BIOGRAPHICAL SKETCH

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NAME: Rosner, Marsha R.

eRA COMMONS USER NAME (credential, e.g., agency login): mrosner

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University	AB	6/1972	Biochemistry
Massachusetts Institute of Technology	PhD	6/1978	Biochemistry
Massachusetts Institute of Technology	Postdoc	9/1981	Biochemistry
Massachusetts Institute of Technology	Instructor	9/1982	Proteomics

A. Personal Statement

I have extensive experience for over 30 years studying signaling pathways and networks, as well as purifying proteins and characterizing them. Throughout my career, I have had a record of successful and productive research projects in the field of signal transduction that are highly relevant to cancer. On an administrative level, I was founder and first Chair of the University of Chicago Committee on Cancer Biology (graduate program), Chair of the Ben May Department for Cancer Research for 13 years and Deputy Director of the University of Chicago Comprehensive Cancer Center (UCCCC) during this period. Associated with this role, I have been and remain a member of the Executive Committee of the UCCCC.

The current focus of my laboratory is to understand fundamental signaling mechanisms leading to the generation of tumor cells and their progression to metastatic disease, particularly in triple-negative breast cancer that lacks targeted therapies. We use systems level approaches including activity-based proteomics, RNAseq, ChIPseq, and mass spectrometry as well as computational, molecular, biophysical, cellular and mouse model-based methodologies to identify and characterize key regulators of tumor growth and metastasis. As an additional tool, we have utilized a specific physiological suppressor of metastasis, Raf Kinase Inhibitory Protein (RKIP or PEBP1), and a downstream target of RKIP in cells, BACH1, to identify both molecular and cellular mediators of metastasis.

Our recent studies have shown that regulators of metastasis control multiple processes within the tumor cell microenvironment including metabolism, redox state, extracellular matrix, and recruitment and programming of tumor-associated macrophages. These factors also direct extracellular vesicles (exosomes) secreted by tumor cells to reprogram other cells in the body toward a pro-metastatic phenotype. Correlating omic-generated data from these studies with clinical data from cancer patients led to the identification of novel signaling modules that we used to build gene signatures that predict the metastatic potential of a tumor. More recently, our studies have led us to potential therapeutic treatments based on the concept of targeting key regulators of tumorigenesis, mimicking the action of metastasis suppressors such as RKIP or reprogramming signaling networks in cells to sensitize tumors to therapeutic agents.

Eves, E.M., Shapiro, P., Naik, K., Klein, U.R., and **Rosner, M.R**., Raf kinase inhibitory protein regulates aurora B kinase and the spindle checkpoint. *Molecular Cell*, **23**, 561-574. (2006)

Sun, M., Song, C-X., Huang, H., Frankenberger, C.A., Sankarasharma, D., Gomes, S., Chen, P., Chen, J., Chada, K., He, C., and **Rosner, M.R.**, An HMGA2/TET1/HOXA9 Signaling Pathway Regulates Breast Cancer Growth and Metastasis, *PNAS,* **110**(24)*:9920. (2013)* PMC3683728

Lee, J., Yun, J., Yeung, K., Bevilacqua, Balázsi, G., and **Rosner, M.R.**, BACH1 and RKIP participate in a Bistable Network that affects Progression to Metastasis in Breast Cancer, *PNAS,* 21;111(3):E364-73. doi: 10.1073/pnas. Epub 2014 Jan 6 *(2014)*

Frankenberger, C., Rabe, D., Bainer R., Sankarasharma D., Chada K., Krausz, T., Gilad Y., Becker L., and **Rosner, M.R**., Metastasis suppressors regulate the tumor microenvironment by blocking recruitment of pro-metastatic tumor-associated macrophages, Cancer Research, *75:*4063-73 (2015*)*. PMID: 26238785

Bainer R, Frankenberger C, Rabe D, An G, Gilad Y, **Rosner M.R.** Gene expression in local stroma reflects breast tumor state and predicts patient outcome. Scientific reports. **6:**39240 (2016).

Skinner, J.j., Wang, S., Lee, J. Ong, C., Sommese, R., Sivaramakrishnan, S., Koelmel, W., Hirschbeck, M., Schindelin, H., Kisker, C., Lorenz, K., Sosnick, T., and **Rosner M.R**. A conserved salt bridge competition triggered by phosphorylation regulates the protein interactome. *PNAS* , **114:** 13453 (2017).

B. Positions and Honors

Positions and Employment

1973-1975	Teaching Fellow (laboratory of Prof. H.-G. Khorana), MIT, Cambridge, MA
1978	Postdoctoral Associate (laboratory of Professor H.-G. Khorana), MIT Cambridge, MA
1978-1981	Postdoctoral Fellow of the American Cancer Society (laboratory of Professor Phillips H. Robbins), MIT, Cambridge, MA
1981	Instructor of Toxicology, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, MA
1982-1987	Assistant Professor of Toxicology, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, MA
1987	Associate Professor of Toxicology, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, MA
1987-1994	Associate Professor, Ben May Institute and the Department of Neurobiology, Pharmacology, and Physiology, University of Chicago, Chicago, IL
1994-2000	Founder and Chair, Committee on Cancer Biology, University of Chicago, Chicago, IL
1994-present	Professor, Ben May Department for Cancer Research, Department of Neurobiology, Pharmacology, and Physiology, Cmtes. on Cancer Biology, Cell Physiology, and Developmental Biology, and the Cancer Research Center, University of Chicago, Chicago, IL
2000- 7/2013	Co-Deputy Director, University of Chicago Cancer Research Center, Chicago, IL
2000- 9/2013	Chair, Ben May Department for Cancer Research, University of Chicago, Chicago, IL
2000-present	Charles B. Huggins Professor, Ben May Department for Cancer Research, University of Chicago, Chicago, IL
2007-present	Fellow, Institute for Genomics and Systems Biology, University of Chicago, Chicago, IL
2009-present	Member, Committee on Genetics, Genomics and Systems Biology, University of Chicago, Chicago IL

Other Experience and Professional Memberships

1986	International Life Sciences Institute Research Foundation Award
1993-1997	Member, Biochemistry and Endocrinology Reviw Committee, Member, American Cancer Society
1994-1997	Member, Editorial Board, Molecular Endocrinology
1994-2005	Member, Children's Memorial Institute for Education and Research Scientific Advisory Committee
1997-2001	Member, Biochemistry Study Section, NIH (Chair 2000-2001)
1997-present	Member, Editorial Board, Gene Therapy and Molecular Biology
1999-present	Member, Board of Trustees, IMSA
2001-2006	Member, Editorial Board, ASBMB, Journal Biological Chemistry
2007-2008	Reviewer, Austrian Science Foundation Hearing of the Doctoral Program "Molecular Mechanisms in Cell Signaling"
2007-2009	TCB Study Section, NIH (ad hoc)
2009-6/2013	Member, Tumor Cell Biology (TCB), Study Section, NIH

Honors and Awards

1972-1973	MIT Endowed Fellowship
1973-1975	Sloan Research Traineeship (Biophysics)
1975-1977	Inst. National Research Service Award
1978-1980	American Cancer Society Postdoctoral Fellowship
1986	International Life Sciences Institute Research Foundation Award
1991	Quantrell Award for Excellence in Undergraduate Teaching, (Cell Biology)
1999-present	Fellow, Institute of Medicine of Chicago
2001	Quantrell Award for Excellence in Undergraduate Teaching
2007-present	Member, Faculty of 1000 Medicine
2011	Gerald N Wogan Prize Lecture, Massachusetts Institute of Technology
2014	Fellow, American Association for the Advancement of Science (AAAS)
2015	Fellow, Institute for Molecular Engineering, University of Chicago

C. Contribution to Science

1. Our lab is among the founders of the field of signal transduction. We were among the earliest groups demonstrating the importance of kinase signaling cascades in the action of factors that promote cell growth. In particular, we showed that Protein Kinase C, through tumor promoters, is able to modulate the action of growth factors by regulating their receptor activity. These studies demonstrated the role of kinase networks in regulating the action of signal responders such as the epidermal growth factor receptor, and laid the foundation for understanding how cells respond to multiple environmental cues.

Friedman, B., Frackelton, A.R., Ross, A.H., Connors, J.M., Fujiki, H., Sugimura, T. and **Rosner, M.R.** Tumor promoters block tyrosine-specific phosphorylation of the epidermal growth factor receptor. *Proc. Natl. Acad. Sci.* USA **81**:3034-3038 (1984).

McCaffrey, P.G., Friedman, B. and **Rosner, M.R.** Diacylglycerol modulates binding and phosphorylation of the epidermal growth factor receptor. *J. Biol. Chem.* **259**:12502-12507 (1984).

Rosner, M.R., McCaffrey, P.G., Friedman, B. and Foulkes, J.G. "Modulation of Growth Factor Action by Tumor Promoters and C Kinase" in *Cancer Cells*, Vol. **3** (Growth Factors and Transformation), eds. Feramisco, J., Ozanne, B. and Stiles, C., Cold Spring Harbor Laboratory: Cold Spring Harbor, pp. 347-351 (1985).

2. We published one of the original papers characterizing MAP kinase (later called ERK). One of the major families of intracellular kinases that regulates cell growth as well as most other physiological processes is the MAP kinase family. Our work showed that a kinase that phosphorylates the epidermal growth factor (EGF) receptor that we purified and characterized was in fact MAP kinase (later termed ERK kinase after cloning). Our work showed that MAP/ERK kinase is activated by the EGF receptor and functions as a downstream mediator. This pathway is now one of the most conserved signaling pathways utilized by growing cells.

Takishima, K., Griswold-Prenner, I., Ingebritsen, T. and **Rosner, M.R**.: Epidermal growth factor (EGF) receptor T669 peptide kinase from 3T3-L1 cells is an EGF-stimulated "MAP" kinase. *Proc. Natl. Acad. Sci. USA*, **88**:2520-2524 (1991).

3. We identified and characterized novel members of the MAP kinase family: Although the members of the ERK family that are most widely known are ERK1 and ERK2, there are other family members that are evolutionarily conserved and also play key roles in transmitting signals within the cells. These include ERK5, which also is activated by an upstream kinase, MEK5. However, there are other family members that are constitutively activated and regulated by proteolytic degradation. Among these are ERK7 and ERK8, which regulate steroid receptor signaling and whose expression is tightly controlled. Because of their low expression and rapid turnover, these kinases were a major challenge to clone and characterize.

Abe M.K, Kuo, W.-L, Hershenson, M.B and **Rosner M.R.** Extracellular signal-regulated kinase 7 (ERK7), a novel ERK with a C-terminal domain that regulates its activity, its cellular localization, and cell growth. *Mol. Cell Biol*. **19**:1301-1312 (1999).

Abe, M.K., Kahle, K.T., Orth, K., Dixon, J.E. and **Rosner, M.R.** ERK7 is an Autoactivated Member of the MAP Kinase family. *J. Biol. Chem.*, **276** (24). 21272-21279. (2001)

Abe, M.K., Saelzler, M.P., Espinosa III, R., Kahle, K.T., Hershenson, M.B., LeBeau, M.M., and **Rosner, M.R**., ERK8, a New Member of the MAP Kinase Family. *J. Biol. Chem.,* **277** (19) 16733-43. (2002)

Kuo, W.-L, Duke, C., Abe, M., Kaplan, E., Gomes, S. and **Rosner, M.R.** ERK7 Expression and Kinase Activity is Regulated by the Ubiquitin-Proteosome Pathway, *J. Biol. Chem*., 279(22), 23073-81. (2004)

4. We characterized a novel regulator of MAP kinase on a both molecular and cellular level: Raf Kinase Inhibitory Protein (RKIP). Raf Kinase Inhibitory Protein (RKIP), also termed Phosphatidylethanolamine binding protein1 (PEBP1), is an important regulator of kinase signaling in cells. RKIP represents a new class of signaling modulators that maintain the balance or homeostasis of biological systems. We and others have shown that depletion or inactivation of RKIP, a metastasis suppressor, results in disruption of normal cellular stasis and can lead to chromosomal abnormalities and metastatic cancer. Our recent studies have utilized RKIP as a tool to elucidate novel pathways that regulate metastasis of triple negative breast cancer. We are the only group that has utilized cellular, molecular and biophysical approaches to characterize the novel molecular mechanism by which RKIP acts as a switch to regulates key signaling pathways (MAP kinase and Protein Kinase A). A major focus of my laboratory relates to understanding the precise mechanism by which RKIP responds to the cellular environment. Our goal is to reactivate or mimic RKIP anti-metastatic activity in order to enable us to regulate this process and control metastatic progression in cancer. See papers under personal statement as well as:

Dangi-Garimella, S., Yun, J., Newman, M., Hammond, S. M., Eves, E.M., Minn, A.J. and **Rosner, M.R**. Raf Kinase Inhibitory Protein suppresses a metastasis signaling cascade involving LIN28 and *let-7, EMBO J*. **28**(4), 347-58. (2009) PMCID: PMC2646152

Yun, J., Frankenberger, C.A., Kuo, W.-L., Boelens, M.C., Eves, E.M., Cheng, N., Liang, H., Li, W.-H., Ishwaran, H., Minn, A.J., and **Rosner, M.R**., Signaling Pathway for RKIP and Let-7 Regulates and Predicts Metastatic Breast Cancer*, EMBO J,* **30(**21):4500-14, (2011) PMC3230370. *Cell Cycle Features – Invited*.

Sun, M., Song, C-X., Huang, H., Frankenberger, C.A., Sankarasharma, D., Gomes, S., Chen, P., Chen, J., Chada, K., He, C., and **Rosner, M.R.**, An HMGA2/TET1/HOXA9 Signaling Pathway Regulates Breast Cancer Growth and Metastasis, *PNAS,* **110**(24)*:9920. (2013)* PMC3683728

Sun, M., Gomes, S., Chen, P., Frankenberger, C.A., Sankarasharma, D., Chung, C.H., Chada, K., and **Rosner, M.R.,** RKIP and HMGA2 regulate breast tumor survival and metastasis through Lysyl Oxidase and Syndecan-2, *Oncogene,* 2013 Aug 26. doi: 10.1038/onc.2013.328.

5. We have proposed novel perspectives on how cancer evolves. One of the major challenges to treatment of cancer is the evolutionary nature of the process that leads to tumor cell heterogeneity and eventual drug resistance. The mechanisms leading to such heterogeneity have largely been attributed to genetic and epigenetic processes. However, we have recently published studies that demonstrate a role for either nonheritable or heritable but nongenetic processes in establishing phenotypic heterogeneity that eventually enables cancer cells to adapt to stressful environments and survive drug treatment. In addition, we have demonstrated how metastasis suppressors in tumor cells can reprogram the microenvironment in ways that generate feedback networks that reinforce heterogeneity.

Frank, S.A., and **Rosner, M.R**., Nonheritable Cellular Variability Accelerates the Evolutionary Processes of Cancer. *PLoS Biology*, **10**(4):e1001296. Epub. (2012) PMCID: PMC3317895

Lee, J., Yun, J., Yeung, K., Bevilacqua, Balázsi, G., and **Rosner, M.R.**, BACH1 and RKIP participate in a Bistable Network that affects Progression to Metastasis in Breast Cancer, *PNAS,* 111(3):E364-73 (2014). PMCID: PMC4096871

Frankenberger, C., Rabe, D., Bainer R., Sankarasharma D., Chada K., Krausz, T., Gilad Y., Becker L., and **Rosner, M.R**., Metastasis suppressors regulate the tumor microenvironment by blocking recruitment of pro-metastatic tumor-associated macrophages, *Can. Res*., 75(19):4063-73 (2015). PMID: 26238785 [PubMed - in process]

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/marsha.rosner.1/bibliography/41162236/public/?sort=date&direction=ascending.

D. Research Support

Ongoing Research Support

1RO1CA184494-01A1 (Rosner) 3/19/15 – 2/29/20
NIH
Tumor-stromal interactions as targets of tumor metastasis suppressors
The major goals of this project are 1) Characterize CCL5-mediated crosstalk between TNBCs and TAMs. 2) Investigate the role of TAMs and Ccl5 in a TNBC mouse model. 3) Investigate the mechanism by which RKIP regulates CCL5 expression and its potential therapeutic application.

1RO1GM121735-01 (Rosner) 9/30/17 – 2/29/22
NIH
Regulation of RKIP Function
The overall goal of this project is to understand the mechanism by which Raf Kinase Inhibitory Protein (RKIP) utilizes phosphorylation to switch berween three functional states and regulates the cellular kinome. The major goal of this project is: 1) Characterize the phosphor-switch and the $RKIP^{GRK2}$ state. 2) Characterize the nature and function of the allosteric switch to a high energy state. 3) Test the effects of allosteric states defined by biophysical studies on RKIP function in cancer.

Completed Research Support

The University of Chicago (Rosner & Halpern) 5/24/13 – 9/31/14
Comprehensive Cancer Center
Program-Specific Pilot Project
Mapping Oxygen Levels in BACH1-Regulated Breast Tumors
The major goals of this project are to: 1) Image oxygen levels in TNBC tumors expressing BACH1 or BACH1-depleted. 2) Identify BACH1-regulated transcripts in TNBC xenograft tumors.

CBC (Rosner, Pan, Munshi) 1/1/14 – 12/31/15
Catalyst Award
Extra-Translational Function of Transfer RNA as Regulators of Cellular Processes
The goal of this collaborative project is to examine the interaction and function of transfer RNA bound to MEK.

9R01 GM087630 (Rosner) 1/10/09 – 08/31/15
NIH
Signaling Pathways in Neuronal Cells
The major goals of this project are to: 1) Determine the mechanism(s) by which RKIP functions as a checkpoint regulator of MAP kinase signaling; 2) Determine the mechanism by which RKIP mediates crosstalk between MAPK and G protein-coupled receptor(GPCR) signaling; and 3) Characterize the structure/function relationships underlying RKIP regulation of the Raf-1/MAPK and GPCR signaling cascades.