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Oncogenic effects of PAFR ligands produced in tumours upon chemotherapy and radiotherapy

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The Opinion article from Gabriel Ichim and Stephen W. G. Tait, 'A fate worse than death: apoptosis as an oncogenic process' (*Nat. Rev. Cancer* **16**, 539–548; 2016)[1], highlights intrinsic mechanisms of failure of commonly used cancer therapies that are heavily dependent on apoptosis. Homeostatic mechanisms are triggered by the presence of dying cells within tissues, favouring the survival of residual tumoural cells in the tumour microenvironment[2]. Understanding these homeostatic mechanisms will provide actionable targets to enhance the effectiveness of therapeutic strategies used in the clinic.

The presence of apoptotic cells with subtumorigenic numbers of mouse melanoma cells promoted tumour engraftment and growth, in a mechanism dependent on the recruitment of inflammatory cells[3]. In a separate study, it was shown that clearance of dying cells by tumour macrophages shifts them towards the protumorigenic M2 phenotype by mechanisms involving the receptor for the lipid mediator platelet-activating factor (PAF), a member of the 1-alkyl,2-acylglycerophosphocholine subclass of lipids[4].

Lipid mediators are generated in the tumour microenvironment and can modulate tumour growth. Prostaglandin E_2 (PGE_2) is among the most studied molecular effectors of tumour repopulation following chemotherapy[5]. PGE_2 is derived from the metabolism of membrane phospholipids, through the action of phospholipase A_2 (PLA_2). Both Ca^{2+}-dependent PLA_2 ($cPLA_2$) and Ca^{2+}-independent PLA_2 ($iPLA_2$; also known as PLA2G6)[6] cleave phosphatidylcholine into arachidonic acid and lysophosphatidylcholine (FIG. 1). Although arachidonic acid can be enzymatically converted into prostanoids, including PGE_2, lysophosphatidylcholine is converted into PAF through the action of lysophosphatidylcholine acyltransferases (LPCAT1, LPCAT2, LPCAT3 and LPCAT4)[7]. Therefore, in situations in which PGE_2 is produced, depending on the levels of LPCAT expression, PAF is also produced. In a positive feedback loop, through the activation of its receptor (PAFR), PAF induces either activation of PLA_2 (REF. 8) or induction of cyclooxygenase 2 (COX2) expression[9,10], leading to the further release of PGE_2. The contribution of PAFR-dependent signalling in tumour repopulation was also demonstrated in its response to chemotherapy and radiotherapy. PAF protects tumour cells from drug-induced cell death, and the administration of PAFR antagonists blocks its protective effect[11–13].

Radiation therapy is among the most potent inducers of PAFR ligands through the oxidation of phospholipids[14], whose formation is independent of LPCAT. Regardless of their origin, however, PAFR ligands favour PGE_2 production. Experimental radiation therapy was more effective in tumour-engrafted *PAFR*-knockout mice, as compared with wild type, owing to decreased tumour repopulation in animals devoid of PAFR signalling. Moreover, PAFR ligands induce tissue remodelling and angiogenic cytokine production, through macrophage polarization towards the M2 phenotype. The accumulating evidence for the involvement of PAFR-dependent signalling in the survival response of tumours to chemo- and radiotherapy supports the concept that PAFR antagonists could be used for adjuvant cancer therapy. Several antagonists have been

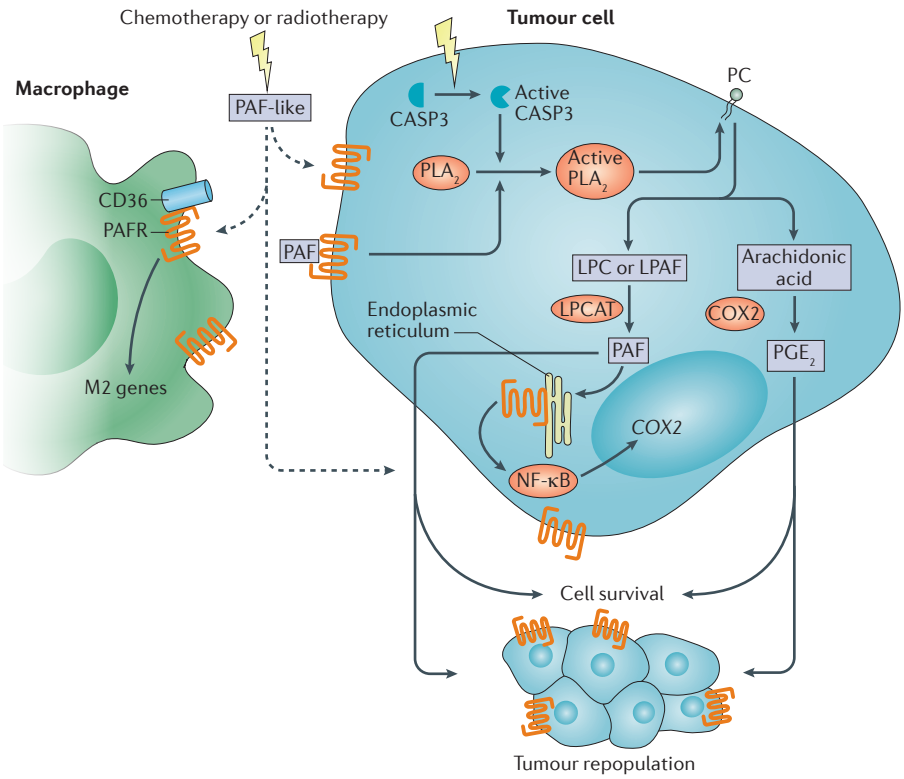

Figure 1 | **Pro-oncogenic effects of platelet-activating factor (PAF) and PAF-like molecules after a cell death stimulus.** In response to a death stimulus, activated caspase-3 (CASP3) promotes activation of phospholipase A_2 (PLA_2), which cleaves membrane phospholipids such as phosphatidylcholine (PC), releasing arachidonic acid, which can be converted into prostaglandin E_2 (PGE_2) and lysophosphatidylcholine (LPC or lyso-PAF (LPAF)), which can then be converted into PAF through the activity of lysophosphatidylcholine acyltransferase (LPCAT). PAF acts in a positive autocrine loop to further activate PLA_2. PAF also interacts with intracellular PAF receptor (PAFR), activating nuclear factor-κB (NF-κB), which in turn induces cyclooxygenase 2 (*COX2*) transcription, thus potentiating PGE_2 production. Both PAF and PGE_2 act as pro-survival stimuli in tumour cells, promoting proliferation of the surviving cells and leading to tumour repopulation. Activation of PAFR in macrophages promotes reprogramming towards an anti-inflammatory and pro-tumorigenic profile (M2 genes). Moreover, irradiation and chemotherapy generate a wide range of PAFR ligands (PAF-like) in the tumour microenvironment that act as PAFR agonists (dashed arrows), amplifying the effect of PAFR activation in tumour cells and macrophages.

developed in the past, but none has yet been tested for clinical use in cancer. PAFR antagonists are likely to complement strategies that target tumour-associated macrophages (colony-stimulating factor 1 receptor (CSF1R) antagonists) and PGE_2 (COX2 inhibitors), which, together, will improve the efficacy of apoptogenic therapies.

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doi:10.1038/nrc.2017.15
Published online 10 Mar 2017

Acknowledgements
Funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, 2013/15719-0 and 2015/22814-5).

Competing interests statement
The authors declare no competing interests.

1. Ichim, G. & Tait, S. W. G. A fate worse than death: apoptosis as an oncogenic process. *Nat. Rev. Cancer* **16**, 539–548 (2016).
2. Huang, Q. *et al.* Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. *Nat. Med.* **17**, 860–866 (2011).
3. Correa, M. *et al.* Transient inflammatory response induced by apoptotic cells is an important mediator of melanoma cell engraftment and growth. *Int. J. Cancer* **114**, 356–363 (2005).
4. Ferracini, M., Rios, F. J. O., Pecenin, M. & Jancar, S. Clearance of apoptotic cells by macrophages induces regulatory phenotype and involves stimulation of CD36 and PAFR receptor. *Mediators Inflamm.* **2013**, 950273 (2013).
5. Kurtova, A. V. *et al.* Blocking PGE_2-induced tumour repopulation abrogates bladder cancer chemoresistance. *Nature* **517**, 209–213 (2015).
6. McHowat, J. *et al.* Platelet-activating factor and metastasis: calcium-independent phospholipase $A_2\beta$-deficiency protects against breast cancer metastasis to the lung. *Am. J. Physiol. Cell Physiol.* **300**, C825–C832 (2011).
7. Murakami, M. & Kudo, I. Recent advances in molecular biology and physiology of the prostaglandin E_2-biosynthetic pathway. *Prog. Lipid Res.* **43**, 3–35 (2004).
8. Oestvang, J., Anthonsen, M. W. & Johansen, B. LysoPC and PAF trigger arachidonic acid release by divergent signaling mechanisms in monocytes. *J. Lipids* **2011**, 532145 (2011).
9. Glaser, K. B., Asmis, R. & Dennis, E. A. PAF receptor mediated PGE2 production in LPS primed P388D1 macrophage-like cells. *Adv Prostaglandin Thromboxane Leukot Res.* **21A**, 249–255 (1991).
10. Ishizuka, E. K., Filgueiras, L. R., Rios, F. J., Serezani, C. H. & Jancar, S. PAFR activation of NF-κB p65 or p105 precursor dictates pro- and anti-inflammatory responses during TLR activation in murine macrophages. *Sci. Rep.* **6**, 16 (2092).
11. Onuchic, A. C. *et al.* Expression of PAFR as part of a prosurvival response to chemotherapy: a novel target for combination therapy in melanoma. *Mediators Inflamm.* **2012**, 175408 (2012).
12. Sahu, R. P. *et al.* Chemotherapeutic agents subvert tumor immunity by generating agonists of platelet-activating factor. *Cancer Res.* **74**, 7069–7078 (2014).
13. Sahu, R. P., Ferracini, M. & Travers, J. B. Systemic chemotherapy is modulated by platelet-activating factor-receptor agonists. *Mediators Inflamm.* **2015**, 820543 (2015).
14. Sahu, R. P. *et al.* Radiation therapy generates platelet-activating factor agonists. *Oncotarget* **7**, 20788–20800 (2016).