulated kinase and c-Jun amino-terminal kinase groups of MAPKs, but not by p38 MAPK (*10*). This implies that other protein kinases may strictly control the selective activation of downstream substrates in a similar way to GSK3.

Selective substrate phosphorylation has broad implications for drug discovery. Diseases associated with elevated GSK3 activity include non–insulin-dependent (type II) diabetes mellitus, Alzheimer's disease, and depression (*3, 11*), whereas mutant inactive forms of GSK3 are associated with certain solid tumors. GSK3 inhibitors such as lithium and small-molecule drugs that compete with adenosine triphosphate can mimic the effects of both the insulin and Wnt signaling pathways (*11, 12*). Thus, prolonged use of such drugs for the treatment of one disease (for example, diabetes) could induce other diseases (such as cancer) that may arise through the activation of Wnt signaling. In contrast, a drug that interacts with the phosphate-binding site of GSK3 may selectively inhibit the phosphorylation of "primed" GSK3 substrates, such as the insulin target glycogen synthase, without affecting the phosphorylation of "nonprimed" substrates, such as the Wnt pathway targets axin and β-catenin. This provides an opportunity for the rational design of specific inhibitors of GSK3 that are selective for different groups of target molecules of this multifunctional kinase. The presence of substrate docking sites on other protein kinases suggests that this strategy may be generally applicable to the design of selective inhibitors of signal transduction.

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PERSPECTIVES: COSMOLOGY

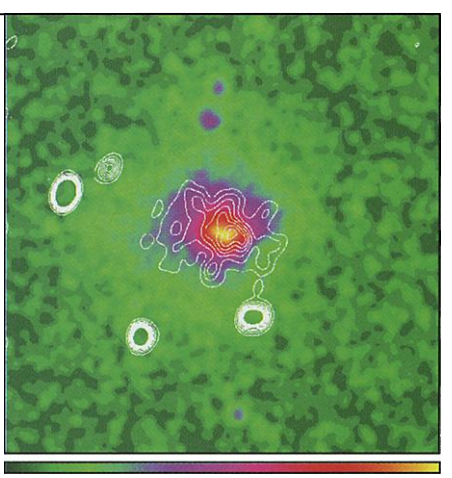
Magnetic Mysteries

Axel Brandenburg

At present—some 14 billion years after the Big Bang—magnetic fields of appreciable strength are found in virtually all galaxies and also in galaxy clusters. Although weak compared with the fields at Earth's or the Sun's surface, these fields are enormous considering the scales involved and may influence the formation of stars and galaxies, the dynamics of galaxy clusters, and energy transport within galaxy clusters. Even 1 to 2 billion years after the Big Bang, such fields must already have existed at about the same strength as today (*1*). How did these fields arise? And did primordial magnetic fields exist in the early universe? Answers to these questions remain speculative, but upcoming space missions promise exciting insights.

Galactic magnetic fields are usually inferred through the presence of polarized (synchroton) emission at radio and shorter (down to submillimeter) wavelengths. Most galaxies show synchrotron emission, but not all galaxy clusters. However, this may be a result of a lack of relativistically fast electrons, which emit such radiation under the influence of a magnetic field, rather than a lack of the field itself. Abell 2163 is an example of a cluster with very strong radio emission (see the first figure).

According to one leading theory, magnetic fields in galaxies and galaxy clusters may have arisen through battery mechanisms in ionization fronts just after the first stars formed (*2*, *3*). Differential forces acting on opposite charges generated a relative drift between them. The resulting field was amplified exponentially through gas motions (*4*). Such "dynamo" processes are certainly possible in principle but cannot easily explain why in some galaxy clusters, the fields are very coherent over several galactic radii (*5*). According to another theory, the ejecta of starburst galaxies may have magnetized galaxy clusters (*6*). In both cases, the field strength may have been boosted by mergers and collisions among clusters, but simulations indicate that the scale of the fields would remain small (*7*).



Strong emission. Radio synchroton emission contours are superimposed on a color-coded x-ray image of the galaxy cluster Abell 2163. The strongest radio emission comes from the center. Cluster diameter, ~2 megaparsecs.

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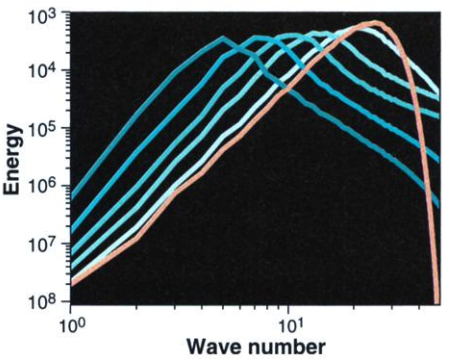
In contrast, if a magnetic field on the scale of several galactic radii already existed at the time of galaxy formation, this would provide an important clue to the origin of fields on large scales. New missions may soon enable detection of very early magnetic fields through measuring the temperature and polarization anisotropies of the cosmic microwave background (CMB) (*8*). The PLANCK space tele-

The author is at NORDITA, Blegdamsvej 17, 2100 Copenhagen, Denmark. E-mail: brandenb@nordita.dk

scope, to be launched in 2007, is expected to detect fields as weak as 10^{-9} gauss (*9*). Later missions are likely to detect even weaker fields. In the meantime, theorists are making ever more detailed predictions of the temperature and polarization signatures of a primordial magnetic field.

Particle physicists have come up with rather speculative processes, which may have generated huge magnetic fields during or just after inflation (the period of very rapid expansion before the universe was 10^{-30} s old) (*9*). These fields would have been diluted during the subsequent "normal" cosmological expansion, probably to something close to the detection limit of PLANCK. Initially, it was not clear how they could have any bearing on the question of large-scale magnetic fields. A field generated at such an early time would not exceed the scale of the horizon, which was just ~3 cm at 10^{-10} s. Such a field would now be at a scale of the solar system, ~10 orders of magnitude smaller than the scale of galaxies.

An unusual feature of turbulence physics may provide the answer. A random magnetic field can display an "inverse cascade" (*4*). This means that structures do not just split up into ever smaller scales, as in ordinary turbulence. Rather, the opposite happens. This is because in highly conducting fluids, in addition to total energy, another quantity is conserved: magnetic helicity, which measures the twist and mutual linkage of magnetic flux structures. Think of the field as being made up of helically polarized waves. There is a limit to how much magnetic helicity can be packed into a wave of given wavelength. If two helical waves interact, it is very hard to dispose of the helicity at small scales without violating magnetic helicity and total energy conservation. It is much easier to accommodate the magnetic helicity in a wave of larger wavelength.



Growth of magnetic structures. In this simulation, the spectral energy propagates to successively smaller wave numbers, that is, successively larger scales, as a result of inverse cascade turbulence. Red line, initial time; blue lines, later times (increasing from right to left).

A dramatic example of such behavior is seen in a numerical simulation (see the second figure) (*10*). An initially random and helical magnetic field was left to decay through viscous and Joule dissipation. The dissipation happens mostly at small scales. At all other scales, magnetic energy gets pumped into progressively larger scales. These results suggest that we may well expect primordial fields at the scales of galaxies if the field has helicity (*11*). It remains uncertain whether the net magnetic helicity required to drive the inverse cascade comes mostly from the original field (*12*) or whether small helicity perturbations can grow to substantial levels.

The increase of the length scale of the primordial magnetic field will not be of much interest if its magnitude was small. Upcoming space missions will soon provide hard facts. If the field was weak, then the fields we observe today must have been generated later. On the other hand, if a strong field (expanded to a present-day value of 10^{-9} gauss) was present, then its detailed structure could be determined and interpreted, with important consequences for the theory of galaxy formation.

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PERSPECTIVES: EVOLUTION

Haploids—Hapless or Happening?

Sarah P. Otto and Philippe Jarne

In biology, it seems, there are exceptions to every rule, although sometimes finding these exceptions can be exceedingly difficult. Typically, animal cells are diploid, that is, they carry two copies of each chromosome, except during a brief phase when haploid gametes (sperm and egg) with half the normal chromosome complement are produced. Although haplodiploidy (haploid males and diploid females) has arisen many times during evolution, so far no animal has been found to exist exclusively in the haploid state (*1*). Enter the false spider mite *Brevipalpus phoenicis* on page 2479 of this issue, a daring exception to the rule that diploidy dominates (*2*). The discovery by Weeks *et al.* (*2*) that *B. phoenicis* exists only in the haploid state calls into question the dogma that diploidy has been selected for during animal evolution because of the fitness benefits it confers.

The false spider mite and its relatives *B. obovatus* and *B. californicus* reproduce by parthenogenesis, that is, females produce only female offspring from unfertilized eggs. The eggs and adult cells of these female mites contain two chromosomes, but it has been difficult to decipher whether the two chromosomes are unrelated, indicating a haploid state, or duplicates of each other (homologs), indicating diploidy. Weeks *et al.* prove that these two chromosomes are genetically distinct and conclude that the female mites are haploid. They found that only one of the two chromosomes contains a nucleolar organizing region, and only one carries an 18*S* ribosomal DNA gene (if the two chromosomes are homologs, they would carry copies of the same genes in the same locations). Furthermore, even though the investigators surveyed 45 clonal lines of *B. phoenicis* at seven highly polymorphic microsatellite loci, they were unable to find any individuals that carried more than one copy (allele) of a particular gene, indicating that these mites are indeed haploid.

How did these haploid oddities arise? Weeks *et al.* noticed that the eggs of *B. phoenicis* were laden with intracellular bacteria. Treatment with antibiotics led to loss of bacteria in roughly half the eggs. The infected offspring continued to develop as females, as expected, but the cured offspring developed into males! This ob-

S. P. Otto is in the Department of Zoology, University of British Columbia, Vancouver V6T 1Z4, Canada. P. Jarne is at CEFE-CNRS, 34293 Montpellier Cedex 05, France. E-mail: otto@zoology.ubc.ca

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