

郑俊克·研究组

*Cell Metab*糖酵解水平精细调控白血病起始细胞的
命运决定

DOI: 10.3969/j.issn.1674-8115.2019.10.001

上海交通大学医学院细胞分化与凋亡教育部重点实验室郑俊克研究组通过建立新型白血病细胞代谢成像体系,揭示了白血病起始细胞 (leukemia-initiating cells, LICs) 以糖酵解为主要能量来源的独特代谢特性,以及代谢状态决定 LICs 在特定骨髓微环境中的定位、归巢和对称分裂等关键细胞命运的新规律。该研究成果以“Metabolic imaging reveals a unique preference of symmetric cell division and homing of leukemia-initiating cells in an endosteal niche”为题于 2019 年 4 月发表于代谢领域国际著名学术期刊 *Cell Metab* (封面文章)。博士研究生郝晓鑫、陈迟琪,博士后谷浩为论文的共同第一作者,郑俊克研究员、于卓副研究员、杨弋教授为论文的共同通信作者。上海交通大学医学院和华东理工大学是论文的共同通信单位。

郑俊克研究组长期从事造血干细胞 (hematopoietic stem cells, HSCs) 干性维持及其恶性转化为 LICs 规律方面的研究,致力于探讨能量代谢和骨髓微环境组分—免疫抑制性受体介导信号对正常造血和相关疾病演变的作用规律。由于干细胞频率或数量的稀缺性以及相关代谢检测手段的局限性,目前关于 LICs 的代谢特征及其与细胞命运决定的关系尚不清楚。近年来,随着代谢组学、代谢指示剂以及基于 Seahorse 能量测定仪的代谢分析等技术的不断发展,使得深入揭示有限细胞数量的干细胞代谢特征和调控规律成为可能。然而,现有的大多数代谢研究方法还只能间接地反映细胞代谢状态,很难实时、动态、在体监测细胞不同代谢通路的精细变化。针对这些问题,郑俊克研究员和杨弋教授深入合作,以临床常见、恶性程度高且缺乏有效治疗手段的 M5 型急性髓系白血病小鼠模型和原代患者标本为研究对象,使用遗传编码的高度灵敏的 NADH/NAD⁺ 代谢感受器 (SoNar) 标记和指示小鼠和患者白血病细胞代谢状态,构建实时在体代谢成像体系,并

阐明了白血病细胞中存在明显的代谢异质性, LICs 倾向富集于糖酵解水平更强 (SoNar-high) 的细胞群中。SoNar-high 细胞能高效归巢、定位于骨内膜微环境,并能够进一步重塑形成更为缺氧的微生态;这群细胞具有更高的对称分裂效率和增殖能力,从而促进受体小鼠白血病的快速发展。SoNar 感受器能在体内外动态、精确提示 LICs 中 NADH/NAD⁺ 细微变化及其与细胞命运的紧密联系。在机制上,丙酮酸脱氢酶激酶 (pyruvate dehydrogenase kinase 2, PDK2) 通过增强 LICs 糖酵解水平而维持其归巢和对称分裂能力,敲低 PDK2 则能有效抑制 LICs 增殖和白血病演变,提示 PDK2 可作为白血病治疗有效的潜在代谢新靶点。此外,该研究也提示代谢状态可能是 LICs 命运的内在决定因素而非伴随结果, LICs 本身的代谢状态也存在很强的异质性。

该研究为理解 LICs 代谢调控与其命运决定的关系提供了不同视角,为精确探讨不同类型干细胞代谢提供了新颖工具和有力借鉴,也为从代谢角度靶向白血病或其他肿瘤提供了潜在治疗策略。此外,郑俊克研究组近年来利用代谢感受器、代谢组学等新型代谢研究体系,不仅阐明了生理状态下 HSCs 糖代谢的主要特征和调控网络 (*Cell Stem Cell*, 2010; *Blood*, 2012、2014; *Cell Biosci*, 2015), 也拓展发现了 HSCs/LICs 氨基酸代谢方式和调控机制。这些研究为深入理解 HSCs 的功能维持基础提供了新的角度,为揭示血液良、恶性疾病演变规律和靶向治疗提供了新的思路。

该工作由上海交通大学医学院与华东理工大学的科研人员合作完成。此次研究是郑俊克研究组在 HSCs/LICs 代谢调控规律方面取得的系列成果上的又一重要进展。该工作得到了国家自然科学基金优秀青年科学基金项目、国家自然科学基金创新群体项目、国家自然科学基金面上项目、上海市科委自然科学基金等项目的资助。

Metabolic imaging reveals a unique preference of symmetric cell division and homing of leukemia-initiating cells in an endosteal niche

引自: *Cell Metab*, 2019, 29(4): 950-965. DOI: 10.1016/j.cmet.2018.11.013.

Abstract:

The metabolic properties of leukemia-initiating cells (LICs) in distinct bone marrow niches and their relationships to cell-fate determinations remain largely unknown. Using a metabolic imaging system with a highly responsive genetically encoded metabolic sensor, SoNar, we reveal that SoNar-high cells are more glycolytic, enriched for higher LIC frequency, and develop leukemia much faster than SoNar-low counterparts in an MLL-AF9-induced murine acute myeloid leukemia model. SoNar-high cells mainly home to and locate in the hypoxic endosteal niche and maintain their activities through efficient symmetric division. SoNar can indicate the dynamics of metabolic changes of LICs in the endosteal niche. SoNar-high human leukemia cells or primary samples have enhanced clonogenic capacities *in vitro* or leukemogenesis *in vivo*. PDK2 fine-tunes glycolysis, homing, and symmetric division of LICs. These findings provide a unique angle for the study of metabolisms in stem cells, and may lead to development of novel strategies for cancer treatment.

**学者介绍**

郑俊克 博士

研究员、博士生导师

ORCID ID: 0000-0002-7023-2400

ZHENG Jun-ke Ph.D

Professor, Doctoral Supervisor

ORCID ID: 0000-0002-7023-2400

郑俊克 (1977—), 上海交通大学医学院细胞分化与凋亡教育部重点实验室研究员。2007 年于上海交通大学获得发育生物学博士学位, 2007—2012 年于美国得克萨斯大学西南医学中心从事博士后研究工作。2012 年 6 月起受聘于上海交通大学医学院细胞分化和凋亡教育部重点实验室。

主要从事造血干细胞干性维持及其恶性转化为白血病干细胞的规律研究。近年来, 针对干细胞代谢和骨髓微环境成分—免疫抑制性受体介导的信号通路在干性维持及恶性转化中的作用开展系列工作, 取得多个重要成果。在 *Nature*、*Cell Metab*、*Cell Stem Cell*、*JCI*、*Blood*、*Leukemia*、*EMBO J*、*Cell Rep* 等著名期刊上发表论文 40 余篇, 他引 1 000 余次。相关工作被 *Cell Metab*、*Cell Stem Cell*、*Blood* 等作为封面文章发表或研究亮点进行介绍, 受到同行高度评价。先后获得国家杰出青年科学基金 (2018 年)、国家自然科学基金优秀青年科学基金 (2014 年) 等项目的支持。2015 年入选上海市曙光学者计划等。

ZHENG Jun-ke (1977—), professor of Key Laboratory of Cell Differentiation and Apoptosis of Chinese Ministry of Education, Shanghai Jiao Tong University School of Medicine. He got his Ph.D in Developmental Biology from Shanghai Jiao Tong University in 2007. He had the postdoc (Instructor) training at Alec Zhang's Lab (2007—2012), Department of Physiology, University of Texas Southwestern Medical Center at Dallas, USA. He was nominated as professor in Shanghai Jiao Tong University School of Medicine in 2012.

Dr. Zheng's lab mainly focuses on the studies of metabolic regulations of the stemness of hematopoietic stem cells and leukemia stem cells. He also works on the niche components-immune inhibitory receptor mediated signaling in the activities of hematopoietic stem cells and leukemia stem cells. He has made several important findings related to glucose/amino acid metabolisms and immune inhibitory receptor mediated pathways in hematopoiesis and leukemogenesis, which have been published in more than 40 papers, including *Nature*, *Cell Metab*, *Cell Stem Cell*, *JCI*, *Blood*, *Leukemia*, *EMBO J*, *Cell Rep*, et al. Several works were published as cover story or highlighted by *Cell Metab*, *Cell Stem Cell*, *Blood*, et al. He was supported by National Science Fund for Distinguished Young Scholars in 2018 and Outstanding Youth Science Foundation of National Natural Science Foundation of China in 2014. He was enrolled into "Shanghai Aurora Plan" in 2015.

造血干细胞代谢调控研究组

郑俊克研究组主要利用代谢感受器、代谢组学、骨髓微环境成像等技术，阐明造血干细胞中糖、氨基酸等代谢调控规律及其与细胞命运决定的相互关联；解析微环境成分—免疫抑制性受体介导的信号调控造血干细胞/白血病干细胞命运的作用和机制；探讨新型代谢靶点和/或免疫治疗靶点在造血干细胞的体外扩增和骨髓移植中的应用，以及血液性疾病治疗策略的发展。

ZHENG's lab mainly works on the metabolic regulations of glucose and amino acids in hematopoietic stem cells to unravel the potential connections between metabolic regulatory networks and their cell fate determinations by using unique metabolic techniques including metabolic sensors, metabolomics and *in vivo* imaging in bone marrow niches. They also focus on unraveling the roles of niche component-immune inhibitory receptor mediated signaling pathways in the cell commitments of hematopoietic stem cells/leukemia stem cells. Based on these novel metabolic targets and/or immune checkpoints, they try to develop new strategies for *ex vivo* expansion of hematopoietic stem cells and their potential application to clinic, and novel therapeutic ways in the eradication of hematological disorders.



5 篇代表性论文：

- 1 Hao X, Gu H, Chen C, et al. Metabolic imaging reveals a unique preference of symmetric cell division and homing of leukemia-initiating cells in an endosteal niche[J]. *Cell Metab*, 2019, 29(4): 950-965.
- 2 Deng M, Gui X, Kim J, et al. LILRB4 signaling in leukemia cells mediates T cell suppression and tumor infiltration[J]. *Nature*, 2018, 562(7728): 605-609.
- 3 Zhang Y, Xia F, Liu X, et al. JAM3 maintains leukemia-initiating cell self-renewal through LRP5/AKT/ β -catenin/CCND1 signaling[J]. *J Clin Invest*, 2018, 128(5): 1737-1751.
- 4 Xia F, Zhang Y, Xie L, et al. B7-H4 enhances the differentiation of murine leukemia-initiating cells *via* the PTEN/AKT/RCOR2/RUNX1 pathways[J]. *Leukemia*, 2017, 31(10): 2260-2264.
- 5 Gu H, Chen C, Hao X, et al. Sorting protein VPS33B regulates exosomal autocrine signaling to mediate hematopoiesis and leukemogenesis[J]. *J Clin Invest*, 2016, 126(12): 4537-4553.