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Editorial

Dying from within: granzyme B converts entosis to emperitosis

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The term granzyme was coined by the late Jorg Tschopp – in one of the most beautiful papers ever published – and Tschopp and Daniele Masson defined the characteristics and members of the family.[1] The family members, cytotoxic T cell (CTL)-specific proteases, neatly fitted existing paradigms of protease specificity, although the functions were (and still remain in some cases) obscure. Granzyme B (GzmB) was always the outlier – it did not conform to the Arg/Lys (trypsin-like) Tyr/Phe (chymotrypsin-like) or Ala/Val (elastase-like) specificity affiliated with all serine proteases known back in the 1980s. It was first predicted[2] and then experimentally demonstrated[3] to have an oddly stringent preponderance for cleaving after Asp residues, leaving many scientists scratching their heads. Was it a signaling protease, or was it a degrading protease?[4]

Fast forward to the discovery of the caspases and their exquisite specificity for cleaving proteins after Asp residues, and it was not long before the link between the CTL protease GzmB and the apoptotic pathway was proposed.[5,6] GzmB is also found in natural killer cells, but for convenience here I will associate this cell type with CTLs. Whereas the role of most of the other granzymes is still hotly debated,[7] genetic and biochemical data firmly establish GzmB as an initiator of apoptosis.

One of the specialties of CTLs is the ability to direct components of their killer granules to the synapse formed between target and killer cell, essentially providing an environment where granule contents are injected into the target cell. Thus it is usually considered that GzmB gains direct access to the contents of the target, initiating apoptosis in a manner analogous to apical apoptotic caspases. Clearly GzmB can have other actions if it leaks from the synapse, and may also be taken back up by CTLs, with unknown consequences.[8] A recent paper in our sister journal *Cell Death and Disease* puts a very interesting spin on such a re-uptake.

An interesting form of non-apoptotic cell death known as entosis results from engulfment of one cell by another, with the engulfed cell dying essentially via degradation within the vacuole/lysosome.[9] Non-phagocytic cells in clinical tumor samples frequently exhibit this death morphology. But what happens when cells engulf CTLs? Should the CTL kill the engulfing cell, or should the engulfer kill the CTL? The solution to this intriguing question has been revealed, and the key ingredient is GzmB.[10] Internalized killer cells undergo a caspase-dependent apoptotic cell-in-cell death, and the engulfing cell is spared. Importantly, GzmB suppresses the lysosome-mediated entosis process because it triggers a caspase-dependent apoptotic cell-in-cell death of internalized killer cells. Presumably, the vacuole restrains the transfer of GzmB to the engulfing cell, and the protease is re-uptaken by the CTL, initiating a true cell suicide. In contrast, CTLs from GzmB-deficient mice undergo canonical entotic cell-in-cell death similar to that of non-cytotoxic immune cells or tumor cells, firmly implicating GzmB. The process has been coined *emperitosis*, a contraction of emperipolesis (a histological description of one intact cell inside another) and apoptosis, and maybe should be considered as an addition to the 13 forms of cell death recognized by the Nomenclature Committee on Cell Death.[10]

This thought-provoking discovery raises the question of whether emperitosis occurs as a part of normal cell behavior, or whether it may be a survival mechanism evolved by tumor cells. If the latter, then finding a way to block the process would be a smart way to enhance tumor kill by CTLs.

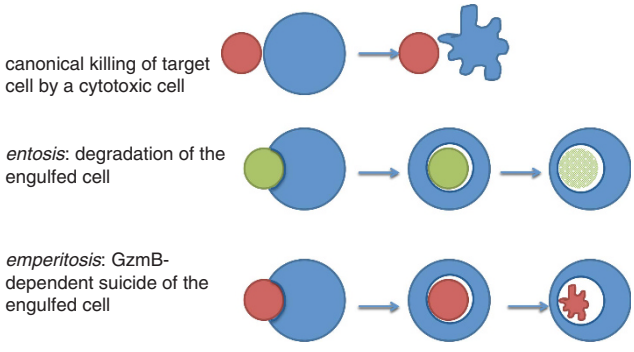

Figure 1 Different cellular fates of cytotoxic cells. In the well-described canonical process, cytotoxic cells kill targets, usually through GzmB-mediated induction of apoptosis. Alternatively, cells can be engulfed and die within a vacuole that has characteristics of a secondary lysosome, a process called *entosis*. When the engulfed cell is a cytotoxic cell, the GzmB-driven apoptotic process is turned back onto the cytotoxic cell, presumably because the vacuole restricts GzmB from attacking the engulfing cell. This recently discovered process, *emperitosis*, may be a key oncodevelopmental mechanism if it allows tumor cells to survive attack by cytotoxic cells

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Conflict of Interest

The authors declare no conflict of interest.

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