Author disclosures are available with the text of this article at www.atsjournals.org.

Joachim Müller-Quernheim, M.D.
Department of Pneumology
University Medicine Center
Freiburg, Germany

Athol Wells, M.D.
Department of Respiratory Medicine
Royal Brompton Hospital
Chelsea, London, United Kingdom

References

1. Paramothayan S, Lasserson T, Walters EH. Immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis. *Cochrane Database Syst Rev* 2003;(3):CD003536.
2. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
3. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, *et al.* An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–614.
4. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, Sasaki H. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest* 2005;128:1475–1482.
5. Sode BF, Dahl M, Nielsen SF, Nordestgaard BG. Venous thromboembolism and risk of idiopathic interstitial pneumonia: a nationwide study. *Am J Respir Crit Care Med* 2010;181:1085–1092.
6. Kotani I, Sato A, Hayakawa H, Urano T, Takada Y, Takada A. Increased procoagulant and antifibrinolytic activities in the lungs with idiopathic pulmonary fibrosis. *Thromb Res* 1995;77:493–504.
7. Scotton CJ, Krupiczojc MA, Konigshoff M, Mercer PF, Lee YC, Kaminski N, Morser J, Post JM, Maher TM, Nicholson AG, *et al.* Increased local expression of coagulation factor X contributes to the fibrotic response in human and murine lung injury. *J Clin Invest* 2009;119:2550–2563.
8. Wygrecka M, Kwapiszewska G, Jablonska E, von Gerlach S, Henneke I, Zakrzewicz D, Guenther A, Preissner KT, Markart P. Role of protease-activated receptor-2 in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:1703–1714.
9. Li CM, Khosla J, Hoyle P, Sannes PL. Transforming growth factor-beta(1) modifies fibroblast growth factor-2 production in type II cells. *Chest* 2001; 120:60S–61S.
10. Kinder BW, Collard HR, King TE Jr. Anticoagulant therapy and idiopathic pulmonary fibrosis. *Chest* 2006;130:302–303.
11. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, Kaner RJ, Olman MA; The Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;186:88–95.
12. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012;366:1968–1977.

DOI: 10.1164/rccm.201205-0883ED

Lung Cancer: New Therapeutic Targets, New Definitions

Lung cancer is the leading cause of cancer death for men and women in the United States (1). This high mortality rate is heavily influenced by the fact that most lung cancers, in contrast to cancers such as breast and colon, are diagnosed at an advanced stage when metastases are present and cure is no longer an option (2). Because of this fact, the 5-year mortality for lung cancer has unfortunately remained relatively unchanged for the past 40 years. Although recent advances in lung cancer screening might alter this landscape in favor of diagnosing more early-stage, resectable tumors, a better understanding of the mechanisms behind lung cancer pathogenesis and the factors that promote metastasis is needed to design new therapies and treatment strategies.

In the current issue of the *Journal*, Antón and colleagues (pp. 96–105) present their findings on the role of the endogenous anticoagulant activated protein C (APC) and its receptor, the endothelial protein C receptor (EPCR), in lung cancer metastasis (3). There are two key findings in their studies: APC–EPCR is a novel signaling axis involved in metastasis of lung adenocarcinoma, and tumor EPCR expression might carry prognostic information for adenocarcinoma patients.

Protein C (PC) and APC are central participants in coagulation. PC is a plasma serine protease that circulates as an inactive zymogen. As the coagulation cascade is triggered, the protease thrombin forms a complex with the endothelial surface protein thrombomodulin (TM). This thrombin/TM complex then converts PC to its active form, APC. APC inactivates factors Va and VIIIa, which, in turn, block downstream thrombin generation and further PC activation. EPCR is a crucial participant in the PC/APC pathway (4) as it binds PC and presents it to the thrombin/TM complex, thereby increasing the activation of PC to APC by approximately 20-fold (5, 6).

But what is the relationship of this hemostatic cascade to lung cancer metastasis? Importantly, APC also binds EPCR, and increasing evidence indicates that much, if not all, of APC intracellular signaling is EPCR dependent. This signaling is directly relevant to cancer. In an EPCR-dependent fashion, APC inhibits p53-dependent apoptosis (7), decreases Rac- and Akt-mediated cell–cell adhesion, and enhances tumor cell invasion and migration (8–10), directly affecting cell survival and a cancer's metastatic potential. Although APC does not appear to affect cancer cell proliferation, it increases endothelial cell proliferation and is proangiogenic via up-regulation of endothelial nitric oxide synthase (11), thereby increasing vascular supply to the tumor. In addition, EPCR serves as a docking protein for other receptors such as the protease-activated receptor 1 (PAR1) and the sphingosine 1-phosphate receptor 1 (S1P1 or Edg1), both of which are linked to the transformation process. Finally, APC-EPCR inhibits lymphocyte migration (12) and production of interferon-γ by natural killer cells (13), which may impair immune surveillance of tumors. These functions imply that APC and EPCR have the potential to significantly influence cancer cell growth, survival, and metastasis.

Anton and colleagues convincingly demonstrate, using *in vitro*, *in vivo*, and human studies, that EPCR affects lung adenocarcinoma metastasis. Using a murine metastasis model in which cells from an adenocarcinoma cell line are seeded hematogenously via intracardiac puncture, decreasing cancer cell EPCR expression using an RNA interference strategy or a pharmacologic inhibitor decreased metastases. In contrast, increased EPCR expression increased metastases. The authors also confirmed the previously identified finding that APC attenuates apoptosis *in vitro*, and although this was not specifically tested in their model, suggest that

Author Contributions: Conception, design, and manuscript drafting: J.F., J.A.K. Supported by NIH K08 HL086668.

decreased metastases might be through an APC-induced prosurvival mechanism in cancer cells.

Perhaps most striking, the authors demonstrated that EPCR expression by pulmonary adenocarcinomas was both prognostic and predictive of response to therapy. Using retrospective data from two clinical trials, the authors separated participants into cohorts of high and low tumor EPCR expression and found that high EPCR expression predicted shorter metastasis-free and total survival. In addition, patients with stage I adenocarcinomas that had high EPCR expression and received postsurgical adjuvant therapy had an overall and progression-free survival benefit, though these analyses had relatively small populations. Although the authors do not comment on the presence of other high-risk features, this effect was independent of tumor size, age, sex, and smoking status, suggesting that tumor EPCR expression carries prognostic information. Thus, EPCR expression status might be used to identify patients that could benefit from further therapy or to guide therapy if EPCR antagonists are found to be effective against lung cancer.

Anton and colleagues have pointed out a new pathway that potentially promotes lung adenocarcinoma spread and could lead to novel therapeutic targets to control metastases, including APC, EPCR, and possibly other intracellular partners such as PAR1 or S1P1. The benefit of such an approach is yet to be determined and will require further evaluation. However, their findings again highlight that lung cancer management is moving beyond the use of pure clinicopathologic classifications and staging to include molecular characterization, creating new designations of lung cancer to refine our therapeutic and prognostic capabilities. The identification of specific "driver" mutations in lung cancer, such as EGFR, has expanded our understanding of oncogenesis and lung cancer care as targeted therapy directed against the mutant protein results in dramatic clinical improvements (14). Expression levels of genes and proteins that do not have somatic mutations also provide prognostic and predictive information in lung cancer. For example, low excision repair cross-complementation group 1 (ERCC1) expression portends a poor prognosis in non–small cell lung cancer but also predicts a better response to platinum-based therapy when compared with high ERCC1–expressing tumors (15). If the findings concerning EPCR are confirmed, EPCR would add to this expanding panel of markers and targets in lung adenocarcinomas to move toward a more refined, molecularly based taxonomy and therapy of lung cancer.

Author disclosures are available with the text of this article at www.atsjournals.org.

James H. Finigan, M.D.
Jeffrey A. Kern, M.D.
Department of Medicine
National Jewish Health
Denver, Colorado

References

1. U.S. Cancer Statistics Working Group. United States cancer statistics: 1999–2007 incidence and mortality Web-based report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; c2010 [accessed 2011 July 25]. Available from: http://www.cdc.gov/uscs
2. SEER Cancer Statistics Review 1975–2008. c2011 [accessed 2011 July 25]. Available from: www.cancer.gov
3. Antón I, Molina E, Luis-Ravelo D, Zandueta C, Valencia K, Ormazabal C, Martínez-Canarias S, Perurena N, Pajares MJ, Agorreta J, *et al.* Receptor of activated protein C promotes metastasis and correlates with clinical outcome in lung adenocarcinoma. *Am J Respir Crit Care Med* 2012;186:96–105.
4. Fukudome K, Esmon CT. Identification, cloning, and regulation of a novel endothelial cell protein C/activated protein C receptor. *J Biol Chem* 1994;269:26486–26491.
5. Oganesyan V, Oganesyan N, Terzyan S, Qu D, Dauter Z, Esmon NL, Esmon CT. The crystal structure of the endothelial protein C receptor and a bound phospholipid. *J Biol Chem* 2002;277:24851–24854.
6. Taylor FB Jr, Peer GT, Lockhart MS, Ferrell G, Esmon CT. Endothelial cell protein C receptor plays an important role in protein C activation in vivo. *Blood* 2001;97:1685–1688.
7. Cheng T, Liu D, Griffin JH, Fernandez JA, Castellino F, Rosen ED, Fukudome K, Zlokovic BV. Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective. *Nat Med* 2003;9:338–342.
8. Finigan JH, Dudek SM, Singleton PA, Chiang ET, Jacobson JR, Camp SM, Ye SQ, Garcia JG. Activated protein C mediates novel lung endothelial barrier enhancement: role of sphingosine 1-phosphate receptor transactivation. *J Biol Chem* 2005;280:17286–17293.
9. Beaulieu LM, Church FC. Activated protein C promotes breast cancer cell migration through interactions with EPCR and PAR-1. *Exp Cell Res* 2007;313:677–687.
10. Kobayashi H, Moniwa N, Gotoh J, Sugimura M, Terao T. Role of activated protein C in facilitating basement membrane invasion by tumor cells. *Cancer Res* 1994;54:261–267.
11. Uchiba M, Okajima K, Oike Y, Ito Y, Fukudome K, Isobe H, Suda T. Activated protein C induces endothelial cell proliferation by mitogen-activated protein kinase activation in vitro and angiogenesis in vivo. *Circ Res* 2004;95:34–41.
12. Feistritzer C, Mosheimer BA, Sturn DH, Riewald M, Patsch JR, Wiedermann CJ. Endothelial protein C receptor-dependent inhibition of migration of human lymphocytes by protein C involves epidermal growth factor receptor. *J Immunol* 2006;176:1019–1025.
13. Kerschen E, Hernandez I, Zogg M, Shuang J, Hessner MJ, Fernandez JA, Griffin JH, Huettner CS, Castellino FJ, Weiler H. Activated protein C targets CD8+ dendritic cells to reduce the mortality of endotoxemia in mice. *J Clin Invest* 2010;120:3167–3178.
14. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, Fong KM, Lee H, Toyooka S, Shimizu N, *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339–346.
15. Zhou W, Gurubhagavatula S, Liu G, Park S, Neuberg DS, Wain JC, Lynch TJ, Su L, Christiani DC. Excision repair cross-complementation group 1 polymorphism predicts overall survival in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. *Clin Cancer Res* 2004;10:4939–4943.

DOI: 10.1164/rccm.201205-0811ED

Diagnostic Criteria for Invasive Pulmonary Aspergillosis in Critically Ill Patients

Invasive pulmonary aspergillosis (IPA) is a severe disease seen chiefly in patients with prolonged neutropenia, bone marrow or solid organ transplantation, or T-cell deficiencies (1, 2). However, IPA also occurs in nonneutropenic critically ill patients with chronic obstructive pulmonary disease (COPD), long-term steroid therapy, hepatic cirrhosis, dialysis, near drowning, or diabetes (3); sepsis due to bacterial, viral, or parasitic agents (4, 5); and severe postsepsis immunoparalysis (6). Histopathology is the only means of confirming IPA, but obtaining a lung biopsy remains challenging. In hematology patients, strict diagnostic criteria have been developed (7): possible IPA is diagnosed in patients with both host factors and clinical signs and