noelectrochemical transducer—an electrochemical generator. Thus, the name of Faraday once more returns. As he was pondering his invention of the dynamo and comparing that to the steam engine in the next coal mine, he said: "Of what use is a newborn baby?" Perhaps he would look with the same feeling on the novel but unproven electrical generator operating through electrochemistry and suggest that breaking carbon fibers in batteries might not offer much attraction compared with the turning of wires in magnetic fields in a classical generator. Possibly, but even as actuators made of soft materials, these new devices offer much to keep us interested.

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PERSPECTIVES: CONDENSED MATTER PHYSICS

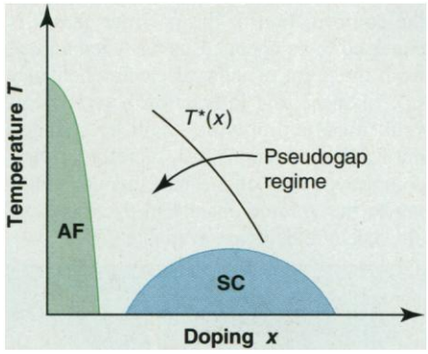
The Cuprate Pairing Mechanism

D. J. Scalapino

What is the basic interaction responsible for the pairing of electrons in the high–transition temperature (T_c) superconducting cuprates? More than a dozen years after Bednorz and Müller's discovery of this class of materials (*1*), the nature of the pairing mechanism remains unsettled. In part, this is due to the rich phase diagram of these materials (*2*), schematically illustrated in the figure. Depending on the temperature and the doping, one finds vastly different properties: an insulating antiferromagnetic phase, a pseudogap metallic phase (*3*), and a superconducting phase with $d_{x^2-y^2}$ symmetry.

The $d_{x^2-y^2}$ symmetry of the superconducting gap was, in fact, predicted by various theoretical calculations (*4*) for models in which a short-range Coulomb interaction led to an exchange coupling $J\mathbf{S}_i\cdot\mathbf{S}_j$ between near-neighbor copper spins and strong magnetic spin fluctuations. These same models at zero doping ($x = 0$) lead to the insulating antiferromagnetic phase. Nevertheless, as Dai *et al.* (*5*) note in their report on page 1344 of this issue, "the role of such [spin] fluctuations in the pairing mechanism and superconductivity is still a subject of controversy." The point is that if spin fluctuations provide the basic pairing mechanism, then the spin fluctuations should also be related to the occurrence of the pseudogap regime and to the thermodynamics of the superconducting transition; that is, one model should explain the entire phase diagram.

In their report (*5*), Dai *et al.* present inelastic neutron-scattering data for $YBa_2Cu_3O_{6+x}$ that shows that the onset temperature $T^*(x)$ of the pseudogap regime coincides with the formation of enhanced spin fluctuations at a finite frequency ω_0 and wave vector $q = (\pi/a, \pi/b, \pi/c)$, the so-called π resonance. In addition, the temperature derivative of the exchange energy $J\langle\mathbf{S}_i\cdot\mathbf{S}_j\rangle_{res}$ associated with this part of the spectrum has a temperature, doping, and magnitude that are consistent with the observed anomaly in the electronic-specific heat near the superconducting transition.



Superconducting jigsaw puzzle. Schematic phase diagram for the cuprates showing temperature T versus hole doping x. The antiferromagnetic (AF) and $d_{x^2-y^2}$ superconducting (SC) regimes are shaded. Below the curve $T^*(x)$, a pseudogap opens in the quasi-particle spectrum.

For conventional low-T_c superconductors, Chester (*6*) showed that the temperature dependence of the lattice ion kinetic energy was related to the change in the electronic-specific heat associated with the superconducting transition providing a link between the electron-phonon interaction and the pairing mechanism. Recently, Scalapino and White (*7*) suggested that if the exchange coupling $J\mathbf{S}_i\cdot\mathbf{S}_j$ played a similar role in the high-T_c cuprates to that of the ions in the traditional low-T_c superconductors, one would expect that the temperature dependence of the exchange energy would reflect the change in internal electronic energy near the superconducting transition. They noted that because $J\langle\mathbf{S}_i\cdot\mathbf{S}_j\rangle$ could be obtained from the q- and ω-dependent magnetic structure factor $S(q,\omega)$ measured in neutron scattering, such experiments could, in principle, provide evidence for an exchange-interaction–based pairing mechanism.

Following this approach, Demler and Zhang (*8*) noted that in the magnetic scattering from $YBa_2Cu_3O_7$, the dominant temperature dependence in $S(q,\omega)$ was associated with the resonance in the spin fluctuation scattering for momentum $(\pi/a, \pi/b, \pi/c)$, the so-called π resonance. In their work, they go on to argue that, in fact, it is the appearance of a spin fluctuation resonance in the superconducting state that enables the antiferromagnetic exchange energy in this state to be lowered relative to the normal state.

In the study of Dai *et al.*, detailed measurements of the spin fluctuations in $YBa_2Cu_3O_{6+x}$ at various temperatures and dopings x are reported. They find that the dominant observed changes in the scattering are associated with this resonance. Furthermore, they find that the onset temperature for these changes is set by the temperature $T^*(x)$ shown in the figure, which is determined from nuclear magnetic resonance and transport measurements to correspond to the onset of the pseudogap regime. After calculating the contribution of the exchange energy associated with the π resonance, Dai *et al.* show that the resonance can provide enough temperature-dependent exchange energy to yield the superconducting-specific heat anomaly as measured by Loram *et al.* (*9*).

As Dai *et al.* note, further neutron-scattering data are needed to provide tighter bounds on the nonresonant part of the spin fluctuation spectrum. In addition, optical data can give tighter bounds on possible models.

To conclude, the results of Dai *et al.* provide support for models in which the exchange interaction $J\mathbf{S}_i\cdot\mathbf{S}_j$ plays a central role. However, the basic pairing interaction remains elusive. That is, even granted that

The author is in the Physics Department, University of California, Santa Barbara, CA 93106–9530, USA. E-mail: djs@spock.physics.ucsb.edu

one should focus on the exchange interaction, the spin fluctuation exchange model differs from Demler and Zhang's (*8*) π-resonance picture, which in turn differs from resonating-valence-bond theories (*10*) and domain-wall stripe theories (*11*) all of which also arise from models with an exchange interaction, are known to fit a number of experimental observations, and likely play a key role in the underdoped regime.

Thus, the work of Dai *et al.* focuses our attention on the exchange interaction and the magnetic excitation spectrum, narrowing but not ending the search for the cuprate pairing mechanism.

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PERSPECTIVES: IMMUNOLOGY

Instruction, Selection, or Tampering with the Odds?

Robert L. Coffman and Steven L. Reiner

Lymphocytes are a late evolutionary addition to the immune system of vertebrates, enabling effective host defense against a wide variety of pathogenic microbes. The effector cells of the immune system, T and B lymphocytes, undergo two distinct modes of differentiation; one endows them with specificity for a particular antigen, the other with specific effector functions (T_H1 versus T_H2 cytokine patterns for $CD4^+$ T cells; specific antibody classes for B cells). Recombination of the V, D, and J segments of antigen receptor genes results in the generation of populations of T and B lymphocytes that express a broad repertoire of antigen receptors. In this way, the immune system is able to respond to a wide array of pathogens. Binding of antigen to the corresponding receptor stimulates the lymphocyte bearing that receptor to differentiate. In the case of T cells, functional differentiation is accompanied by distinct expression patterns for genes encoding cytokines and surface receptors. When stimulated by antigen, precursor T cells bearing the CD4 marker [T helper (T_H) cells] differentiate into either T_H1 cells or T_H2 cells. T_H1 cells produce interferon-γ (IFN-γ) and tumor necrosis factor–β (TNF-β) and protect against intracellular pathogens; T_H2 cells, which produce interleukin (IL)-4, IL-5, and IL-13, help to control extracellular pathogens, and mediate allergy (*1*).

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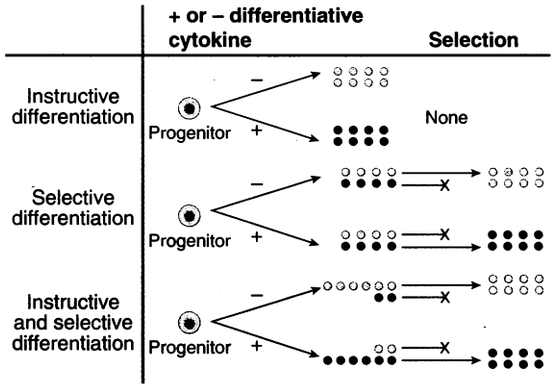
The best characterized influence on the differentiation of T_H cells is the cytokine environment (*1*). T_H cells first activated by antigen in the presence of IL-12 develop predominantly into T_H1 cells, whereas those activated in the presence of IL-4 develop predominantly into T_H2 cells. There is a debate about whether the cytokines that induce T_H1 or T_H2 differentiation "instruct" the developmental fate of naïve T_H cells or "select" for cells that through a random (stochastic) process of gene activation already produce a combination of cytokines indicative of a T_H1 or T_H2 cell (see the figure).

Several observations published in the past year offer new, somewhat surprising, insights into the way in which differentiative inducer cytokines regulate T_H cell differentiation. Using fluorescent tags to record the number of cell divisions of individual cells, naïve T_H cells were shown to require a specified number of cell divisions before becoming competent to produce cytokines indicative of either the T_H1 or T_H2 pathway. Different numbers of divisions are required for different cytokines (*2, 3*). Furthermore, stable cytokine expression is accompanied by demethylation and increased chromatin accessibility of the cytokine genes (methylation is an epigenetic mechanism for silencing genes) (*2, 4*). The most unexpected finding is that IL-2, IL-4, and, possibly, other cytokines are expressed from only one of two alleles in many individual T_H cells (*5*). These seemingly unrelated findings do not clearly resolve the simple question of instructed differentiation versus random differentiation and selection; instead they suggest that elements of both models may contribute to T_H cell differentiation.



Modeling T helper cell differentiation. In the instructive model of T_H cell differentiation, all daughter cells adopt one of two developmental states specified by the presence or absence of specific differentiative signals (**upper panel**). In the selection model, daughter cells adopt differentiation states in a random (stochastic) manner (**middle panel**). Pure populations can subsequently arise if one cell type is selectively expanded or maintained in preference to the other. In a model that combines both instruction and selection, the ratio of the two types of daughter cells varies depending on exposure to extrinsic differentiation inducing cytokines (**lower panel**). If the shift in the ratio of the two cell types is extreme, pure populations could be generated without further selection. Pink and purple circles represent two alternate differentiation states.

Cell proliferation appears necessary for the differentiation of T_H subsets. The initial expression of both T_H1 and T_H2 cytokines is cell cycle–dependent, but IFN-γ expression appears during the initial cell division whereas IL-4 requires at least three divisions (*2*). Furthermore, lineage commitment in the earliest stages of differentiation is strikingly inefficient and heterogeneous. Even under optimal conditions for either T_H1 or T_H2 differentiation, the number of cells that express subset-specific cytokine genes is low and is invariably accompanied by low frequencies of cells expressing atypical cytokine patterns. Thus, the T_H cell fate decision has intrinsic heterogeneity, and sibling cells can develop different, even opposite, phenotypes.

Gene loci for effector cytokines such as IL-4, IL-13, and IFN-γ are epigenetically repressed in naïve T cells (their chromatin structure is closed and their cytosines methylated) (*2, 4*). The link between tran-

R. L. Coffman is in the Department of Immunobiology, DNAX Research Institute of Molecular and Cellular Biology, Palo Alto, CA 94304, USA. E-mail: Coffman@dnax.org. S. L. Reiner is in the Gwen Knapp Center for Lupus and Immunology Research, University of Chicago, Chicago, IL 60637, USA. E-mail: sreiner@midway.uchicago.edu