

David A. Sweetser, MD, PhD



Sweetser Laboratory

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The Sweetser laboratory investigates how leukemia and other cancers develop with the goal of developing novel, safer, and more effective therapies. We have two major lines of research - the first investigating the function of a novel family of tumor suppressor genes and the second investigating the supportive role of the bone marrow niche in leukemia. Our lab has identified how the Groucho/TLE family of co-repressors function as potent tumor suppressors of acute myeloid leukemia, and has been defining their roles in normal development and cell function. Knock-out mice for Tle1 and Tle4 have identified critical roles for these proteins in hematopoiesis, bone, lung, and brain development, as well as a critical role in limiting inflammation. It is this ability to regulate inflammatory pathways that appears to underlie their tumor suppressor activity. We have defined critical inflammatory signaling pathways mediating cell proliferation and synergistic cross talk within the cancer niche that stimulated the proliferation and survival of leukemia. The laboratory is also involved in characterizing cancer predisposition genes and genes influencing therapy toxicity. As the MGH site director for the Undiagnosed Diseases Network and Chief of Medical Genetics and Metabolism at MGH, Dr. Sweetser is also leading a group of clinicians and researchers actively engaged in elucidating the underlying basis of a wide variety of human diseases.

Genetics of Acute Myeloid Leukemia

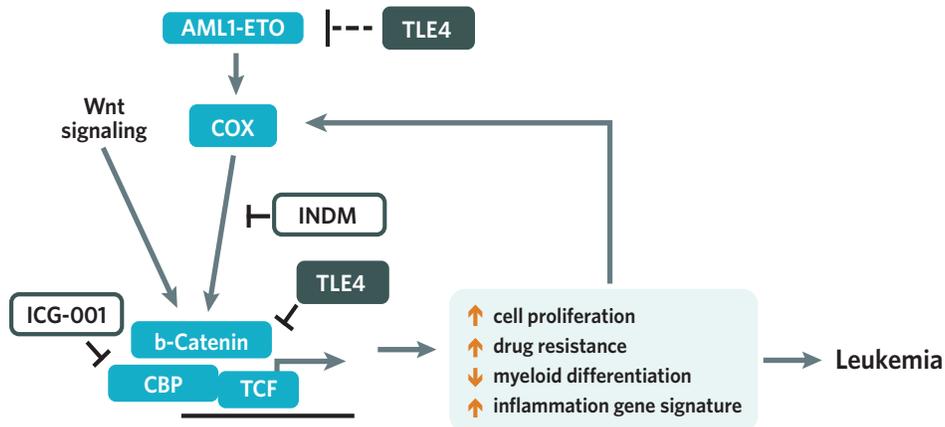
Our laboratory is working to elucidate cooperating networks underlying leukemogenesis and to develop novel targeted therapies for cancer. Current projects are detailed below.

Evaluation of the Role of the Groucho/TLE Family of Corepressors in Cancer and Development

Our laboratory has defined TLE1 and TLE4 as members of a novel family of tumor suppressor genes, the TLE/Groucho proteins, the inactivation of which appears to be a key cooperating event with other oncogenes in the development of a subset of acute myeloid leukemias and other cancers including melanoma.

The Groucho/TLE family of corepressor proteins can modulate many of the major pathways involved in development and

oncogenesis, including Wnt/ β -catenin, Notch, Myc, NF κ B, and TGF β . However, we are only beginning to understand their potential role in oncogenesis. These genes appear to behave as tumor suppressor genes in the pathogenesis of other myeloid malignancies and lymphomas. However, the role of this gene family in malignancies is complex. For example, in synovial cell sarcoma, TLE1 is over-expressed and behaves as an oncogene by pairing with the SS18-SSX fusion oncogene and ATF2 to silence other tumor suppressor genes. Current work in the lab seeks to clarify the role these proteins play in malignancy as well as in normal development. TLE1 and TLE4 are potent inhibitors of the AML1-ETO oncogene in the most common subtype of AML. The mechanism of this inhibition appears to involve both regulation of gene transcription and chromatin structure. In



Schematic diagram summarizing proposed TLE4 regulation of AML1-ETO/COX/Wnt axis. The TLEs have potent anti-inflammatory effects and inhibitory effects on oncogene pathways involving AML1-ETO and B-catenin, which also underlie their tumor suppressor activity.

large part this cooperative effect appears to involve regulation of Wnt signaling and inflammatory gene pathways. This work has led to the demonstration that specific anti-inflammatory agents can have potent anti-leukemic effects. We have also been studying the role of TLE1 in melanomas. In this context TLE1 appears to have a critical role in inhibiting the oncogenicity of oncogenic BRAF. The mechanism of this inhibition is being investigated.

Our laboratory is also working to understand the role these proteins play in normal development. To assist in this evaluation, we have generated conditional Tle1 and Tle4 knockout mice and are characterizing the role these proteins play in the development of a variety of tissues. Our studies to date indicate TLE1 is a potent repressor of inflammation via its ability to repress NF κ B, while TLE4 is a critical modulator of neuronal and B-cell and T-cell differentiation, and is required for hematopoietic stem cell maintenance, as well as bone development.

The Role of the Bone Marrow Niche in Nurturing Leukemia

The bone marrow niche is remodeled in the process of leukemia development to provide a supportive environment that contributes

to leukemic cell proliferation, survival, and resistance to chemotherapy. Our lab is working to define the critical cells and components of this niche with an eye towards designing targeted adjunctive therapies.

The Undiagnosed Diseases Network

The Harvard Medical School hospital consortium of MGH, Brigham and Women's Hospital and Children's Hospital together with 10 other clinical sites around the US comprise the NIH sponsored Undiagnosed Diseases Network. As Chief of Medical Genetics at MGH, and the MGH site director for the UDN, Dr. Sweetser is coordinating a team of expert clinicians and researchers, using comprehensive clinical phenotyping, whole exome/whole genome sequencing, paired with RNASeq and metabolomics profiling, and in collaboration with zebrafish and Drosophila model organism cores to identify the underlying basis of a variety of challenging human diseases. Over a dozen new genetic disorders have been characterized with these efforts. The Sweetser lab also participates in the functional characterization of identified candidate genes.

Selected Publications:

Xing S, Shao P, Li F, Zhao X, Seo W, Wheat JC, Ramasamy S, Wang J, Li X, Peng W, Yu S, Liu C, Taniuchi I, Sweetser DA, Xue HH. Tle corepressors are differentially partitioned to instruct CD8+ T cell lineage choice and identity. 2018 Aug 6; *J Exp Med.* 215(8):2211-2226.

Shin TH, Brynczka, Dayyani F, Rivera M, Sweetser DA. TLE4 Regulation of Wnt-mediated Inflammation Underlies its Role as a Tumor Suppressor in Myeloid Leukemia. *Leuk Res.* 2016, 48:46-56.

Ramasamy S, Saez B, Mukhopadhyay S, Ding D, Ahemd AM, Chen X, Pucci F, Yamin R, Pittet MJ, Kelleher CM, Scadden DT, Sweetser DA. Tle1 tumor suppressor negatively regulates inflammation in vivo and modulates NF- κ B inflammatory pathway. *PNAS* 2016, 113:1871-6.

Wheat JC, Krause DS, Shin TH, Chen X, Wang J, Ding D, Yamin R, Sweetser DA. The Corepressor Tle4 Is a Novel Regulator of Murine Hematopoiesis and Bone Development. 2014 *PLoS One* 9:e105557

Zhang Y, Wang J, Wheat J, Chen X, Jin S, Sadrzadeh H, Fathi AT, Peterson RT, Kung AL, Sweetser DA, Yeh JR. AML1-ETO mediates hematopoietic self-renewal and leukemogenesis through a COX/beta-catenin signaling pathway. *Blood*, 121:4906-4916, 2013.

Yeh JR, Munson K, Alagib K, Goldfarb A, Sweetser DA, Peterson RT. Discovering chemical modifiers of oncogene-regulated hematopoietic differentiation. *Nat Chem Biol.* 5:236-243, 2009.