Research team discovers glucose control may improve the anti-tumor activity of gamma delta T cells in diabetes

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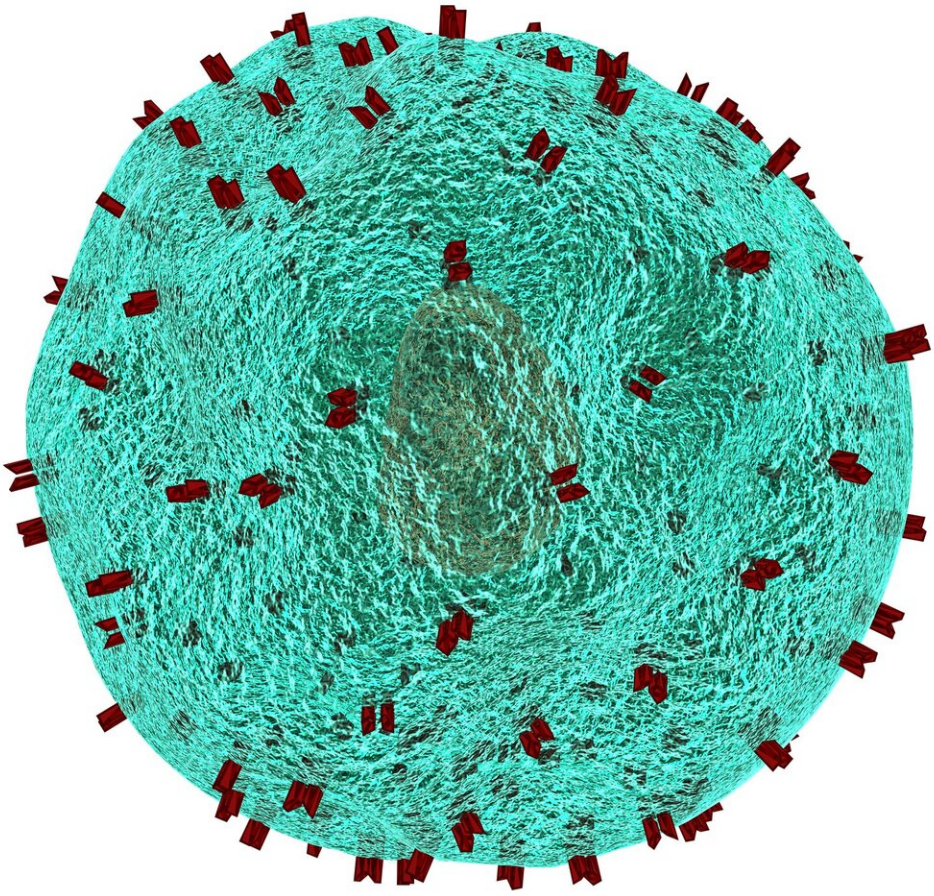

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A research team at LKS Faculty of Medicine, The University of Hong Kong (HKUMed) has discovered that high glucose impairs the anti-tumor activity of immune effector gamma delta T cells (γδ-T cells), which contributes to the increased cancer risk in diabetes, and that metabolic reprogramming by glucose control may improve the anti-tumor activity of γδ-T cells.

This study provides novel therapeutic targets for enhancing the anti-tumor immunity of γδ-T cells and further reducing the risk of tumor development and progression in diabetes. The discovery has been published in the journal *Cellular & Molecular Immunology*.

As the ninth major cause of death worldwide, diabetes and its related comorbidities greatly burden the global economy and health care systems. Approximately 10% of adults worldwide have diabetes mellitus, and more than 90% have type 2 diabetes mellitus (T2DM). Diabetes is associated with increased incidence and mortality for many types of cancers, including pancreatic, liver, breast, colorectal, and endometrial cancer. Since elevated blood glucose can stimulate cancer cell proliferation and progression, hyperglycemia may contribute to the high risk of developing cancers in diabetes.

In addition, the high cancer risk is also thought to be associated with abnormal immunity because glucose metabolism is critical for the proliferation, differentiation, and function of immune cells and shaping the immune response. While γδ-T cells play an essential role in tumor immunosurveillance, the impact of hyperglycemia on

immunosurveillance and cancer risk in diabetes is not well understood.

Recently, it has been shown that the phosphoantigen pamidronate-activated human γδ-T cells and their exosomes could efficiently kill tumor cells by secreting cytotoxic effectors and control tumor growth. These characteristics of γδ-T cells make them promising candidates for cancer immunotherapy. However, whether and how glucose metabolism affects the anti-tumor effects of γδ-T cells remains unknown.

The research team found that high glucose induced a high level of lactate production and secretion in γδ-T cells, which in turn prevented the trafficking of the cytolytic machinery to the γδ-T-cell-tumor synapse and impaired the anti-tumor activity of γδ-T cells.

Professor Tu Wenwei of the Department of Pediatrics and Adolescent Medicine, School for Clinical Medicine, HKUMed, who led the research, noted, "Our study demonstrated for the first time that diabetes have both quantitative and qualitative defects in γδ-T cells in terms of number and cytotoxicity against tumor cells. Thus, defects in γδ-T cells may contribute to the high cancer risk in diabetes. We further elucidate a fundamental mechanism associated with γδ-T-cell defects in diabetes. Strikingly, we found that metabolic reprogramming by glucose control or metformin treatment can reverse metabolic abnormalities and restore the anti-tumor activity of γδ-T cells induced by high glucose.

"The results highlight glucose metabolic pathways as targets to reverse immune defects in diabetes and suggest that metabolic reprogramming by glucose control or metformin treatment may improve the anti-tumor activity of γδ-T cells to prevent the development of cancer in diabetes."

The findings of the study have significant implications for controlling and preventing the development of cancer in diabetes. This study elucidates for the first time that dysregulated glucose metabolism

induces the defective cytotoxicity of γδ-T cells against tumor cells in diabetes. Additionally, metabolic reprogramming by glucose control or metformin treatment can restore the anti-tumor activity of γδ-T cells, which may provide novel therapeutic targets for enhancing the anti-tumor immunity of γδ-T cells and further reducing the risk of tumor development and progression in diabetes.

More information: Xiaofeng Mu et al, Glucose metabolism controls human γδ T-cell-mediated tumor immunosurveillance in diabetes, *Cellular & Molecular Immunology* (2022). DOI: 10.1038/s41423-022-00894-x

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