The work by Maisonpierre *et al.* (*4*) introduces an inhibitory ligand, Ang2, for the Tie2 regulatory RTK that normally helps maintain vascular integrity. A model is emerging of a regulatory mechanism through which blood vessels are constructed, maintained, remodeled, and eliminated. Other factors are also involved, during embryonic vasculogenesis and angiogenesis, and for physiological and pathological angiogenesis in the adult. For example, gene-knockout mice have also implicated a G protein–coupled receptor in vascular regulation, because in the absence of $G_{\alpha}13$, embryos die at E8.5 to E9.5, with defects in vascular assembly and angiogenesis (*12*). Moreover, a reciprocal paracrine signal has been revealed by gene-knockout mice that lack the genes for neuregulin, which is expressed in the endocardium of the heart, and the ErbB-2/3/4 RTKs, which are expressed in myocardium. Knockouts of this ligand or of its receptors produces defects in the developing heart analogous to those observed when Ang1 or Tie2 is missing (*13–16*). A similar role is suggested by gene-knockout mice for platelet-derived growth factor and its receptors in other tissue vasculature (*17, 18*). Furthermore, there is clear evidence in the adult for additional angiogenesis inducers and for an increasing number of angiogenesis inhibitors that act directly on endothelial cells (*19–21*). Thus, regulation of angiogenesis in ovulation and implantation, in wound healing, and in chronic pathological situations such as tumor progression will indeed be complex, but tractable using the power of animal models.

That complexity notwithstanding, the evidence is compelling that VEGF and the angiopoietins, and their cognate receptors, are critical components of the vascular regulatory machinery. It will be of particular interest to establish the possible contributions of Ang2 to tumor angiogenesis, whereby the quiescent vasculature (likely maintained in part by Ang1/Tie2) is activated to elicit and chronically effect the angiogenic phenotype that accompanies tumor growth and metastasis. Ang2 could well serve as an initial angiogenic signal, locally opening up the vessel structure to allow protease degradation of the basement membrane surrounding the endothelium and accessibility to that endothelium by angiogenesis inducers such as VEGF, thereby eliciting capillary sprouting and in turn new blood vessels that sustain a tumor as it expands.

References and Notes

1. W. Risau and I. Flamme, *Annu. Rev. Cell Dev. Biol.* **11**, 73 (1995).
2. J. Folkman and P. A. D'Amore, *Cell* **87**, 1153 (1996).
3. W. Risau, *Nature* **386**, 671 (1997).
4. P. C. Maisonpierre *et al.*, *Science* **277**, 55 (1997).
5. F. Shalaby *et al.*, *Nature* **376**, 62 (1995).
6. G.-H. Fong, J. Rossant, M. Gertsenstein, M. L. Breitman, *ibid.*, p. 66.
7. D. J. Dumont *et al.*, *Genes Dev.* **8**, 1897 (1994).
8. T. Sato *et al.*, *Nature* **376**, 70 (1995).
9. M. C. Puri, J. Rossant, K. Alitalo, A. Bernstein, J. Partanen, *EMBO J.* **14**, 5884 (1995).
10. S. Davis *et al.*, *Cell* **87**, 1161 (1996).
11. C. Suri *et al.*, *ibid.*, p. 1171.
12. S. Offermanns, V. Mancino, J.-P. Revel, M. I. Simon, *Science* **275**, 533 (1997).
13. K.-F. Lee *et al.*, *Nature* **378**, 394 (1995).
14. M. Gassmann *et al.*, *ibid.*, p. 390.
15. D. Meyer and C. Birchmeier, *ibid.*, p. 386.
16. R. Kramer *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 4833 (1996).
17. P. Leveen *et al.*, *Genes Dev.* **8**, 1875 (1994).
18. P. Soriano, *ibid.*, p. 1888.
19. N. Bouck, V. Stellmach, S. Hsu, *Adv. Cancer Res.* **69**, 135 (1996).
20. J. Folkman, in *The Molecular Basis of Cancer*, J. Mendelsohn, P. M. Howley, M. A. Israel, L. A. Liotta, Eds. (Saunders, Philadelphia, 1995), vol. 9, pp. 206–232.
21. D. Hanahan and J. Folkman, *Cell* **86**, 353 (1996).
22. T. Mustonen and K. Alitalo, *J. Cell Biol.* **129**, 895 (1995).

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CONDENSED MATTER PHYSICS

Low-Energy Excitations in High-Temperature Superconductors

Patrick A. Lee

Many common metals undergo a phase transition at some low critical temperature T_c and become superconductors. This phenomenon was explained in the famed BCS (Bardeen-Cooper-Schrieffer) theory (*1*) in terms of the coupling of electrons into Cooper pairs. In these materials, the superconducting ground state gains binding energy as a result of the pairing. It costs a finite amount of energy, called the energy gap, to break up the pairs to form excitations called quasiparticles. These are quantum mechanical superpositions of the electron and the hole excitations of the metallic state. These quasiparticles are interesting objects in their own right, but at low temperatures their number is exponentially small, and they hardly make their presence felt.

Until a decade ago, it was generally believed that the relative angular momentum of the electrons in Cooper pairs is *s* wave. Consequently, the energy gap is independent of the momentum **k** of the quasiparticle. This independence is in contrast to the only other case of Cooper pairing between fermions known at the time, namely, the superfluid state in liquid ^{3}He (*2*). There the pairing state is anisotropic (*p* wave), and the energy gap may vanish along some momentum direction. These nodal points in the energy gap play an important role because quasiparticles near the nodes can be created in large numbers and they are responsible for the low-temperature properties. Today the prevailing view is that in high-T_c superconductors, the Cooper pairs are formed in the *d*-wave state. The role of the quasiparticles is then more analogous to that in superfluid ^{3}He, and experimentalists are beginning to study them in detail. On page 83 of this issue, Krishana *et al.* (*3*) report a particularly interesting example of this class of experiments.

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Although the *s*-wave BCS pairing theory works perfectly for practically all metallic superconductors, even a decade ago there was suspicion that a few superconductors are exceptions. The main evidence was that the low-temperature properties are not exponentially activated, pointing to the existence of nodes in the energy gap. The suspected unconventional superconductors were the so called "heavy fermion" superconductors (*4*) containing rare-earth ions such as Ce or U and a number of organic superconductors (*5*). The field of unconventional superconductivity took a dramatic turn in 1986 with the discovery of high-temperature superconductivity in cuprates (*6*). Apart from the high T_c, the metallic state (and to a lesser extent, the superconducting state) of these materials is so unusual that it was widely speculated that the pairing state is not the conventional *s* wave. After a number of brilliant experiments (*7*), it is now widely accepted that the Cooper pairs in the cuprates are formed in the *d*-wave symmetry. This symmetry implies that the energy gap vanishes at four points on the Fermi surface of these two-dimensional materials. From angle-resolved photoemission experiments, the locations of these nodes are known to be along the diagonals in the Brillouin zone (see figure) (8). Meanwhile, the evidence for unconventional superconductivity in heavy fermions and in the organic metals continues to mount, and recently, another class of material, Sr_2RuO_4, may have joined its ranks (9). Nevertheless, the definitive phase-sensitive experiment has yet to be done in these materials, and the cuprates now stand as the best-characterized and most-studied of all the unconventional superconductors.

Now that the symmetry classification of the Cooper pairing in the cuprates appears to be resolved, the stage is set for detailed studies of the quasiparticles. These particles are distinct from those in conventional superconductors in that they have a unique energy versus momentum relation that determines the low-temperature properties. Krishana *et al.* (3) studied the transport of heat by these quasiparticles in a magnetic field. Far from being routine, this study uncovered a surprisingly rapid destruction of the quasiparticle heat flow by a relatively small magnetic field. These results are not understood at present and point to the need for a reassessment of our current understanding of the quasiparticles and perhaps the superconducting state itself.

The energy spectrum of the quasiparticle is given by

$$E(\mathbf{k}) = \{[\varepsilon(\mathbf{k}) - E_F]^2 + \Delta^2(\mathbf{k})\}^{1/2} \quad (1)$$

where $\mathbf{k}$ is the momentum vector, $\varepsilon(\mathbf{k})$ is the electronic energy in the metallic state, and $\Delta(\mathbf{k})$ is the gap function, which for *d*-wave symmetry takes the approximate form $\Delta(\mathbf{k}) = 1/2\Delta_0[\cos(k_x a) - \cos(k_y a)]$, where a is the lattice constant. Note that $\Delta(\mathbf{k})$ vanishes along the lines $k_x = \pm k_y$. Near the node, the quasiparticle energy can be approximated by

$$E(\mathbf{k}) = (v_F^2 k_1^2 + v_2^2 k_2^2)^{1/2} \quad (2)$$

where v_F is the Fermi energy in the metallic state, $v_2 = \Delta_0 a/\sqrt{2}$, and k_1 and k_2 are the components of the momentum normal and parallel to the local Fermi surface, measured relative to the nodal points. Equation 2 describes a conelike excitation spectrum (see figure), with velocities v_F and v_2 perpendicular and parallel to the Fermi surface, respectively. It turns out that in the presence of a superfluid flowing with velocity v_s, the quasiparticle energy is modified as

$$E_{vs}(\mathbf{k}) = E(\mathbf{k}) + \mathbf{k}\cdot v_s \quad (3)$$

In a superconductor, a superfluid flow field occurs around a vortex that forms in the presence of a magnetic field. Thus, the cone of excitation shown in the figure will move up and down in the presence of v_s. It will be interesting to make measurements on the quasiparticles and observe these effects.

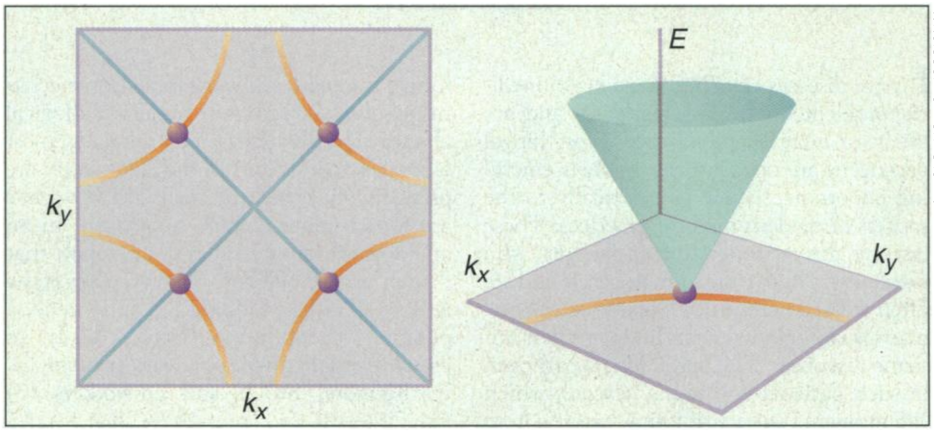


ILLUSTRATION: P. MORRIGHAN

Quasiparticle picture. The Fermi surface—a graphical depiction of electron energy versus momentum in a material—as determined by angle-resolved photoemission (*8*), is given by the red line. In an ordinary superconductor, an energy gap occurs along the entire Fermi surface. In a *d*-wave superconductor, the energy gap vanishes along the blue line, giving rise to four nodes, indicated by the dots where the gap vanishes. The quasiparticle excitation obeys an energy versus momentum relation (Eq. 2) that is in the shape of a cone near the node. The propagation of these quasiparticles were studied by Krishana *et al.* (*3*).

One consequence of Eq. 3 is that in the presence of a magnetic field H perpendicular to the sample, the superfluid flow field around the vortices produces a finite density of states at the Fermi energy, corresponding to those cones of excitation that have moved down in energy. This phenomenon was predicted to give rise to a linear term in the specific heat as a function of temperature, with a coefficient proportional to $H^{1/2}$ (*10*). There is recent experimental evidence in support of this remarkable prediction (*11*). It is, however, desirable to make transport measurements on the quasiparticles, because these are often more sensitive than thermodynamic measurements. Unfortunately, the dc electrical current carried by the quasiparticles is shorted out by the superfluid flow, so the quasiparticles must be studied at microwave frequencies or by thermal conductivity. One consequence of these experiments is the remarkable demonstration that disorder scattering plays a minor role in the best high-T_c cuprate crystals, so that the quasiparticles propagate essentially freely over long distances at low temperatures. This free propagation was first inferred from microwave measurements (*12*) and recently confirmed in a Hall thermal conductivity experiment (*13*). The thermal conductivity in the cuprates is dominated by the lattice contribution, and it has long been a difficult task to separate the lattice and the electronic contributions. This experiment takes advantage of the fact that in a magnetic field, only the charged quasiparticles respond, giving rise to a component of the thermal current perpendicular to the thermal gradient, analogous to the conventional Hall effect. This specific response allows the experimenters to separate the lattice and electronic contributions and extract the mean free path for quasiparticles (*13*). It was found that the mean free path increases rapidly below T_c reaching a distance of 2500 Å at 15 K. This result is a striking demonstration of the high quality of the cuprate crystals that are available today.

The thermal current carried by the quasiparticles is determined by its group velocity $dE/d\mathbf{k}$, which changes direction as $\mathbf{k}$ moves around the nodal point. This dependence is a consequence of the cone-like excitation spectrum. It is interesting that the electrical current carried by the quasiparticle is constant, given by ev_F; this is a consequence of the quasiparticle being a superposition of electron and hole, which carry the same electrical current but at opposite velocities. It was discovered that the thermal conductivity depends on the orientation of a magnetic field applied parallel to the copper-oxygen planes (*14*). The mechanism is that the superfluid flow associated with the vortices causes, as described by Eq. 3, a reversal of the quasiparticle group velocity, leading to a reduction in the thermal conductivity. It was further realized that when the magnetic field is in the direction of the node, the superfluid velocity is perpendicular to $\mathbf{k}$, so that this effect is minimized. The result is an anisotropy in the field dependence of the thermal conductivity, which helps establish the fact that the nodes are along the diagonal of the Brillouin zone.

Krishana *et al.* (3) carried out high-precision thermal conductivity measurements in a magnetic field perpendicular to the copper-oxygen plane. They discovered a surprise: The thermal conductivity resulting from the quasiparticles decreased rapidly as the magnetic field was increased, and it appeared to vanish beyond a certain critical field. The abruptness of this change is most unexpected and is currently unexplained. It certainly exposes the inadequacy of our understanding of the quasiparticles and perhaps the ground state itself, just at a time when there is a sense of confidence that the *d*-wave description of the cuprate superconductors may be established. Further experimental and theoretical work will be needed before we can tell whether we can get away with a minor modification of our current understanding, or whether a more profound revision is called for.

References

1. J. Bardeen, L. Cooper, J. R. Schrieffer, *Phys. Rev.* **106**, 162 (1957); *ibid.* **108**, 1175 (1957).
2. D. M. Lee, D. D. Osheroff, R. C. Richardson, *Rev. Mod. Phys.*, in press.
3. K. Krishana *et al.*, *Science* **277**, 83 (1997).
4. For a review, see M. Sigrist and K. Ueda, *Rev. Mod. Phys.* **63**, 239 (1991).
5. For a review, see D. Jerome, in *Organic Conductors: Fundamentals and Applications*, J. P. Farges, Ed. (Dekker, New York, 1994).
6. J. G. Bednorz and K. A. Mueller, *Z. Phys. B* **64**, 189 (1986).
7. D. J. van Harlingen, *Rev. Mod. Phys.* **67**, 515 (1995); C. C. Tsuei *et al.*, *Phys. Rev. Lett.* **73**, 593 (1994).
8. Z. X. Shen *et al.*, *Phys. Rev. Lett.* **70**, 1553 (1993); Z. X. Shen and D. S. Dessau, *Phys. Rep.* **253**, 162 (1995).
9. Y. Maeno *et al.*, *Nature* **372**, 532 (1994).
10. G. Volovik, *JETP Lett.* **58**, 469 (1993).
11. K. A. Moler *et al.*, *Phys. Rev. Lett.* **73**, 2744 (1994).
12. D. A. Bonn, D. Dosanjh, R. Liang, W. N. Hardy, *ibid.* **68**, 2390 (1992).
13. K. Krishana, J. M. Harris, N. P. Ong, *ibid.* **75**, 3529 (1995).
14. F. Yu *et al.*, *ibid.* **74**, 5136 (1995); H. Aubin *et al.*, *ibid.* **78**, 2624 (1997).

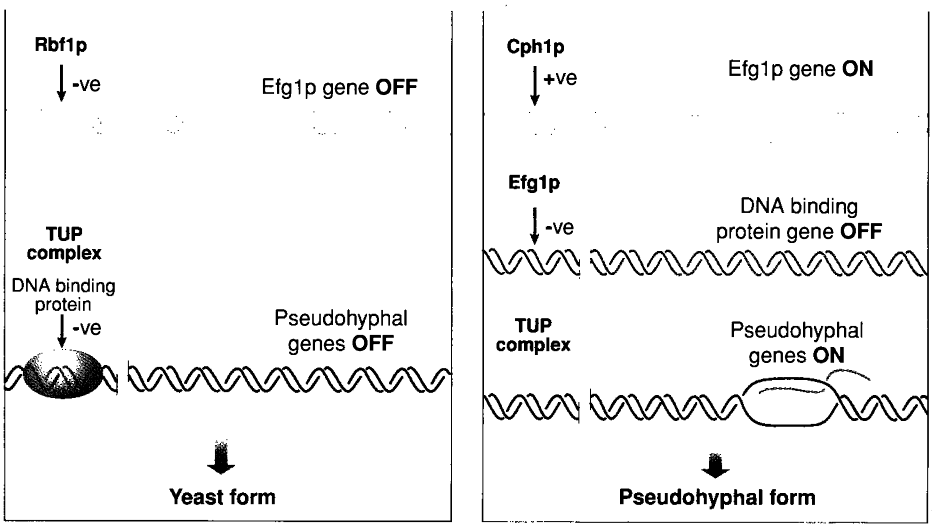
TRANSCRIPTION

Which Came First, the Hypha or the Yeast?

P. T. Magee

Fungal diseases have become a major medical problem in the last few years and are likely to increase in severity. Most fungal pathogens are opportunists, so their emerging importance is due paradoxically to the success of modern medical practices: These diseases thrive in debilitated patients, who now survive much longer than before and are often treated with procedures (such as bone marrow transplants) that diminish their immune responses. The major fungal pathogen in such patients is *Candida albicans*, which can grow in a variety of forms, ranging from budding yeast to threadlike hyphae. Pseudohyphae, which vary in shape from attached strings of yeastlike cells to long filaments with constrictions at the septae, constitute a third form. Thus, *C. albicans* is not, as usually described, dimorphic, but is more properly considered polymorphic; the relations among the various morphological forms are not well understood. The report by Braun and Johnson (*1*) on page 105 of this issue provides exciting information about polymorphism in this organism and, together with two other recent reports (*2*, *3*), will make investigators think in new ways about how *C. albicans* regulates its cell shape.

Braun and Johnson demonstrate that *C. albicans* requires the general transcriptional repressor *TUP1* to maintain the yeast form. When both copies of the *Candida TUP1* gene are deleted (phenotype designated Tup^-), the organism grows exclusively in the pseudohyphal form. The general view has been (as the authors state) that the "default" form is the yeast, and some induction mechanism is necessary to cause the morphological change. The filaments that occur under most laboratory conditions in the Tup^- strain are pseudohyphae, but true cylindrical hyphae are found under certain conditions. In an analogous finding, Ishii *et al.* (*2*) report that disruption in *C. albicans* of both copies of the *RBF1* (RPG-box binding factor 1) gene, a putative transcription factor, leads to pseudohyphal growth on a variety of media. Furthermore, Stoldt and co-workers (*3*) show that drastically decreasing the cellular concentration of a Myc-like transcription factor, Efg1p (enhanced filamentous growth), leads to a cellular morphology somewhat like pseudohyphae, whereas overexpression of the *EFG1* gene causes a very strong pseudohyphal phenotype. All these results suggest that pseudohypha formation is under negative control. Although it still may be true that some transcriptional activator is required for the yeast-to-pseudohypha transition, Braun and Johnson show that a previously identified transcriptional activator, *CPH1* (also known as *ACPR*) (*4*), is not. In wild-type *C. albicans*, deletion of both copies of *CPH1* prevents pseudohypha formation (*5*), but strains in which both copies of *TUP1* and both copies of *CPH1* are deleted show the Tup^- phenotype—constitutive filamentous growth. *TUP1/tup1* heterozygotes suppress the *cph1/cph1* phenotype; that is, *TUP1/tup1 cph1/*



A model for the regulation of pseudohyphal growth in *C. albicans*. The genes required for pseudohyphal growth are under the negative control of a complex consisting of Tup1p and probably other proteins. When this complex is targeted to the pseudohyphal genes by a DNA binding protein, the genes are off (**left**). When the DNA binding protein is absent, the genes are transcribed and the cell grows in the pseudohyphal form (**right**). The DNA binding protein is negatively regulated by Efg1p; when *EFG1* is overexpressed, synthesis of the DNA binding protein is prevented and the cells are in the pseudohyphal state, as shown on the right. *EFG1* is negatively regulated by Rbf1p and positively regulated by Cph1p when the latter is activated by the MAP kinase cascade. When *RBF1* is deleted, Efg1p is overexpressed and the pseudohyphal genes are on. When *CPH1* is deleted, Efg1p is not made and the cells cannot turn on the pseudohyphal genes.

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