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REPLY

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

Gabriel Ichim and 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)[1]. 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)[2]. Caspase protease activity is essential for apoptotic cell death. Among hundreds of diverse substrates, caspases cleave Ca^{2+}-independent phospholipase A_2 ($iPLA_2$) leading to its activation[3,4]; active $iPLA_2$ cleaves phosphatidylcholine to give arachidonic acid and lysophosphatidylcholine (LPC). Through cyclooxygenase enzymatic activity, arachidonic acid can be converted into prostaglandin E_2 (PGE_2) — a prostanoid that has tumour-promoting properties. Consequently, this provides one means whereby caspase-dependent apoptosis could promote cancer[5].

Chammas and colleagues[2] highlight oncogenic functions for platelet-activating factor receptor (PAFR) signalling; this is mediated following receptor binding to platelet-activating 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 caspase-activated $iPLA_2$) 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 non-enzymatic manner (dependent on phospholipid oxidation)[6,7], 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.

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Competing interests statement
The authors declare no competing interests.

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