Editorial

A naturally generated decoy of the prostate apoptosis response-4 protein overcomes therapy resistance in tumors

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Comment on: Hebbar N, Burikhanov R, Shukla N, *et al.* A Naturally Generated Decoy of the Prostate Apoptosis Response-4 Protein Overcomes Therapy Resistance in Tumors. Cancer Res 2017;77:4039-50.

Received: 25 September 2017; Accepted: 7 October 2017; Published: 18 October 2017.

doi: 10.21037/amj.2017.10.03

View this article at: http://dx.doi.org/10.21037/amj.2017.10.03

Despite advances in targeted therapies, standard chemotherapy remains the main line of treatment for most cancer patients. However, intrinsic resistance as well as acquired resistance remains an important obstacle to cancer treatment and having an impact on reducing patient's survival. The identification of mechanisms of resistance and biomarkers that may overcome resistance to chemotherapeutic drugs is one of the main goals of cancer research. This editorial examines the recent work of Hebbar *et al.* (1), whose data bring out new information into the mechanisms of Par-4 action on the tumour cells chemosensitivity and their potential to overcome resistance to cancer therapy.

Experimental evidences suggest that the tumour suppressor gene *PAWR* [PKC apoptosis WT1 regulator, also called prostate apoptosis response-4 (PAR-4)] plays a central role in cell death process and can be considered as a candidate for selective cancer therapy (2-4). PAR-4 encodes a 342-amino acid protein containing two nuclear localization signals (NLS), a leucine zipper domain in the carboxy-terminal region and a selective for apoptosis induction in tumour cell (SAC) domain in the central part of the molecule (5,6). Par-4 protein is expressed in different tissues, and can be located in the cytoplasm, nucleus, or can be secreted (3).

An important feature of Par-4 is that its endogenous expression is not sufficient to cause cell death but is essential to increase the sensitivity of most cancer cells to a second apoptotic stimulus, including chemotherapeutic drugs such as the taxane docetaxel (6-10). Par-4 protein plays a role in both the intrinsic and extrinsic apoptotic pathways. Par-4 induces apoptosis for its ability to activate the Fas-FasL-FADD-caspase 8 signalling pathway, by inhibiting the NF-kB cell survival pathway, which requires the phosphorylation of PAR-4 at the T155 residue mediated by PKA, and also due to its ability to negatively regulate the expression of the anti-apoptotic Bcl-2 protein (11). Par-4 secretion occurs through the classical pathway of the endoplasmic reticulum (ER-Golgi), and is stimulated by factors that induce ER-Golgi stress. The GRP78 protein functions as a receptor for Par-4 and the Par-4/GRP78 interaction leads to the induction of apoptosis by ER-Golgi stress pathway and activation of the FADD/caspase-8/caspase-3 pathway (12). The intracellular role of Par-4 in different cell types and in response to anticancer drugs has been well documented by studies from different research groups, however so far the role of secreted Par-4 has been reported mainly by the Vivek Rangneker group, which first identified the differential expression of Par-4 in prostate cancer cells undergoing apoptosis by calcium (5).

Due to its selective ability to induce apoptosis in tumour cells, Par-4 has gained great interest. Par-4 is a substrate of caspases during apoptosis induced by different agents (13-15). Chaudhry *et al.* (13) demonstrated for the first time that caspase-3 cleaves Par-4 in the D131A residue during apoptosis induced by cisplatin, generating Par-4

fragments with approximately 19–25 KDa, that accumulate in the nucleus to enhance an apoptosis both in normal and cancer cells. The article by Hebbar *et al.* (1) describes the identification of a fragment of the amino terminal region of PAR-4, referred to as Par-4 amino-terminal fragment (PAF), resulting from the cleavage of Par-4 by caspase 3, which is secreted by cells sensitive to therapy and induces apoptosis in cancer cells therapy-resistant to different agents. To investigate whether treatment with the taxane paclitaxel in therapy-sensitive cancer cells could induce apoptosis in therapy-resistant cells, the authors evaluated the effects of paclitaxel treatment on co-culture of paclitaxel-sensitive (A459/RFP) and paclitaxel-resistant cancer cells (A459/GEF). They observed that in co-culture, treatment with paclitaxel leads to death by apoptosis both paclitaxel-sensitive and paclitaxel-resistant cancer cells. A similar result was observed *in vivo* in xenografts generated by the co-injection of paclitaxel sensitive and resistant A459 cells, indicating the occurrence of a paracrine effect of a soluble factor released by cells sensitive to paclitaxel treatment. Subsequently, using antibodies to several candidate proteins, known to be secreted and that could cause the observed paracrine effect, they observed that the antibody against Par-4 inhibited apoptosis in 70% of paclitaxel-resistant cancer cells treated with conditioned medium from sensitive cells treated with paclitaxel. Further, using different antibodies against Par-4, Hebbar *et al.* (1), identified a 15 kDa fragment (PAF) of Par-4 as the soluble factor, responsible for the paracrine effect of apoptosis induction on paclitaxel-resistant cancer cells.

Hebbar *et al.* (1) demonstrated that the paracrine effect of apoptosis induction by PAF is not restricted to the model of paclitaxel-resistant lung cancer cells but can be observed in cells of different types of cancer resistant to anti-cancer drugs. Most importantly, the authors also demonstrated that the effect of the PAF fragment is selective for cancer cells not affecting non-cancer cells, as observed for intra- and extracellular Par-4 (4). Further, the authors investigated the mechanism of apoptosis induced by PAF, showing that activation of the FADD/caspase 8/caspase 3 pathway is essential for PAF induced apoptosis, and that PAF-induced apoptosis is independent of the binding to GRP78, required for Par-4 secretion. Furthermore, the authors have identified that PAF contains the VASA sequence, previously identified as important for the binding of Fbxo45 to Par-4 leading to its ubiquitination and degradation (16). Interestingly, PAF competes for the binding of Fbxo45 with Par-4, preserving the integrity of Par-4 to act by inducing apoptosis.

In summary, the article by Hebbar *et al.* (1) brings to light a new facet of the action of the tumor suppressor gene PAR-4 on chemosensitivity to anti-cancer drugs, where a soluble fragment, released by Par-4 cleavage by caspase, has the ability to enter into cancer cells and bind to ubiquitin ligase Fbxo45, allowing Par-4 to induce apoptosis in cancer cells resistant to therapy. Although, the study by Hebbar *et al.* (1) brings important new information about the role of PAR-4 in cancer cell death to overcome resistance to therapy, new experimental and clinical studies conducted by different groups are needed to validate the biological significance and potential clinical applications of these findings.

Acknowledgements

Funding: The author gratefully acknowledge the support of Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urology, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.10.03). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2017.10.03
Cite this article as: Nagai MA. A naturally generated decoy of the prostate apoptosis response-4 protein overcomes therapy resistance in tumors. AME Med J 2017;2:156.

