



Ichim, G. and Tait, S. W.G. (2017) Cancer therapy-induced PAFR ligand expression: any role for caspase activity? *Nature Reviews Cancer*, 17(4), p. 253. (doi:[10.1038/nrc.2017.16](https://doi.org/10.1038/nrc.2017.16))

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/138574/>

Deposited on: 29 March 2017

Enlighten – Research publications by members of the University of Glasgow  
<http://eprints.gla.ac.uk>

# Cancer therapy-induced PAFR ligand expression: any role for caspase activity?

*Gabriel Ichim*

*Stephen W.G. Tait*

Our recent Opinion article discussed the oncogenic effects of engaging apoptosis and their impact on cancer (Nat. Rev. Cancer 16, 539–548; 2016)<sup>1</sup>. We would like to thank Roger Chammas, Luciana Nogueira de Sousa Andrade and Sonia Jancar for their correspondence on our article (Nat. Rev. Cancer (2017) doi:10.1038/nrc.2017.15)<sup>2</sup>. Caspase protease activity is essential for apoptotic cell death. Among hundreds of diverse substrates, caspases cleave Ca<sup>2+</sup>-independent phospholipase A2 (iPLA2) leading to its activation<sup>3,4</sup>; active iPLA2 cleaves phosphatidylcholine to give arachidonic acid and lysophosphatidylcholine (LPC). Through cyclooxygenase enzymatic activity, arachidonic acid can be converted into prostaglandin E2 (PGE2) — a prostanoid that has tumour-promoting properties. Consequently, this provides one means whereby caspase-dependent apoptosis could promote cancer<sup>5</sup>.

Chammas and colleagues<sup>2</sup> highlight oncogenic functions for platelet-activating factor receptor (PAFR) signalling; this is mediated following receptor binding to plateletactivating factor (PAF) and related PAFR ligands. Various cell-killing anticancer therapies, notably radiation, are strong inducers of PAF and PAFR ligands. As the authors discuss, during apoptosis PAF might be produced from LPC (generated by caspaseactivated iPLA2) through the action of lysophosphatidylcholine acyltransferases (LPCATs). Although we find this possibility interesting, it is unknown whether apoptotic cells generate PAF in a caspase-dependent manner. Indeed, radiation and chemotherapies induce PAF and PAFR ligands in a nonenzymatic manner (dependent on phospholipid oxidation)<sup>6,7</sup>, arguing against a major role for caspase-dependent generation of PAF. Given this, the rationale for directly targeting PAFR signalling in cancer therapy seems more compelling than that for inhibiting putative, caspase-dependent PAF generation.

---

<sup>1</sup> Ichim, G. & Tait, S. W. A fate worse than death: apoptosis as an oncogenic process. Nat. Rev. Cancer 16, 539–548 (2016).

<sup>2</sup> Chammas, R., Andrade, L. N. D. S. & Jancar, S. Oncogenic effects of PAFR ligands produced in the tumor microenvironment exposed to chemo- and radiotherapy. Nat. Rev. Cancer <http://dx.doi.org/10.1038/nrc.2017.15> (2017).

<sup>3</sup> Zhao, X. et al. Caspase-3-dependent activation of calcium-independent phospholipase A2 enhances cell migration in non-apoptotic ovarian cancer cells. J. Biol. Chem. 281, 29357–29368 (2006).

<sup>4</sup> Lauber, K. et al. Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. Cell 113, 717–730 (2003).

<sup>5</sup> Huang, Q. et al. Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat. Med. 17, 860–866 (2011).

<sup>6</sup> Sahu, R. P. et al. Radiation therapy generates plateletactivating factor agonists. Oncotarget 7, 20788–20800 (2016).

<sup>7</sup> Sahu, R. P. et al. Chemotherapeutic agents subvert tumor immunity by generating agonists of plateletactivating factor. Cancer Res. 74, 7069–7078 (2014).