BIOGRAPHICAL SKETCH

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NAME: Adrienne D. Cox, PhD

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POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Pomona College; Claremont, CA	BA	06/1974	Zoology
Eastern Virginia Medical School; Norfolk, VA	PhD	06/1987	Biomedical Sciences
La Jolla Cancer Research Foundation (now SanfordBurnham Prebys Medical Discovery Institute); La Jolla (San Diego), CA	Postdoc.	06/1992	Cancer Biology

A. Personal Statement

I am a cancer cell biologist with many years of experience in biochemical, molecular and cellular biological approaches to the study of RAS family-mediated signal transduction and transformation. My laboratory is particularly interested in understanding the roles of isoform differences between KRAS, NRAS and HRAS, the role of subcellular localization of RAS and RHO pathway proteins and their interactors, and in identifcation of inhibitor combinations of kinase effector pathways such as the RAF-MEK-ERK MAPK cascade to treat RASdriven cancers. We focus on RAS- and RHO-driven cancers including pancreatic, colorectal, lung, head & neck and melanoma, and gastric cancer, respectively. Our research has highlighted the importance and complexity of identifying tractable targets and useful biomarkers. I have assisted pharma and biotech companies in the development of small molecule inhibitors for targeted cancer therapeutics. In addition to my laboratory's performance of both basic and translational oncology research, I am also highly committed to collaborations that advance science and aid in training the next generation of diverse scientists. As a mentor to undergraduates, predocs and postdocs in my own laboratory, I am proud that my trainees have achieved independent careers in academia and industry, at the bench, at the lectern and running diversity programs at distinguished institutions. In addition to my service on numerous dissertation and mentoring committees, I participate in professional development opportunities for trainees and their mentors, such as piloting a UNCwide mentoring workshop and a new course in Rigor and Reproducibility funded by UNC's NIH-funded BEST award. I am the faculty advisor to UNC's graduate student Scientific Writing and Communication Club (SWAC), and a cohort facilitator for the Initiative for Maximizing Student Development (IMSD) program. I am Director of UNC's Cancer Cell Biology T32 Training Program (CCBTP), serve on numerous internal and external institutional advisory boards and committees for cancer biology training programs, and am President of the national Cancer Biology Training Consortium (CABTRAC).

a. Hobbs GA, Baker NM, Miermont AM, Thurman RD, Pierobon M, Tran TH, Anderson AO, Waters AM, Diehl JN, Papke B, Hodge RG, Klomp JE, Goodwin CM, DeLiberty JM, Wang J, Ng TWS, Gautaum P, Bryant KL, Esposito D, Campbell SL, Petricoin EF III, Simanshu DK, Aguirre AJ, Wolpin BM, Wennerberg K, Rudloff U, Cox AD, Der CJ. (2020) Atypical $KRAS^{G12R}$ mutant is impaired in PI3K signaling and macropinocytosis in pancreatic cancer. Cancer Discov 10:104-123. PMCID: PMC6954322

b. Bryant KL, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, Gunda V, Pierobon M, Waters AM, George SD, Tomar G, Papke B, Hobbs GA, Yan L, Hayes TK, Diehl JN, Goode GD, Chaika NV, Wang Y, Zhang GF, Witkiewicz AK, Knudsen ES, Petricoin EF 3rd, Singh PK, Macdonald JM, Tran NL, Lyssiotis CA, Ying H, Kimmelman AC, Cox AD, Der CJ. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. Nat Med. 2019 April;25(4):628-640. PMCID: PMC6484853

c. Zhou B, Wang L, Zhang S, Bennett BD, He F, Zhang Y, Xiong C, Han L, Diao L, Li P, Fargo DC, Cox AD**, Hu G. (2016) INO80 governs superenhancer-mediated oncogenic transcription and tumor growth in melanoma. Genes Dev 30:1440-1453. PMCID: PMC4926866 **co-corresponding author.

B. Positions and Honors

1988-1992	Postdoctoral Fellow, The Sanford-Burnham Institute, La Jolla, CA
1992-1994	Res. Assist. Professor, Pharmacology, University of North Carolina, Chapel Hill, NC
1994-2001	Assistant Professor, Radiation Oncology and Pharmacology, UNC-Chapel Hill, NC
1993-present	Member, Lineberger Comprehensive Cancer Center, UNC-Chapel Hill, NC
2001-2017	Associate Professor, Radiation Oncology and Pharmacology, UNC-Chapel Hill, NC
2003-present	Chief, Division of Cancer Biology, Radiation Oncology, UNC-Chapel Hill, NC
2004-2009	Chartered Member, NCI study section BMCT (Basic Mechs of Cancer Therapeutics)
2007-2011	Director, Cell & Molecular Biology (CMB) NIH T32 Training Program
2008	Visiting Senior Academic Scholar, Wolfson College, Cambridge Univ., Cambridge, UK
2014-2017	Member, American Cancer Society (ACS) study section CDD (Cancer Drug Discovery)
2011-2016	Associate Director, Cancer Cell Biology (CCBTP) NCI T32 Training Program
2015-present	Member, External Advisory Board, NCI T32 Cancer Training Grant, University of Virginia
2016-present	Director, Cancer Cell Biology (CCBTP) NCI T32 Training Program
2016-present	Member, Board of Directors, CABTRAC (Cancer Biology Training Consortium)
2017-present	Member, External Advisory Board, NIH T32 Solid Tumor Training Program, Duke U.
2018-present	Professor, Radiation Oncology and Pharmacology, UNC-Chapel Hill, Chapel Hill, NC
2018-present	Member, EABs, NCI T32 Training Programs at U. Chicago, Dana-Farber Cancer Institute, Virginia Commonwealth U. (CCSG)
2019-present	Member, EABs, NCI T32 Training Programs at U. Colorado Denver, Wake Forest U.
2020-present	President, CABTRAC (Cancer Biology Training Consortium)

Consultant

Eli Lilly, Kyras Therapeutics, Merck Research Labs, Mirati Therapeutics, Pfizer Central Research, ScheringPlough Research Inst, SpringWorks Therapeutics

Grant Reviewership

Chartered Member, NCI study section BMCT; NIH/NCI SEPs (many various, including services as Chair, and on Subcommittee F); AACR; Chartered Member, ACS study section CDD (Cancer Drug Discovery); Komen; DOD Breast, Prostate, Rad Onc; CBCRP; Israeli Sci. Fnd; Ital Assoc Cancer Res; others.

Editorial Reviewership

Int J Cell Biol, Int J Sig Trans, Small GTPases, Mol Pharm (editorial boards); Cancer Cell, Cancer Res, Dev Cell, JCB, JBC, JCS, JCI, Nat Chem Biol, Nat Comm, Nat Med, MCB, Mol Med, Oncogene, PNAS, others.

Honors/awards

National Merit Scholar, NSF graduate fellowship, NRSA postdoctoral fellowship, NIH/NCI training grant, NIH/NCI FIRST award; Organizer, 7th FASEB Meeting on Small GTPases, Saxtons River, VT; Plenary lecturer, Annual Symp Korea Inst Radiol & Medical Sci (KIRAMS), Seoul, Korea; Keynote speaker, EVMS Graduate Student Research Day; Keynote Speaker, 8th Tuscany Retreat on Cancer Research and Apoptosis; Keynote speaker, UTSW Cancer Biology Retreat; Visiting Faculty, U. Copenhagen and U. Tromsø (Norway); Visiting Senior Academic Scholar, Wolfson College, Cambridge U., UK; UNC-CH teaching excellence awards; UNCCH 2020 University Mentoring Award for Lifetime Achievement

Patent

US 7,838,531/8,257,915 B2: Farnesyltransferase inhibitors for treatment of laminopathies, cellular aging and atherosclerosis.

C. Contributions to Science

1. Prenylation of RAS proteins regulates their membrane association and biological activities, but prenylation inhibitors are not anti-RAS drugs. My initial foray into RAS biology came when it was just beginning to be appreciated that RAS proteins were modified by C-terminal prenylation by a farnesyl isoprenoid, and that this modification might be a molecular target for therapy of RAS-driven disease. I contributed to demonstrations that farnesylation is the critical modifiation for HRAS membrane association and biological activities. I also discovered that wild type HRAS has a more stringent requirement for a precise lipid modification than oncogenic HRAS. I explored the specificity of farnesyl transferase inhibitors (FTIs), and the mechanisms and biological consequences of their actions in RAS-transformed cells. Although FTIs were originally and widely touted as anti-RAS drugs, it was eventually discovered that only HRAS is inhibited by these agents, whereas KRAS and NRAS are not, because they are alternatively prenylated by the related enzyme, GGTase-I. This was a huge turning point for the field, to recognize that not all RAS proteins are created equal, and has ramifications that are currently under intense investigation even today. My laboratory described individual contributions of affinity for the FTase enzyme and alternative prenylation as underpinnings of the resistance of the KRAS4B isoform to FTIs. Although FTIs have not been widely successful as anti-RAS and anti-cancer drugs, as originally predicted, we collaborated with the laboratory of Francis Collins to provide some of the first evidence that FTIs such as lonafarnib might be effective in the premature aging disease, Hutchinson-Gilford progeria syndrome (HGPS) (patent above). We have also explored the actions and targets of GGTase-I inhibitors and other compounds such as FTS/Salirasib (publication list, below). Now that FTIs are back for clinical use in HRAS-mutant cancers, we have explored the role and mechanisms of the FTI tipifarnib in HRAS-mutant head and neck squamous cell carcinomas. This work has just been submitted for publication.

a. Kato K, Cox AD, Hisaka MM, Graham SM, Buss JE and Der CJ. (1992). Isoprenoid addition to Ras protein is the critical modification for its membrane association and transforming activity. Proc Natl Acad Sci USA 89:6403-6407.
b. Cox AD, Hisaka MM, Buss JE and Der CJ. (1992). Specific isoprenoid modification is required for the function of normal, but not oncogenic, Ras protein. Mol Cell Biol 12:2606-2615.
c. Fiordalisi JJ, Johnson RL 2nd, Weinbaum CA, Sakabe K, Chen Z, Casey PJ and Cox AD. (2003) High affinity for farnesyl transferase and alternative prenylation contribute individually to K-Ras4B resistance to farnesyl transferase inhibitors. J Biol Chem 278: 41718-41727.
d. Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely K, Gordon LB, Der CJ, Cox AD and Collins FS. (2005) Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA 36:12879-84.

2. Subcellular localization of Ras family GTPases regulates effector utilization and can lead to life or death biological outcomes. Since either mutations or pharmacological inhibition of RAS posttranslational modifications that render constitutively active RAS both oncogenic and cytosolic could generate dominant negative activity, we characterized the output of cytosolic effector domain mutants of HRAS as dominant negatives and concluded that selective localization-based sequestration of effectors could have distinct consequences for specific aspects of RAS signaling and transformation. We also contributed to several related and highly innovative studies from the laboratory of Mark Philips (NYU), who observed that, contrary to the dogma that RAS functions solely at the plasma membrane, RAS is also activated at and can signal from endomembranes. Further, the effector signaling specificity of RAS proteins targeted to internal membranes differs according to their specific localization. For example, whereas KRAS is normally growth-promoting, ectopic expression of a phosphomimetic version of KRAS4B S181E caused cell death in vitro, and mouse tumor xenografts expressing phosphorylatable KRAS4B but not nonphosphorylatable KRAS4B S181A was not. We also observed distinct, location-dependent GTPase substrate utilization by regulatory proteins, leading to very different outcomes. For example, the RhoGEF ECT2, an activator of several RHO family members, activates

RAC1 in the nucleus whereas it activates RHOA in the cytosol of ovarian and lung cancer cells. In this context, RAC1 activation is pro-oncogenic whereas RHOA activation is not.

a. Fiordalisi JJ , Holly SP, Johnson RL II, Parise LV and Cox AD. (2002) A distinct class of dominant negative Ras mutants: cytosolic, GTP-bound Ras effector domain mutants that inhibit Ras signaling and transformation, and enhance cell adhesion. J Biol Chem 277:10813-10823.
b. Bivona TG, Quatela SE, Bodemann BO, Ahearn IM, Soskis MJ, Miura J, Wiener HH, Wright L, Saba SG, Yim D, Fein A, Pérez de Castro I, Thompson CB, Cox AD and Philips MR. (2006) Phosphorylation of KRas by PKC regulates a farnesyl-electrostatic switch that promotes association with Bcl-XL on mitochondria and induces apoptosis. Mol Cell 21:481-493.
c. Huff LP, DeCristo MJ, Trembath D, Kuan PF, Yim M, Liu J, Cook DR, Miller CR, Der CJ, Cox AD. (2013) The role of Ect2 nuclear RhoGEF activity in ovarian cancer cell transformation. Genes Cancer 4:460-75 (cover article). PMCID: PMC3877668
d. Justilien V, Ali SA, Jamieson L, Yin N, Cox AD, Der CJ, Murray NR, Fields AP. (2017) Ect2-dependent rRNA synthesis Is required for KRAS-TRP53-driven lung adenocarcinoma. Cancer Cell 31:256-269. PMCID: PMC5310966

3. Ras family small GTPases are regulated by C-terminal phosphorylation in an isoform-dependent manner. We observed that RAS-related proteins harbored sequences similar to the C-terminal membranetargeting sequence of KRAS4B containing the critical PKCα phosphorylation site, suggesting that C-terminal phosphorylation of small GTPases might be both more widespread and more critical to their localization and function than had been recognized. Others had previously identified C-terminal phosphorylation of RHOA and RAP1 by PKA. In a systematic effort to determine the role and importance of this modification in RAS and RHO GTPases, we found that phosphorylation of membrane targeting sequences often causes release from the plasma membrane, relocalization to the cytosol and/or internal membranes, and downregulation of activity. We found that RND3 is regulated differently than RND2, WRCH-1/RHOU is regulated differently than WRCH2/RHOV, RALA is regulated differently than RALB, etc. We also identified an unprecedented tyrosine phosphorylation on some of these sequences; found that closely related family members are phosphorylated by different kinases; and determined that the metastasis-associated phosphatase, PRL3, regulates select RHO GTPases and its activity depends on its own phosphorylation by SRC. Such modifications, which are evolutionarily conserved and highly isoform-dependent, are now recognized to be critical to GTPase signaling.

a. Fiordalisi JJ, Keller PJ and Cox AD. (2006) PRL tyrosine phosphatases regulate Rho family GTPases to promote invasion and motility. Cancer Res 66:3153-3161.
b. Madigan JP, Brady DC, Dewar BJ, Ridley AJ, Philips MR, Leitges M, Der CJ and Cox AD. (2009) Regulation of Rnd3 localization and function by PKCa-mediated phosphorylation. Biochem J 424:153-161. PMCID: PMC2868966
c. Alan JK, Berzat AC, Dewar BJ, Graves LM, Cox AD. (2010) Regulation of the Rho family small GTPase RhoU/Wrch-1 by C-terminal phosphorylation requires Src. Mol Cell Biol 30:4324-38. PMCID: PMC2937548
d. Martin TD, Mitin N, Cox AD, Yeh JJ, Der CJ. (2012) Phosphorylation by protein kinase Cα regulates RalB small GTPase protein activation, subcellular localization, and effector utilization. J Biol Chem 287:1482736. PMCID: PMC3340265

4. Membrane targeting of small GTPases is complex; it includes both permanent and dynamic posttranslational modifications as well as sequence specifications. It has long been recognized that RAS association with the plasma membrane requires both farnesylation and a "second signal". We helped to demonstrate that sequence information around the palmitoylation sites was also required. Not all small GTPases require permanent prenylation to achieve plasma membrane localization and transforming activities; multiple dynamic modifications could support WRCH-1/RHOU transformation and regulation of epithelial morphogenesis. We observed that oncogenic transformation mediated by KRAS4A, the long-neglected KRAS isoform, is supported by an unusual hybrid membrane targeting motif specified by both palmitoylation and bipartite polybasic sequences. We have also explored other types of modifications such as redox control of Rho family GTPases that appear to regulate activation state more than subcellular localization (see link to complete bibliography

below). Finally, RHOA activity coordinates with junctional proteins such as E-cadherin to regulate cytoskeletal organization and signaling and create therapeutic vulnerabilities in diffuse gastric cancer.

a. Berzat AC, Buss JE, Chenette EJ, Weinbaum CA, Shutes A, Der CJ, Minden A, Cox AD. (2005) Transforming activity of the Rho family GTPase, Wrch-1, a Wnt-regulated Cdc42 homolog, is dependent on a novel carboxyl-terminal palmitoylation motif. J Biol Chem 280: 33055-65.
b. Brady DC, Alan, JK, Madigan JP, Fanning AS and Cox AD. (2009) The transforming Rho family GTPase, Wrch-1, disrupts epithelial cell tight junctions and epithelial morphogenesis. Mol Cell Biol 29: 1035-49. PMCID: PMC2643799
c. Tsai FD, Lopes MS, Zhou M, Fiordalisi JJ, Gierut J, Cox AD, Haigis KM, Philips MR. (2015) The KRas4A splice variant is widely expressed in cancer and utilizes a hybrid membrane targeting motif. Proc Natl Acad Sci USA 112: 779-84. PMCID: PMC4311840
d. Zhang H, Schaefer A, Wang Y, Hodge RG, Blake DR, Diehl JN, Papageorge AG, Stachler M, Liao J, Zhou J, Wu Z, Akarca FG, de Klerk LK, Derks S, Pierobon M, Hoadley KA, Wang TC, Church G, Wong KK, Petricoin EF, Cox AD, Lowy DR, Der CJ, Bass AJ. (2020) Gain-of-function *RHOA* mutations promote focal adhesion kinase activation and dependency in diffuse gastric cancer. Cancer Discov 10: 288-305. PMCID: PMC7007383

5. Targeting RAS by targeting effector signaling specificity and delivery. Much attention has been logically directed to the RAF-MEK-ERK MAP kinase cascade, which was the first discovered effector pathway downstream of RAS signaling. It is clearly crucial, and it is currently targetable. The PI3K-AKT-mTOR pathway is similarly recognized as critical to RAS signaling. However, it is also true that numerous RAS effectors or potential effectors have been identified and yet we still do not understand the full complexity, or how specific RAS effectors are selected, and under what circumstances. We do know that, although RAS signaling cascades are typically drawn as simple linear pathways, each is almost invariably composed of multiple isoforms at each node, and that even closely related isoforms can have very distinctive roles and effects due to differential posttranslational modifications and subcellular localization. These studies have informed our ongoing investigations of the mechanisms of resistance to RAS effector-targeted therapeutics (see full publication list), some of which now support clinical trials of MEK or ERK inhibitor + autophagy inhibitors.

a. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ (2014) Drugging the undruggable RAS: Mission possible? Nat Rev Drug Discov. 13:828-51. PMCID: PMC4355017
b. Hayes TK, Neel NF, Hu C, Gautam P, Chenard M, Long B, Aziz M, Kassner M, Bryant KL, Pierobon M, Marayati R, Kher S, George SD, Xu M, Wang-Gillam A, Samatar AA, Maitra A, Wennerberg K, Petricoin EF III, Yin HH, Nelkin B, Cox AD, Yeh JJ, Der CJ. (2016) Long-term ERK inhibition in KRAS-mutant pancreatic cancer is associated with MYC degradation and senescence-like growth suppression. Cancer Cell 29:75-89. PMCID: PMC4816652
c. Zhou B, Ritt DA, Morrison DK, Der CJ and Cox AD. (2016) Protein kinase CK2alpha maintains ERK activity in a CK2alpha kinase-independent manner to promote resistance to inhibitors of RAF and MEK but not ERK in BRAF-mutant melanoma. J Biol Chem, doi:10.1074/jbc.M115.712885. PMCID: PMC5016172
d. Ozkan-Dagliyan I, George SD, Diehl JN, Schaefer A, Papke B, Klotz-Noack K, Waters AM, Goodwin CM, Gautaum P, Pierobon M, Peng S, Gilbert TSK, Lin KH, Dagliyan O, Wennerberg K, Petricoin, EF III, Tran NL, Bhagwat SV, Tiu R, Peng S-B, Herring LE, Graves LM, Sers C, Wood KC, Cox AD, Der CJ. (2020) Low-dose vertical inhibition of the RAF-MEK-ERK cascade causes apoptotic death of KRAS-mutant cancers. Cell Rep 31:107764-e9. PMCID: PMC7393480

For a more complete list of publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/adrienne.cox.1/bibliography/41139337/public/?sort=date&direction=descending