BIOGRAPHICAL SKETCH

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NAME: Mitchell, Beverly S.

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

POSITION TITLE: George E. Becker Professor of Medicine
Director, Stanford Cancer Institute

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
Smith College, Northampton, MA	A.B.	1965	Biochemistry
Harvard Medical School, Boston, MA	M.D.	1969	Medicine
University of Washington, Seattle, WA	Resident	1969-72	Internal Medicine
University of Zurich, Zurich, Switzerland	Fellow	1973-75	Metabolism
University of Michigan, Ann Arbor, MI	Fellow	1975-77	Hematology/Oncology

A. Personal Statement

I have had a career-long research interest in the role of purine metabolic pathways in the regulation of cell growth and differentiation, with particular emphasis on applications to the treatment of acute leukemias. More recently, we have focused on the role of specific pathogenic mutations, such as those in the C-terminus of nucleophosmin, in generating responses to agents that induce reactive oxygen species, as well as on the epigenetic events and signaling pathways that regulate ribosomal RNA synthesis in leukemic cells. I have also led a LLS SCOR focused on finding new treatments for MDS. With this background, I am delighted to service as an internal advisor for the NCI Leukemia Spore Application from Northwestern University.

B. Positions and Honors

Employment/Experience

1977-1991 Instructor to Professor, Internal Medicine, Division of Hematology/Oncology, University of Michigan
1987-1991 Professor, Department of Pharmacology, University of Michigan
1991- 2005 Wellcome Distinguished Professor of Cancer Research, Departments of Pharmacology and Medicine and Lineberger Cancer Center, University of North Carolina at Chapel Hill
1994-2003 Chief, Division of Hematology/Oncology, University of North Carolina at Chapel Hill
1994-2005 Associate Director for Translational Research, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill
2005- George E. Becker Professor of Medicine, Department of Medicine (Oncology), Stanford University
2005-2008 Deputy Director, Stanford Cancer Institute, Stanford University
2008- Director, Stanford Cancer Institute, Stanford University

Honors and Awards

1965 A.B. summa cum laude and Phi Beta Kappa; Sigma Xi
1979 Jerome W. Conn Award for Excellence in Research, University of Michigan

1982-1987 Scholar Award of the Leukemia Society of America
1983 H. Marvin Pollard Award for Outstanding Resident Teaching
1988 Stohlman Award, Leukemia Society of America
1989, 1991 American Society of Clinical Investigation, Association of American Physicians
1993-1995 Scientific Advisory Board, National Cancer Institute, Division of Cancer Treatment
1998-2003 Board of Scientific Counselors, National Cancer Institute
2000-2001 Vice President, President, American Society of Hematology
2001 National Academy of Sciences, Institute of Medicine
2003-2006 Vice Chair, Medical and Scientific Affairs, Leukemia and Lymphoma Society of America
2005 Co-Chair, Burroughs Wellcome Fund Translational Award Committee
2006 Smith College Medal - Distinguished Alumna
2011 Phyllis Bodel Lecturer – Yale University
2011 Albion Walter Hewlett Award, Stanford University
2012 American Society of Hematology Mentor Award
2015 Fellow of the American Association for the Advancement of Science

C. Contribution to Science

1. Based on the earlier demonstration of the relationships between deficiency of the enzymes adenosine deaminase and purine nucleoside phosphorylase and immunodeficiency diseases by Giblett et al., we showed that the metabolites 2'-deoxyadenosine and 2'-deoxguanosine were selectively toxic to T lymphoblasts (PNAS, 1978), that toxicity resulted from selective metabolism to the corresponding nucleoside triphosphates via nucleoside kinases (J. Clin. Invest.1984), and that inhibition of these enzymes led to the lysis of T lymphoblasts in vitro and in vivo (Science, 1981, Blood, 1983). Based on this work, Pentostatin, an inhibitor of adenosine deaminase, and guanosine arabinoside (AraG), an analog of 2'-deoxyguanosine, were developed as therapeutics for lymphoproliferative diseases.
    a. Mitchell BS, Mejias E, Daddona PE, and Kelley WN. Purinogenic immunodeficiency diseases: selective toxicity of deoxyribonucleosides for T-cells. Proc Natl Acad Sci (USA) 1978; Oct;75(10):5011-5014. PMID: 311004
    b. Kazmers IS, Mitchell BS, Daddona PE, Wotring LL, Townsend LB, and Kelley WN. Inhibition of purine nucleoside phosphorylase by 8-aminoguanosine: selective toxicity for T lymphoblasts. Science 1981 Dec 4; 214(4525):1137-1139. PMID: 6795718
    c. Mitchell BS, Edwards NL, and Koller CA. Deoxyribonucleoside triphosphate accumulation by leukemic cells. Blood 1983 Aug;62(2):419-424. PMID: 6603241
    d. Sidi Y, and Mitchell BS. 2'-deoxyguanosine toxicity for B and mature T lymphoid cell lines is mediated by guanine ribonucleotide accumulation. J Clin Invest 1984 Nov;74(5):1640-1648. PMID: 6334099

2. We demonstrated that the enzyme 2'-deoxycytidine kinase is responsible for the phosphorylation and efficacy of 2'-deoxycytidine analogs such as AraC, an important drug for the treatment of acute myeloid leukemias (AML). We cloned and characterized the gene encoding the enzyme (PNAS, 1993, JCI, 1995), and showed that its overexpression enhanced the cytotoxicity of nucleoside analogs (Cancer Res, 1996), while resistance to AraC is mediated by mutations within the active site of the enzyme (Cancer Res, 1992). This work led to an enhanced understanding of the pivotal role of this enzyme and, in other work, of the corresponding nucleotidases in the efficacy of induction therapy in AML.
    a. Owens JK, Shewach DS, Ullman B, Mitchell BS. Resistance to 1-beta-D-arabinofuranosylcytosine in human T-lymphoblasts mediated by mutations within the deoxycytidine kinase gene. Cancer Res 1992 May 1;52(9):2389-2393. PMID: 1568208
    b. Song JJ, Walker S, Chen E, Johnson EE 2nd, Spychala J, Gribbin T and Mitchell, BS. Genomic structure and chromosomal localization of the human deoxycytidine kinase gene. Proc Natl Acad Sci USA, 1993 Jan 15;90(2):431-434. PMID: 8421671
    c. Chen EH, Johnson EE 2nd, Vetter SM, and Mitchell BS. Characterization of the deoxycytidine kinase promoter in human lymphoblast cell lines. J Clin Invest, 1995 Apr;95(4):1660-1668. PMID: 7706474

d. Hapke DM, Stegmann AP, and Mitchell BS. Retroviral transfer of deoxycytidine kinase into tumor cell lines enhances nucleoside toxicity. Cancer Res, 1996 MAY15;56(10):2343-2347. PMID: 8625309

3. We showed that depletion of guanine nucleotides by inhibitors of the enzyme inosine monophosphate dehydrogenase leads to inhibition of T lymphocyte activation (JCI, 1991). We subsequently cloned and characterized the IMPDH type II gene (JBC, 1997) and developed genetic models of IMPDH deficiency in mice that recapitulated deficiencies in T lymphocyte function (MCB, 2003). We have recently demonstrated that GTP depletion through IMPDH inhibition prevents ribosomal RNA synthesis during T lymphocyte activation by preventing RNA Polymerase I from binding to the rDNA promoter (Blood, 2015). This body of work laid the early foundation for the development of IMPDH inhibitors such as Cellcept as immunosuppressive agents and has subsequently delineated their mechanism of action.
    a. Turka LA, Dayton J, Sinclare G, Thompson CB, and Mitchell BS. Guanine ribonucleotide depletion inhibits T cell activation. Mechanism of action of the immunosuppressive drug mizoribine. J Clin Invest 1991 Mar;87(3):940-948. PMID:
    b. Zimmerman AG, Wright KL, Ting JP, Mitchell BS. Regulation of inosine-5'-monophsophate dehydrogenase type II gene expression in human T cells. Role for a novel 5' palindromic octamer sequence. J Biol Chem 1997 Sep 5;272(36):22913-22923. PMID:
    c. Gu JJ, Tolin AK, Jain J, Huang H, Santiago L, Mitchell BS. Targeted disruption of inosine-5'-monophosphate dehydrogenase type I gene in mice. Mol Cell Biol, 2003 Sep;23(18):6702-6712. PMID: 12944494
    d. Nguyen, LX, Nguyen LX, Lee Y, Urbani L, Utz PJ, Hamburger AW, Sunwoo JB, Mitchell BS. Regulation of ribosomal RNA synthesis in T Cells: requirement for GTP and Ebp1, Blood, 2015. PMID: 25691158.

4. Recent studies have focused on the role of nucleolar proteins and their relationship to ribosomal RNA (rRNA) synthesis in acute leukemia and myelodysplastic syndrome. rRNA synthesis has recently emerged as a potentially selective therapeutic target for highly proliferative malignancies such as acute leukemia As a key intermediary in cellular proliferation, it is subject to complex regulation that is governed by both cell signaling and epigenetic pathways (Blood, 2012; J. Cell Physiol, 2015). We have demonstrated that Akt activation, which occurs commonly in human tumors, directly enhances rRNA synthesis by stabilizing the protein TIF-1A, an essential co-factor with RNA Pol I in the initiation of transcription, and by phosphorylating casein kinase IIα, which in turn phosphorylates and activates TIF-1A (PNAS, 2013). Furthermore, activated Akt binds to a newly described isoform of TIF-IA, TIF-90, which is expressed at higher levels in leukemic cells and which interacts directly with PolI to stimulate rRNA synthesis (Blood, 2014). These results demonstrate that activated Akt has direct effects on enhancing ribosomal biogenesis through rRNA that are completely independent of the mTOR pathway and provide a rationale for its direct therapeutic targeting.
    a. Aparna Raval, Kunju J. Sridhar, Shripa Patel, Brit B Turnbull, Peter L. Greenberg and Mitchell BS. Reduced ribosomal RNA expression and increased ribosomal promoter DNA methylation in CD34+ cells from patients with myelodysplastic syndrome. Blood. 2012: 24:4812-8. PMID: 23071274
    b. Nguyen, T. and Mitchell, BS. (2013) AKT activation enhances ribosomal RNA synthesis through casein kinase II and TIF-1A. Proc. Natl. Acad. Sci. (USA) 2013 Dec 17:110(51):20681-6. PMID: 24297901
    c. Nguyen, T, Huang, M, Chan, SM, Ngo, TD, Raval, A, Kim, KK, Majeti, R, and Mitchell, BS. Interaction of TIF-90 and Filamin A in the regulation of rRNA synthesis in leukemic cells. Blood, 124:579-89, 2014. PMID: 25014775
    d. Nguyen, LX, Raval, A, Garcia, JS, Mitchell, BS. Regulation of ribosomal gene expression in cancer. J. Cell Physiol., 2015. PMID 24850755
    e. Nguyen LX, Zhu L, Lee Y, Ta L, Mitchell BS. Expression and Role of the ErbB3 Binding Protein 1 in Acute Myelogenous Leukemic Cells. Clin Cancer Res. 2016 Jan 26. pii: clincanres.2282.2015

5. The nucleolar protein nucleophosmin I is mutated at the C-terminus in approximately 30% of AML patients. The mutation results in the translocation of the protein to the cytoplasm of leukemic cells, but the precise role and consequences of the re-localization is not known. We demonstrated that a specific cysteine residue that results from the mutation is sufficient to account for the cytoplasmic localization and that expression of the mutated protein containing this cysteine sensitizes cells to pro-oxidant drugs such as arsenic trioxide (Leukemia, 2013). Increased levels of reactive oxygen species resulting from oncoprotein expression (Myc and others) or from pro-oxidant drugs account for the aggregation of another nucleolar shuttle protein, nucleostemin, and its retention in the nucleolus (JBC, 2011). We have also recently shown that the sensitivity of leukemic cells bearing NPM1 and other mutations to ROS-inducing drugs results from the process of autophagy, which markedly blunts antioxidant responses by down-regulating the Nrf2- antioxidant pathway (submitted). These studies suggest approaches to define subpopulations of AML that will have enhanced responses to pro-oxidant drugs.
    a. Huang M, Whang P, Chodaparambil JV, Pollyea DA, Kusler B, Xu L, Felsher DW, Mitchell BS. Reactive oxygen species regulate nucleostemin oligomerization and protein degradation. J. Biol. Chem. 286:11035-46, 2011 Apr 1;286(13). PMID: 21242306
    b. Huang M, Thomas D, Li MX, Feng W, Chan SM, Majeti R, Mitchell BS. (2013) Role of cysteine 288 in nucleophosmin cytoplasmic mutations: sensitization to toxicity induced by arsenic trioxide and bortezomib. Leukemia. 27(10):1970-80. PMID: 23877794
    c. Garcia JS, Huang M, Medeiros BC, Mitchell BS. Selective Toxicity of Investigational Ixazomib for Human Leukemia Cells Expressing Mutant Cytoplasmic NPM1: Role of Reactive Oxygen Species. Clin Cancer Res. 2016 Dec 3 doi:10.1158/1078-0432. CCR-15-1440

Complete List of Published Work in MyBibliography:
https://med.stanford.edu/profiles/beverly-mitchell?tab=publications

D. Research Support

ACTIVE

2P30CA124435-09 (Mitchell) 06/04/07-05/31/21
National Cancer Institute
Stanford University Cancer Institute
The major goal of this project is to build on institutional strengths in both technology development and translational research to foster interdisciplinary collaborations directed at the detection, prevention and treatment of cancer patients. Research programs include Cancer Biology, Radiation Biology, Cancer Stem Cells, Cancer Imaging Research, Translational Oncology, Lymphoma and Leukemia, Immunotherapy of Cancer, and Population Sciences. Shared resources subsidized by this grant support the investigations in experimental and clinical research.

PENDING

CLIN1-09214
California Institute for Regenerative Medicine
Development of Sudemycin 6 in Patients with Myelodysplastic Syndrome
B. Mitchell, PI