

Role-shifting PKC ζ fosters its own proapoptotic destruction by complexing with Bcl10 protein at the nuclear envelope of human cervical carcinoma cells

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Many features of deadly human cervical cancers (HCCs) still require elucidation. Among HCC-derived cell lines, here we used the C4-I one since its quantitative gene expression pattern most closely mimics invasive HCCs, including protein kinase-C ζ (PKC ζ) overexpression. Via proteomic, bioinformatic, and biochemical approaches (see for technical details [1,2]) we identified 31 and 33 proteins coimmunoprecipitating with PKC ζ from nuclear membranes (NMs) of, respectively, untreated or VP-16-exposed C4-I cells. Such proteins belonged to eight functional groups, whose compositions and relative sizes changed with either context. Of the 56 proteins identified, only eight were shared between the two subproteomes, including Bcl10. Surprisingly, proteins known to associate with Bcl10, like Carma1/3 and Malt1 in so called CBM signalosomes were absent. Notably, in VP-16-treated C4-I cells, PKC ζ •Bcl10 complexes increasingly accrued at NMs, where PKC ζ phosphorylated Bcl10—as PKC ζ also did *in vitro* and in cell-free systems—both processes being thwarted by interfering RNA (iRNA) PKC ζ depletion. Caspase-3 was associated with PKC ζ •Bcl10 complexes and proteolyzed PKC ζ leading to its inactivation/destruction—both events were prevented by Bcl10 iRNA suppression. Thus, PKC ζ 's molecular interactions and functional roles changed strikingly according to the untreated or apoptogen-treated cells context, and by complexing with Bcl10, PKC ζ surprisingly favored its own demise, which suggests both proteins as HCCs therapeutic targets.

References

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