Correspondence

A role for caspase-8 and TRAIL-R2/DR5 in ER-stress-induced apoptosis

Cell Death and Differentiation (2018) 25, 226; doi:10.1038/cdd.2017.155; published online 6 October 2017

Glab *et al.*¹ examined in a recent paper apoptosis induced by some drivers of endoplasmic reticulum (ER) stress. They conclude that in contrast to a previously published report,² DR5/TRAIL-R2 and caspase-8 are universally dispensable in ER-stress-induced apoptosis. We argue here that their own data and other published reports indicate that in many models, DR5 and/or caspase-8 are essential players in apoptosis mediated by the unfolded protein response (UPR), upon chronic ER stress.

The authors analyze the effects of knocking down caspase-8, DR5, Bim and Bid. The authors describe that Bim is not essential at least in one of their three models. In line with these results, we and other authors have shown that Bim is dispensable for apoptosis mediated by the UPR in some systems even though the protein is induced; in these cases, the apoptotic cell death can be attributed to Noxa or to Caspase-8 (see Table 1 in Iurlaro *et al.*³ and refs. 4–6). We find inconsistent that the title and abstract mention that caspase-8 and DR5 are dispensable in ER-stress-induced apoptosis, but not that Bim is not required in their system, in contrast to earlier findings.⁷

The authors' own data (ref. 1, Figure 3c) indicate that Bid is crucial in one of their models: HCT116. Moreover, although the authors report a drastic reduction of apoptosis with some treatments, they also show that over 20% of Bax, Bak-deficient cells undergo apoptosis (ref. 1, Figures 2e and f). We suggest that this apoptosis is

mediated by caspase-8 as described in Bax, Bak-deficient HCT116 and MEFs treated with UPR-inducing stimuli.^{4,6} Indeed, a certain role for caspase-8 is shown by the authors in Supplementary Figure 2,¹ but this is not mentioned in the title or abstract.

Regarding the role of DR5, authors do observe reduction of cell death in one knockout clone. Importantly, the authors seem focused to disprove one study, while ignoring numerous studies that have shown a role of DR5 and caspase-8 in apoptosis activated by different UPR-inducing stimuli such as thapsigargin or glucose deprivation^{3,8,9} (Table 1). Moreover, it is possible that in cells knocked out for DR5, it is DR4 or other death receptors (reviewed in Iurlaro *et al.*³) that may be participating in caspase-8 activation and Bid cleavage, as we have recently described in ATF4-mediated cell death.⁶

Altogether, these data indicate that DR5, caspase-8, Bim, Bid and Noxa are required for ER stress and UPR-mediated death in a cell type-dependent manner.

Conflict of Interest

The authors declare no conflict of interest.

Cristina Muñoz-Pinedo^{*1} and Abelardo López-Rivas^{*2}

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Table 1 Examples of reports showing a role for caspase-8 and/or DR5 in apoptosis mediated by components of the UPR or the integrated stress response

Mediator	Stimulus	Cell type	Reference
Caspase-8	Tunicamycin	HEK293, MCF7 <i>bax</i> ^{-/-} <i>bak</i> ^{-/-} BMK	Tomar <i>et al.</i> (2013), PMID 24021263
Caspase-8, FADD	Bortezomib/MG132 Bortezomib/MG132	HEK293, MDAMB231, MCF7 Atg5 ^{+/+} and Atg5 ^{-/-} MEFs, FADD ^{+/+} and FADD ^{-/-} MEFs, KG-1 HeLa, H460, MEFs	Ullman <i>et al.</i> (2011), PMID 21576355 Pan <i>et al.</i> (2001), PMID 21628531 Young <i>et al.</i> (2012), PMID 22362782
Caspase-8, RIPK1	Tunicamycin, thapsigargin	CASP9 ^{-/-} MEFs, <i>bax</i> / <i>Bak</i> ^{-/-} MEFs	Laussmann <i>et al.</i> (2011), PMID 21455219 Deegan <i>et al.</i> (2014), PMID 25470234
DR5	Thapsigargin	MEFs and HEK293T	Estornes <i>et al.</i> (2014), PMID 25476903
DR5, caspase-8	Thapsigargin, tunicamycin Thapsigargin CB-5083	HCT116, LNCaP, A2780S and DU145 MCF10A HCT116, SK-MES-1, KSM11, RPMI-8226 HCT116	Yamaguchi <i>et al.</i> , ⁸ PMID 15322075 Martín-Pérez <i>et al.</i> , ⁹ PMID 24453000 Lu <i>et al.</i> , ² PMID 24994655 Anderson <i>et al.</i> (2015), PMID 26555175
DR5, DR4	Glucose deprivation	HCT116, HCT116 Bax, Bak (–/–), HeLa HCT116,	Iurlaro <i>et al.</i> (2017), PMID 28242652
DR4/TRAIL-R1	Tunicamycin, thapsigargin Tunicamycin, thapsigargin	MDA-MB231, H1703 A549	Dufour <i>et al.</i> (2017), PMID 28039489 Li <i>et al.</i> (2015), PMID 25770212

¹Cell Death Regulation Group, Oncobell Program, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain and ²Cell Death Signalling Group, Andalusian Center for Molecular Biology and Regenerative Medicine – CABIMER, CSIC-Universidad de Sevilla-Universidad Pablo de Olavide, Seville, Spain

*Corresponding author: C Muñoz-Pinedo, IDIBELL – Hospital Duran i Reynals 3a planta, Gran Vía de l'Hospitalet, 199, 08908 Spain. Tel: +34 932 60 71 30; Fax: +34 932 60 74 26; E-mail: cmunoz@idibell.cat or A López-Rivas, CABIMER, Avda Américo Vespucio, 24, 41092 Seville, Spain. Tel: +34 954 46 79 97; Fax: +34 954 46 16 64; E-mail: abelardo.lopez@cabimer.es