To press departments
TUM, MRI, MÜK, UBC, BCCA, KMS-Stiftung, CP, and TRANSAID:
Under embargo until Wednesday April 28, 2021,
12 a.m. Central European Summer Time (CEST), 6 a.m. Eastern Standard Time (EST)

MondoA: Protector Of The Evil - And a Promising New Target in Metabolic Leukemia Therapy.

Researchers have recently discovered that a key player in the MYC-network plays a critical role in stress adaption in childhood leukemia. This molecule, termed MondoA because of its very large size, maintains aggressiveness and leukemic burden by modulating the metabolic stress response in the most common form of childhood leukemia. The metabolic requirements of cellular proliferation in cancer, first described by Otto Warburg (Nobel prize 1931), have recently gained renewed interest, are still not fully understood. MYC is a well-known oncogene with a wide range of target genes, which drives cell proliferation in many cancers. It operates within a protein network (interactome) that integrates multiple cellular signals to control many aspects of cell behavior. The discovery by researchers from TUM School of Medicine and the University of British Columbia elucidates the role of MondoA within that network. It has evolved for millions of years, dating back to the emergence of early animal species (Eisenman 2014). The work was pre-published today with the running title *MondoA Drives Malignancy in B-ALL* in Blood, Journal of the American Society of Hematology: https://ashpublications.org/blood/article/doi/10.1182/blood.2020007932

"Based on our studies, it appears that MondoA provides leukemia cells with cellular plasticity, allowing cells to switch rapidly from mitochondrial respiration to glycolysis, depending on the microenvironmental context. Moreover, our studies suggest that in the absence of MondoA, cells become highly glutamine dependent, warranting further research into combining MondoA inactivation with glutamine restriction as a therapeutic strategy."

Poul H Sorensen, MD, PhD, Johal Chair in Childhood Cancer Research, Distinguished Scientist, BC Cancer Research Centre, shared senior author of the study.

The knowledge of proliferation-induced metabolic stress and metabolic vulnerabilities in cancers have already found successful application in leukemia therapy. These metabolic therapies allow for less intensive use of classical chemotherapeutics such as mutagenic agents, reducing the potential risk of long-term adverse effects or the occurrence of therapy-related cancers. Importantly, the new findings clarify the role of MondoA in nutrient addiction of leukemia, indicating that interference with MondoA or its downstream targets by their candidate inhibitors could render those cells inept to adaption and hence be a novel therapeutic target for B-precursor ALL. Given the toxicities of conventional therapies and the widespread failure of more recent molecular therapies in most entities of childhood cancer, new targeted therapeutic options are an urgent medical need.

"I am absolutely happy now, that we may have a new therapeutic option for kids with ALL, that hopefully avoids some of the grave long-term toxicities of current genotoxic therapies. It was definitely worth all the hard work of six years."

Alexandra Sipol, first author, now scientist at Munich Leukemia Laboratory (MLL)

"We managed to identify a new risk factor, MondoA, in a patient cohort, went back to the lab to understand the underlying mechanism and now I hope we return back to the bedside using these insights to improve patient care."

Erik Hameister, shared first author, now clinical scientist and hematologist in training at the University Hospital Zurich

Rapidly proliferating cells, such as malignant cells, must adapt to proliferation-induced metabolic stress, and require anti-metabolic stress responses to maintain homeostasis and survival. In the MYC-interactome, MondoA competes with MYC for partners that are required for MYC functions, differentially mediating proliferation, differentiation and metabolism. Hence, both proliferation and adaptation to metabolic stress are regulated within the MYC interactome. This research expanded the role of MondoA as a MYC opponent by revealing that 85% of MondoA target genes are shared with MYC. Restraining MYC may be required because its unleashed action would generate too much proliferation-induced cell stress, e.g. reactive oxygen species (ROS) whose damaging effects would tip the leukemic cell over the edge. MondoA appears to limit MYC driven proliferative stress, thus protecting the malignant cell from being killed by unbridled MYC effects.

"MondoA is a huge molecule with delicate functions. The finetuning effect of MondoA on metabolism is truly amazing: It limits glucose uptake, but also increases glucose metabolism to generate amino acids from intermediates of glycolysis. Thereby and by simultaneously interfering with pyruvate entry into the Krebs cycle, it favors the production of building blocks at the expense of energy generation. MondoA is teaching us that cancer is not just unlimited proliferation, but also requires meticulous fine tuning of metabolism. Thereby, MondoA illustrates Siddhartha Mukherjee 's dictum "Cancer - The Emperor of All Maladies".

Stefan Burdach, Professor of Pediatrics and Pediatric Hematology/Oncology at TUM School of Medicine, senior author of the study

Beyond immune cells, MondoA also plays an important role in many other cellular systems, e.g. in the pathogenesis of the metabolic syndrome. It makes you obese and keeps you from running fast. Interestingly, the protein can be targeted using a novel designer drug that the Burdach team evaluated in leukemic cells. Recently identified in cholesterol-biosynthesis associated pathways, MondoA is expressed in numerous cell types including muscle and pancreas and can be targeted using a novel designer drug, a low-molecular weight competitive inhibitor. It was provided to the authors of this study by Dr. Daniel Kelly, who is investigating muscle metabolic fitness at the Cardiovascular Institute, University of Pennsylvania. Supported by the successful pharmacological targeting of MondoA in leukemic cells, Munich investigators of the recently approved German Center of Child and Youth Health now postulate that this pathway is critical and may be targeted in other immune and metabolic diseases such as autoimmune disorders, or in supporting resilience by physical exercise. The functional plasticity of immune cells responsive to metabolic contextuality is an emerging field in medical research with tremendous translational relevance.

Christoph Klein, coordinator of the Munich application to the German Center of Child and Youth Health comments: „This discovery illustrates the importance of systemic networks

that can only be discovered when we work together across disciplines and institutions - this is the path to design the future of personalized medicine for children."

The work, performed at TUM Children's Cancer Research Center (Professor Stefan Burdach), involved a cooperation with Professor Poul H Sorensen, MD, PhD, Johal Chair in Childhood Cancer Research, University of British Columbia and Distinguished Scientist, British Columbia Cancer Research Centre, which was funded by the TUM August-Wilhelm Scheer Visiting Professor Program to Dr. Sorensen as a visiting scientist at the Burdach laboratory.

A.S. received grants from CURA PLACIDA, Children’s Cancer Research Foundation (CP102/120815) and TRANSAID Stiftung für Krebskranke Kinder (8810001358 GCP).

Visual Summary: MondoA Drives Malignancy in B-ALL: