Human profilin 1 is a negative regulator of CTL mediated cell-killing and migration

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Actin dynamics are essential for proper cytotoxic T lymphocyte (CTL) functions e.g. migration, formation of the immunological synapse (IS) and killing through lytic granules (LGs). Profilin1 (PFN1) plays a major role in control of actin dynamics yet the functional role of PFN1 in CTL remained elusive. We identified PFN1 as the only PFN isoform expressed in primary human CTL. We identified PFN1 as a negative regulator of CTL-mediated target cell elimination and LG release. During CTL migration, PFN1 modulates cell average velocity, protrusion formation patterns and protrusion sustainability whilst cell migration persistence and emergence and retraction rates of protrusions are not significantly affected. Mimicking a tumor microenvironment *in vitro*, we show that PFN1 downregulation enhances invasion of CTL into a 3D matrix and that CTL do not show decreased viability in a hydrogen peroxide enriched microenvironment. CTL of pancreatic cancer patients showed a substantially decreased PFN1 expression compared to healthy individuals, emphasizing a potential relevance of PFN1 in cancer. In summary, we conclude that PFN1 is a negative regulator of CTL-mediated cytotoxicity with potential impact on tumor-related functionality of CTL.