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MICROENVIRONMENT

Source influences function

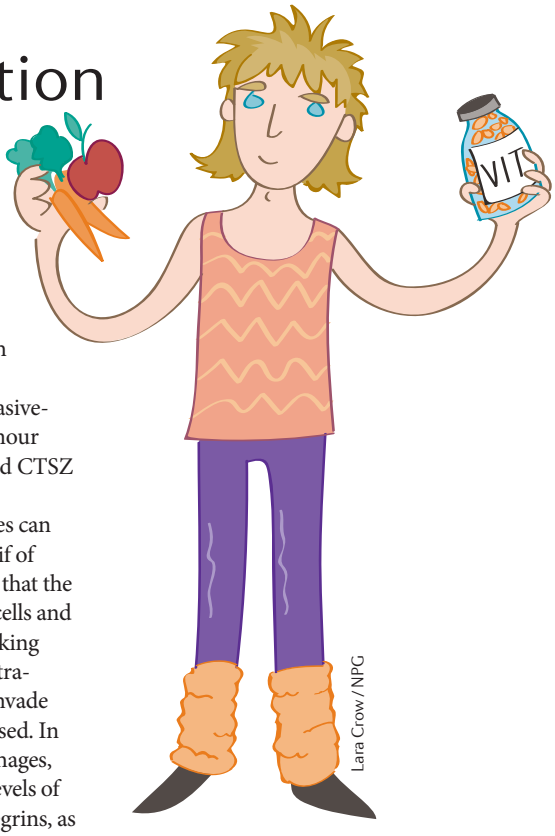
Cathepsin Z (CTSZ) is unique among cathepsins as it not only has protease activity but also contains an Arg–Gly–Asp (RGD) motif that allows it to interact with integrins. Akkari *et al.* found that several tumour-promoting roles of CTSZ in pancreatic neuroendocrine tumours (PanNETs) depend on the RGD–integrin interaction and that CTSZ derived from tumour cells has different functions from CTSZ derived from tumour-associated macrophages (TAMs).

The authors first showed that CTSZ was expressed in both tumour cells and TAMs of PanNETs derived from the RIP1-Tag2 mouse model and human PanNET lesions. RIP1-Tag2 mice crossed with *Ctsz*$^{-/-}$ mice had fewer premalignant lesions and a reduced overall tumour burden, and these tumour cells were defective in many tumorigenic processes, including proliferation and invasion.

Most bone marrow (BM) cells differentiate into macrophages in RIP1-Tag2 PanNETs. Therefore, to determine the contributions of TAM-derived and tumour cell-derived CTSZ, the authors conducted bone marrow transplantations (BMTs) of wild-type or *Ctsz*$^{-/-}$ BM into RIP1-Tag2 mice or RIP1-Tag2 mice that lacked *Ctsz*. No differences were observed in tumour volume in RIP1-Tag2 mice transplanted with wild-type or *Ctsz*$^{-/-}$ BM, and wild-type BMT could not rescue the reduced tumour growth in RIP1-Tag2 mice that lacked *Ctsz*; this indicates that tumour growth is most probably driven by tumour cell-derived CTSZ. However, *Ctsz*$^{-/-}$ BMT in RIP1-Tag2 mice reduced the number of invasive lesions, and wild-type BMT in RIP1-Tag2 mice that lacked *Ctsz* increased tumour invasiveness, indicating that TAM-derived CTSZ can promote tumour invasion. Re-expression of CTSZ in *Ctsz*$^{-/-}$ tumour cells also increased tumour growth relative to *Ctsz*$^{-/-}$ tumours; however it also increased invasiveness, indicating that both tumour cell-derived and TAM-derived CTSZ promote this property.

Adhesion of other cell types can be mediated by the RGD motif of CTSZ, and the authors found that the ability of RIP1-Tag2 tumour cells and BM-derived macrophages lacking CTSZ to adhere to various extracellular matrix proteins and invade through them was compromised. In tumour cells, but not macrophages, loss of CTSZ led to reduced levels of signalling downstream of integrins, as evidenced by reduced focal adhesion kinase (FAK) and SRC phosphorylation. This signalling, as well as proliferation and invasion, could be rescued by expression of a catalytically inactive CTSZ mutant, but not by expression of CTSZ with a mutation in the RGD motif, indicating that these functions are primarily mediated by the RGD motif and not proteolysis.

Intriguingly, surface levels of CTSZ on PanNET tumour cells increased when these cells were exposed to conditioned media from wild-type, but not *Ctsz*$^{-/-}$, macrophages, but no change in internal CTSZ was observed. Furthermore, recombinant CTSZ and macrophage-conditioned media were able to increase tumour cell invasion *in vitro*, and this required integrins β1 and β3. This suggests that a major role of secreted TAM-derived CTSZ is to bind to tumour cells and promote interactions with integrins that in turn enhance invasion.



Lara Crow / NPG

These data provide evidence that tumour cell-intrinsic CTSZ can promote proliferation, whereas both tumour cell-intrinsic and TAM-secreted CTSZ can promote invasion, possibly because of differences in subcellular localization. Whether CTSZ has similar functions in other tumour types is an interesting future question.

Sarah Seton-Rogers

> “these functions are primarily mediated by the RGD motif”

ORIGINAL RESEARCH PAPER Akkari, L. *et al.* Distinct functions of macrophage-derived and cancer cell-derived cathepsin Z combine to promote tumor malignancy via interactions with the extracellular matrix. *Genes Dev.* **28**, 2134–2150 (2014)