High glucose enhances cytotoxicity-mediated by cytotoxic T lymphocytes

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High glucose, also termed hyperglycemia, is a typical symptom of diabetes. Uncontrolled high glucose is implicated in the pathogenesis of diabetes-associated complications such as heart attack, diabetic nephropathy, nerve damage and higher risk for infection. Cytotoxic T lymphocytes (CTLs) play a central role in destruction of pathogen-infected or tumor cells via killing mechanisms such as perforin/granzymes, Fas/FasL pathway and pro-inflammatory cytokines. Growing evidence indicates that CTLs are the key factor in initiation and progression of diabetes. However, the impact of high glucose on effector functions of T cells still remains elusive. In this study, we used normal glucose (5.6 mM) and high glucose (25 mM) to mimic healthy and diabetic conditions, respectively. We found that high glucose induces enhanced cytotoxicity of cytotoxic T lymphocytes. To investigate the underlying mechanisms, we analyzed the expression of cytotoxic proteins, including perforin, granzymes, FasL and TNF-related apoptosis inducing ligand (TRAIL). Interestingly, we identify that among those cytotoxic proteins, only TRAIL is significantly up-regulated in CTLs by high glucose compared to normal glucose. Our results also show that CTLs cultivated in high glucose can substantially enhance the destruction of human beta-cells in an antigen-independent manner in comparison with their counterpart in low glucose. Our findings, therefore, suggest a novel mechansim of CTL-mediated destruction of beta cells, which might play an important role in progression of diabetes.