PGM3 insufficiency: a glycosylation disorder causing a notable T cell defect

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Background: Hypomorphic mutations in the gene *Phosphoacetylglucosamine mutase 3* (*PGM3*) cause a glycosylation disorder leading to immunodeficiency. This disorder is often associated with recurrent infections and atopy. The exact etiology remains unclear.
Objective: This study aims to characterize the phenotypes and immunological features associated with PGM3 insufficiency and to investigate potential disease mechanisms.
Methods: A systematic review of 44 published cases with PGM3 variants was performed, followed by T-cell phenotyping of two patients with PGM3 variants. A genotype-phenotypic severity study was conducted by comparing the residual PGM3 expression of 12 reconstituted variants in human B cells. A PGM3 inhibitor was then used to assess its effect on CD4+ T cell proliferation and differentiation.
Results: Patients identified with PGM3 variants frequently presented with recurrent infections and atopy, accompanied by reduced naïve CD4+ T cell counts. A genotype-phenotype study showed that low levels of residual PGM3 expression correlates with disease severity. Notably, inhibition of PGM3 activity was observed to impair TCR-mediated CD4+ T cell proliferation and the synthesis of UDP-GlcNAc, complex N-glycans, O-GlcNAc, glycolytic stress, and mitochondrial respiration during proliferation in a dose-dependent manner. Partial loss of PGM3 activity was observed to preferentially enhance Th1 and Th2 differentiation while attenuating Th17 and Treg differentiation, consistent with clinical observations.
Conclusion: PGM3 emerges as a critical regulator of CD4+ T cell proliferation and differentiation. These findings provide new insights into the diverse clinical manifestations and therapeutic development of PGM3 insufficiency.