Novel immune evasion mechanisms involving mitochondria in the tumor microenvironment

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Abstract

In the tumor microenvironment (TME), cancer cells evade immune surveillance, particularly T cell-mediated attack, through various mechanisms. Metabolic reprogramming within the TME is critical for antitumor immune responses, with mitochondrial dysfunction in tumor-infiltrating lymphocytes (TILs) impairing antitumor immunity. However, the detailed mechanisms remain unclear. Here, we identified shared mitochondrial DNA (mtDNA) mutations in TILs coexisting with cancer cells in clinical specimens. We found that aberrant mitochondria with mtDNA mutations from cancer cells can transfer to TILs. T cells that acquired mtDNA mutations from cancer cells exhibited metabolic abnormalities, senescence, and defects in effector functions and memory formation, leading to impaired antitumor immunity. These T cells also showed a terminally differentiated exhaustion phenotype. Consequently, mtDNA mutations in tumor tissue are a poor prognostic factor for immune checkpoint inhibitors in patients with melanoma or non-small-cell lung cancer. These findings reveal a novel mechanism of cancer immune evasion via aberrant mitochondrial transfer and can contribute to the development of future cancer immunotherapies.

Biography

Yosuek Togashi earned his M.D. from Kyoto University School of Medicine in 2006 and initially worked as a clinician in the Department of Respiratory Medicine. After serving as an Assistant Professor at Kyoto University, he obtained his Ph.D. in Genome Biology in 2015. His early career was distinguished by a research fellowship at the Japan Society for the Promotion of Science. He subsequently began basic and translational research in cancer immunology as a postdoctoral fellow at the National Cancer Center (Nishikawa Lab) in 2016. Since 2021, he has been a Professor at Okayama University, focusing on translational research of the tumor microenvironment.