Functional genomics and systems Immunology in mapping the metabolic basis of cancer immunity

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Abstract

The goals of our research program are to discover the mechanisms linking the metabolic state of immune cells (immunometabolism) with tissue homeostasis and function, and to use these insights for better treatments for cancer and other diseases. We are particularly interested in understanding metabolic drivers, nutrient signaling pathways and systems-level regulatory networks in basic T cell and dendritic cell biology and antitumor immunity. To gain an integrative view, we combine the traditional hypothesis-driven or 'reductionist' approach with systems biology principles, including in vivo CRISPR screening, systems proteomics and data-driven network algorithms, to identify new concepts and therapeutic targets for immunometabolism that cannot be surmised from simpler systems. In our recent study, via single-cell CRISPR screens, we have mapped the transcriptional networks and metabolic checkpoints underlying cell fate regulomes in tumor-specific $CD8^+$ T cells in vivo (Zhou et al., Nature 2023). In our unpublished studies, we have uncovered organelle signaling and metabolic processes, including the interplay between lysosomal and mitochondrial signaling, in shaping $CD8^+$ tissue-resident memory (T_{RM}) development. Furthermore, building upon the discovery of Regnase-1 as a potent negative regulator of T cell anti-tumor immunity from CRISPR screens, we are undertaking major efforts to develop Regnase-1 gene-edited CAR T cells for solid tumor immunotherapy. I will discuss our recent progress in target discovery and network reconstruction in T cells and how we translate these fundamental discoveries into next-generation cellular immunotherapy for cancer.

Biography

Dr. Hongbo Chi is Member and Robert G. Webster Endowed Chair in Immunology and co-directs Center of Excellence for Pediatric Immuno-Oncology at St. Jude Children's Research Hospital. Dr. Chi is an Elected Fellow of the American Association for the Advancement of Science (AAAS). Dr. Chi's laboratory has contributed seminal discoveries to the field of immunometabolism, by pioneering the concept of metabolic reprogramming of cell fate and establishing mTOR and metabolic checkpoints in immune function and disease. Their work has helped establish the concepts of T-cell metabolic quiescence and quiescence exit, nutrients as "Signal 4" to license T-cell activation, and metabolic and nutrient dependence of dendritic cell subsets. The Chi laboratory has also integrated systems immunology, especially in vivo high-throughput perturbation screening, with immunity and metabolism to reconstruct causal networks and discover novel actionable disease targets (e.g., targeting Regnase-1 is being translated for cancer therapies). Dr. Chi's pioneering discoveries in immunometabolism and systems immunology have broadened our knowledge of adaptive immunity and opened new possibilities for therapeutic interventions of cancer and immune-mediated diseases. His work is highly regarded and widely referenced, earning him the honor of a Highly Cited Researcher in immunology continuously (2020–present) by Institute for Scientific Information.