

Title: Role of Mutations in Epigenetic Regulators in Pathogenesis of Myeloid Malignancies



Speaker

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Chairman

Yuko Kitagawa, MD, PhD

Professor, Department of Surgery, Graduate School of Medicine, Keio University, Japan

Ross L. Levine, MD

Education and Training

2002-2006 Dana Farber Cancer Institute/Partners Cancer Care, Boston, MA
Fellow, Hematology/Medical Oncology
1999-2002 Massachusetts General Hospital, Boston, MA.
Intern/Resident in Internal Medicine
1994-1999 Johns Hopkins University School of Medicine, Baltimore, MD.
Doctor of Medicine
1990-1994 Harvard College, Cambridge, MA.
A.B., Biology, *magna cum laude*

Research/Fellowships

2003-2007 Postdoctoral Research Fellow
Brigham and Women's Hospital/Harvard Medical School
D. Gary Gilliland, Ph.D. M.D., Professor of Medicine, Investigator, Howard Hughes Medical Institute
1997-1999 Howard Hughes Medical Institute Research Training Fellowship

Johns Hopkins University School of Medicine
 Lora Hedrick Ellenson, M.D., Associate Professor of Pathology, Gynecology and
 Obstetrics, and Oncology
 1991-1994 Undergraduate Research Assistant
 Brigham and Women's Hospital/Harvard Medical School
 Gary S. Richardson, M.D., Instructor in Medicine

Positions and Employment

2007-2011 Assistant Member, Human Oncology and Pathogenesis Program & Leukemia Service,
 Memorial Sloan Kettering Cancer Center, tenure-track
 2007-2011 Assistant Professor of Medicine, Weill Cornell Medical College
 2011- Associate Member, Human Oncology and Pathogenesis Program & Leukemia Service,
 Memorial Sloan Kettering Cancer Center, tenure-track
 2011- Associate Professor of Medicine, Weill Cornell Medical College

Honors and Awards

2012 Laurence Baker Visiting Professor, University of Michigan
 2012 Leukemia and Lymphoma Society Scholar
 2011 Boyer Award for Clinical Research, Memorial Sloan Kettering Cancer Center 2011
 American Society of Clinical Investigation
 2011 Sir William Osler Young Investigator Award, Interurban Clinical Club
 2007 Geoffrey Beene Junior Chair
 2007 Howard Hughes Medical Institute Early Career Award
 2006 Doris Duke Charitable Foundation Clinical Scientist Development Award
 2006 American Society of Hematology Basic Research Fellow Award
 2006 American Society of Clinical Oncology Young Investigator Award
 1999 *Alpha Omega Alpha*, Johns Hopkins School of Medicine
 1998-1999 Howard Hughes Medical Institute Award for Completion of Medical Studies
 1994 Harvard University, *magna cum laude*
 1991-1994 Harvard University, John Harvard Scholarship

Licensure and Board Certification

2002 Certification, Internal Medicine (American Board of Internal Medicine)
 2005 Certification, Hematology (American Board of Internal Medicine)
 2005 Certification, Medical Oncology (American Board of Internal Medicine)
 2007 Medical License, State of New York, #245520

Professional Societies

2002- Member, American Society of Hematology
 2008- Member, American Association for Cancer Research

Publications (selected from 107 publications)

1. Doege CA, Inoue K, Yamashita T, Rhee DB, Travis S, Fujita R, Guarnieri P, Bhagat G, Vanti WB, Shih A, **Levine R.L.**, Nik S, Chen EI, Abelovich A. Early-stage epigenetic modification during somatic cell reprogramming by Parp1 and Tet2. *Nature*. 2012 Aug 30;488(7413):652-5. PMID: 22902501
2. Diab A, Zickl L, Abdel-Wahab O, Jhanwar S, Gulam MA, Panageas KS, Patel JP, Jurcic J, Maslak P, Paietta E, Mangan JK, Carroll M, Fernandez HF, Teruya-Feldstein J, Luger SM, Douer D, Litzow MR, Lazarus HM, Rowe JM, **Levine R.L.**, Tallman MS. Acute myeloid leukemia with translocation t(8;16) presents with features which mimic acute promyelocytic leukemia and is associated with poor prognosis. *Leuk Res*. 2013 Jan;37(1):32-6. PMID: 23102703.

3. Kämpjärvi K, Mäkinen N, Kilpivaara O, Arola J, Heinonen HR, Böhm J, Abdel-Wahab O, Lehtonen HJ, Pelttari LM, Mehine M, Schrewe H, Nevanlinna H, **Levine R.L.**, Hokland P, Böhling T, Mecklin JP, Bützow R, Aaltonen LA, Vahteristo P. Somatic MED12 mutations in uterine leiomyosarcoma and colorectal cancer. *Br J Cancer*. 2012 Nov 6;107(10):1761-5. PMID: 23132392.
4. Busque L, Patel JP, Figueroa ME, Vasanthakumar A, Provost S, Hamilou Z, Mollica L, Li J, Viale A, Heguy A, Hassimi M, Socci N, Bhatt PK, Gönen M, Mason CE, Melnick A, Godley LA, Brennan C, Abdel-Wahab O, and **Levine, R.L.**, Recurrent Somatic TET2 Mutations in Normal Elderly Individuals With Clonal Hematopoiesis. *Nature Genetics*. 2012 Nov; 44(11):1179-81. PMID: PMC3483435
5. Callahan MK, Rampal R, Harding JJ, Klimek VM, Chung YR, Merghoub T, Wolchok, JD, Solit DB, Rosen N, Abdel-Wahab O, **Levine R.L.**, Chapman PB. Progression of RAS-Mutant Leukemia during RAF Inhibitor Treatment. *N Engl J Med*. 2012 Dec 13;367(24):2316-21. PMID: 23134356.
6. Pollyea DA, Zehnder J, Coutre S, Gotlib J, Gallegos L, Abdel-Wahab O, Greenberg P, Zhang B, Liedtke M, Berube C, **Levine R.L.**, Mitchell BS, Medeiros BC. Sequential azacitidine plus lenalidomide combination plus elderly patients with untreated acute myeloid leukemia. *Haematologica*. 2012 Dec 14. [Epub ahead of print] PubMed PMID: 23242596
7. Baljevic M, Abdel-Wahab O, Rampal R, Maslak PG, Klimek VM, Rosenblat TL, Douer D, **Levine R.L.**, Tallman MS. Translocation t(11;17) in de novo Myelodysplastic Syndrome Not Associated with Acute Myeloid or Acute Promyelocytic Leukemia. *Acta Haematol*. 2013;129(1):48-54. PMID: 23147462.
8. Ward PS, Lu C, Cross JR, Abdel-Wahab O, **Levine R.L.**, Schwartz GK, Thompson CB. The Potential for Isocitrate Dehydrogenase Mutations to Produce 2-Hydroxyglutarate Depends on Allele Specificity and Subcellular Compartmentalization. 2013 Feb 8;288(6):3804-15. PMC3567635.
9. Shih AH, Chung SS, Dolezal EK, Zhang SJ, Abdel-Wahab OI, Park CY, Nimer SD, **Levine R.L.**, Klimek VM. Mutational analysis of therapy-related myelodysplastic syndromes and acute myelogenous leukemia. *Haematologica*. 2013 Jan 24. [Epub ahead of print] PubMed PMID: 23349305.
10. Gautier EL, Westertep M, Bhagwat N, Cremers S, Shih A, Abdel-Wahab O, Lütjohann D, Randolph GJ, **Levine R.L.**, Tall AR, Yvan-Charvet L. HDL and Glut1 inhibition reverse a hypermetabolic state in mouse models of myeloproliferative disorders. *J Exp Med*. 2013 Feb 11;210(2):339-53. PMID: 23319699
11. Lobry C, Ntziachristos P, Ndiaye-Lobry D, Oh P, Cimmino L, Zhu N, Araldi E, Hu W, Freund J, Abdel-Wahab O, Ibrahim S, Skokos D, Armstrong SA, **Levine R.L.**, Park CY, Aifantis I. Notch pathway activation targets AML-initiating cell homeostasis and differentiation. *J Exp Med*. 2013 Feb 11;210(2):301-19. PMID: 23359070
12. Meyer JA, Wang J, Hogan LE, Yang JJ, Dandekar S, Patel JP, Tang Z, Zumbo P, Li S, Zavadil J, **Levine R.L.**, Cardozo T, Hunger SP, Raetz EA, Evans WE, Morrison DJ, Mason CE, Carroll WL. Relapse-specific mutations in NT5C2 in childhood acute lymphoblastic leukemia. *Nat Genet*. 2013 Mar;45(3):290-4. PMID: 23377183
13. Deplus R, Delatte B, Schwinn MK, Defrance M, Méndez J, Murphy N, Dawson MA, Volkmar M, Putmans P, Calonne E, Shih AH, **Levine R.L.**, Bernard O, Mercher T, Solary E, Urh M, Daniels DL, Fuks F. TET2 and TET3 regulate GlcNAcylation and H3K4 methylation through OGT and SET1/COMPASS. *EMBO J*. 2013 Feb 12;32(5):645-55. PMC3590984
14. Sanda T, Tyner JW, Gutierrez A, Ngo VN, Glover J, Chang BH, Yost A, Ma W, Fleischman AG, Zhou W, Yang Y, Kleppe M, Ahn Y, Tarek J, Kelliher M, Neuberg D, **Levine R.L.**, Moriggi R, Muller M, Gray NS, Jamieson CH, Weng AP, Staudt LM, Druker BJ, Look AT. TYK2-STAT1-BCL2 Pathway Dependence in T-Cell Acute Lymphoblastic Leukemia. *Cancer Discov*. 2013 Mar 7. [Epub ahead of print]. PMID:23471820
15. Ramos P, Casu C, Gardenghi S, Breda L, Crielaard BJ, Guy E, Marongiu MF, Gupta R, **Levine R.L.**, Abdel-Wahab O, Ebert BL, Van Rooijen N, Ghaffari S, Grady RW, Giardina PJ, Rivella S. Macrophages support pathological erythropoiesis in polycythemia vera and β -thalassemia. *Nat Med*. 2013 Mar 17. doi: 10.1038/nm.3126. [Epub ahead of print]. PMID: 23502961

IAAO2013 Title of the Talk:**Role of Mutations in Epigenetic Regulators in Pathogenesis of Myeloid Malignancies****ABSTRACT:**

Clinical, cytogenetic, and gene-based studies have been used to inform biology and improve prognostication for patients with acute myeloid leukemia (AML), myelodysplasia (MDS), and myelodysplastic neoplasms (MPN). Most recently, a series of candidate gene and whole genome studies have identified recurrent somatic mutations in AML patients including TET2, ASXL1, DNMT3A, and EZH2 mutations. We and others have shown these mutations are of prognostic relevance, and can be used to improve risk stratification in AML. We identified genetic predictors of outcome that improved risk stratification in AML independent of age, WBC count, induction dose, and post-remission therapy and validated their significance in an independent cohort. Importantly, these mutational predictors involved complex genotypes, suggesting combinations of mutations mark prognostically relevant groups and segregate AML into distinct, biologically significant subsets. Integrating mutational data with dose-intensity revealed that high-dose daunorubicin improved survival in patients with DNMT3A/NPM1 mutations or MLL translocations relative to treatment with standard dose daunorubicin, but not in patients wild-type for these alterations. These data provide important clinical implications of genetic alterations in AML by delineating mutation combination genotypes that predict outcome in AML and improve AML risk stratification. Of biologic importance, the TET family of proteins have been shown to place a hydroxyl mark on methylated DNA and lead to DNA demethylation. We and others have found that TET2 mutations leads to loss of DNA hydroxymethylation and a hypermethylation phenotype in leukemia patients. In addition, in vitro and in vivo studies show that TET2 loss leads to impaired hematopoietic differentiation, increased stem cell self-renewal, and myeloid transformation in vivo. These data demonstrate that novel mutations coopt the epigenetic state of hematopoietic stem/progenitor cells in order to contribute to transformation and that these mutations have biologic and prognostic relevance.