Programmed death, cells on the last train to glory

Patrycja Nowak-Sliwinska¹ · Arjan W. Griffioen²

Published online: 7 March 2020

© Springer Science+Business Media, LLC, part of Springer Nature 2020

Cell death and the mechanisms of it are an increasing interest of researchers world-wide. This is best reflected by the number of scientific articles on cell death over the last 3 years (2017–2019), which increased by 64% as compared to the 3 years before (2014–2016) from 57,000 to 93,500 articles. Reports on apoptosis, necroptosis and ferroptosis are in the lead of these numbers. It is clear that this interest in programmed cell death is based on the fact that knowledge on this subject provides insight in biology in general, as well as in the processes of disease and resulting opportunities for therapeutic intervention.

From the editors' desks

Three years ago we decided to adorn *Apoptosis* with an award winning cover image related to programmed cell death and change this image every year [1]. Last year's cover had an image of a dog kidney cell in which apoptosis was induced by influenza virus, provided by Dr. Walter Malorni and Dr. Antonella Tinari [2]. For the volume of 2020 we selected an image that was received from Dr. Ivan Poon (La Trobe University, Melbourne, Australia) on the distribution of endoplasmic reticulum during the disassembly of apoptotic cells. A confocal microscopy image is shown of A431 human epidermoid carcinoma cells undergoing apoptosis following treatment with raptinal, a mitochondria-targeted

apoptosis inducer. The A431 cells were transfected with mApple-Sec61B (green) to monitor the location of endoplasmic reticulum, and stained with NucRed (blue) and PKH26 (red) to monitor nuclear material and cell membrane, respectively [3]. Earlier work of Dr. Poon dealt with a novel mechanism in apoptosis of generating extracellular vesicles during apoptosis via a beads-on-a-string membrane structure [4]. An impressive image of these beaded apotopodia was on the cover of *Apoptosis* in 2018 [5]. This work also described how the membrane channel pannexin-1 is a key negative regulator of this process [6]. Other work of the same group, which is worth mentioning, describes different molecular regulators of apoptotic cell disassembly and demonstrate that the formation of apoptotic bodies is important for the efficient clearance of apoptotic cells [7]. We are indebted to Dr. Ivan Poon for the 2020 cover image and we are eagerly encouraging everybody to submit images for the cover of 2021.

Other changes to the journal, such as the reduced number of accepted manuscripts and joining of two issues together in one printed release will be continued for the next year, as we feel these contributed to the significant rise of the predicted 2019 impact factor of *Apoptosis*, which will be in the 4.5 range.

The editors' choice

The above mentioned growing interest in cell death also reflects the submissions to *Apoptosis*. The majority of submitted manuscripts being in the research fields of cardiovascular disease and cancer, is a continuing trend. A few recently published papers on cell death mechanisms is worth highlighting. Over the last years a number of exciting papers were published in the field of cancer, especially in regulating drug sensitivity. Using transcriptomic data bases, a number of small molecules was identified that could target the squamous subtype of pancreatic cancer. It was found that the SRC inhibitors (dasatinib and PP2) and MEK1/2 inhibitor (pimasertib) synergized with gemcitabine, specifically

Reference to death in the old American folk song from the 1920s recorded as 'This Train'.

✉ Patrycja Nowak-Sliwinska
Patrycja.Nowak-Sliwinska@unige.ch

✉ Arjan W. Griffioen
a.griffioen@amsterdamumc.nl

¹ School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

² Angiogenesis Laboratory, Department of Medical Oncology, Amsterdam UMC, Cancer Center Amsterdam, 1081 HV Amsterdam, The Netherlands

in the squamous subtype of cancer. Specificity of these agents was demonstrated by showing complete abrogation of activity by overexpression of SRC or MEK1/2 [8]. Chloroquine-induced inhibition of autophagy was found to revert resistance to paclitaxel and inhibited metastatic potential of small cell lung adenocarcinoma, via reactive oxygen-mediated modulation of the catenin pathway. It was suggested that pre-treatment with chloroquine can be applied in the clinic [9]. Cetuximab and oridonin are reported to synergize in induction of cell death. It is now shown that the combination treatment not only induces apoptosis but also autophagy in laryngeal squamous cell carcinoma, suggesting clinical application [10]. IL6/GP130 inhibitors were found to increase the activity of 5-fluorouracil in colon cancer, suggesting a promising strategy for future therapy [11]. An antimicrobial compound with anti-cancer activity, prodigiosin, was found to inhibit glioblastoma cells, through inhibition of the JNK and the AKT/mTOR pathways, while inducing an excessive level of autophagy [12]. This study suggests unexpected opportunities for this compound.

Also altered regulation of intrinsic and extrinsic apoptosis pathways was often the subject of submitted manuscripts. One study examined dysregulation of 133 genes and associated miRNAs in colorectal carcinoma. It identified several apoptosis regulated genes and miRNAs, suggestive of potential targets for therapeutic use [13]. Next to these original reports two reviews on chemo- and radioresistance in glioblastoma [14] and negative regulators of cell death pathways [15] were published.

A number of interesting reports represented the field of cardiovascular disease. It was shown that microvesicles isolated from peripheral blood after ischemic-reperfusion injury protect against this injury through alleviating endoplasmic reticulum stress [16]. A very interesting paper reported that elevated SDF-1 in a variety of diseases, e.g. ischemic myocardial infarction, contributes to TNF-alpha mediated cardiac cell death [17]. Another report described the promoting effect of minocycline cardiomyocyte mitochondrial autophagy, to prevent sepsis-induced cardiac dysfunction [18].

Next to apoptosis and autophagy-dependent cell death, a lot of attention was also given to alternative ways of cell death such as pyroptosis [19–22], ferroptosis [15], necroptosis [23, 24].

The team of editors and publishers highly values the excellent contributions of our reviewers. We can never express enough gratitude to these experts, whose work is an absolute requirement for the quality of a scientific journal. Of course we are also grateful to the support of authors who submit that manuscripts to *Apoptosis*. We, as the editors-in-chief of *Apoptosis*, will do our utmost to continue service to the field of science, by making the journal a forum for enhancing science and enabling scientific debate.

References

- Griffioen AW, Nowak-Sliwinska P (2017) Apoptosis turns 21. *Apoptosis* 22:1485–1486
- Griffioen AW, Nowak-Sliwinska P (2019) Cell death rocks. *Apoptosis* 24:205–207
- Caruso S, Atkin-Smith GK, Baxter AA, Tixeira R, Jiang L, Ozkocak DC, Santavanond JP, Hulett MD, Lock P, Phan TK, Poon IKH (2019) Defining the role of cytoskeletal components in the formation of apoptopodia and apoptotic bodies during apoptosis. *Apoptosis* 24:862–877
- Atkin-Smith GK, Tixeira R, Paone S, Mathivanan S, Collins C, Liem M, Goodall KJ, Ravichandran KS, Hulett MD, Poon IK (2015) A novel mechanism of generating extracellular vesicles during apoptosis via a beads-on-a-string membrane structure. *Nat Commun* 6:7439
- Nowak-Sliwinska P, Griffioen AW (2018) Apoptosis on the move. *Apoptosis* 23:251–254
- Poon IK, Chiu YH, Armstrong AJ, Kinchen JM, Juncadella JJ, Bayliss DA, Ravichandran KS (2014) Unexpected link between an antibiotic, pannexin channels and apoptosis. *Nature* 507:329–334
- Atkin-Smith GK, Miles MA, Tixeira R, Lay FT, Duan M, Hawkins CJ, Phan TK, Paone S, Mathivanan S, Hulett MD, Chen W, Poon IKH (2019) Plexin B2 is a regulator of monocyte apoptotic cell disassembly. *Cell Rep* 29:1821–1831 (e1823)
- Er JL, Goh PN, Lee CY, Tan YJ, Hii LW, Mai CW, Chung FF, Leong CO (2018) Identification of inhibitors synergizing gemcitabine sensitivity in the squamous subtype of pancreatic ductal adenocarcinoma (PDAC). *Apoptosis* 23:343–355
- Datta S, Choudhury D, Das A, Mukherjee DD, Dasgupta M, Bandyopadhyay S, Chakrabarti G (2019) Autophagy inhibition with chloroquine reverts paclitaxel resistance and attenuates metastatic potential in human nonsmall lung adenocarcinoma A549 cells via ROS mediated modulation of beta-catenin pathway. *Apoptosis* 24:414–433
- Cao S, Huang Y, Zhang Q, Lu F, Donkor PO, Zhu Y, Qiu F, Kang N (2019) Molecular mechanisms of apoptosis and autophagy elicited by combined treatment with oridonin and cetuximab in laryngeal squamous cell carcinoma. *Apoptosis* 24:33–45
- Li S, Tian J, Zhang H, Zhou S, Wang X, Zhang L, Yang J, Zhang Z, Ji Z (2018) Down-regulating IL-6/GP130 targets improved the anti-tumor effects of 5-fluorouracil in colon cancer. *Apoptosis* 23:356–374
- Cheng SY, Chen NF, Kuo HM, Yang SN, Sung CS, Sung PJ, Wen ZH, Chen WF (2018) Prodigiosin stimulates endoplasmic reticulum stress and induces autophagic cell death in glioblastoma cells. *Apoptosis* 23:314–328
- Slattery ML, Mullany LE, Sakoda LC, Wolff RK, Samowitz WS, Herrick JS (2018) Dysregulated genes and miRNAs in the apoptosis pathway in colorectal cancer patients. *Apoptosis* 23:237–250
- Taylor MA, Das BC, Ray SK (2018) Targeting autophagy for combating chemoresistance and radioresistance in glioblastoma. *Apoptosis* 23:563–575
- Razaghi A, Heimann K, Schaeffer PM, Gibson SB (2018) Negative regulators of cell death pathways in cancer: perspective on biomarkers and targeted therapies. *Apoptosis* 23:93–112
- Liu M, Wang Y, Zhu Q, Zhao J, Wang Y, Shang M, Liu M, Wu Y, Song J, Liu Y (2018) Protective effects of circulating microvesicles derived from ischemic preconditioning on myocardial ischemia/reperfusion injury in rats by inhibiting endoplasmic reticulum stress. *Apoptosis* 23:436–448
- Jarrah AA, Schwarskopf M, Wang ER, LaRocca T, Dhume A, Zhang S, Hadri L, Hajjar RJ, Schecter AD, Tarzami ST (2018) SDF-1 induces TNF-mediated apoptosis in cardiac myocytes. *Apoptosis* 23:79–91

18. Zhang E, Zhao X, Zhang L, Li N, Yan J, Tu K, Yan R, Hu J, Zhang M, Sun D, Hou L (2019) Minocycline promotes cardiomyocyte mitochondrial autophagy and cardiomyocyte autophagy to prevent sepsis-induced cardiac dysfunction by Akt/mTOR signaling. *Apoptosis* 24:369–381
19. Zeng CY, Li CG, Shu JX, Xu LH, Ouyang DY, Mai FY, Zeng QZ, Zhang CC, Li RM, He XH (2019) ATP induces caspase-3/gasdermin E-mediated pyroptosis in NLRP3 pathway-blocked murine macrophages. *Apoptosis* 24:703–717
20. Jiang L, Poon IKH (2019) Methods for monitoring the progression of cell death, cell disassembly and cell clearance. *Apoptosis* 24:208–220
21. Zhang CC, Li CG, Wang YF, Xu LH, He XH, Zeng QZ, Zeng CY, Mai FY, Hu B, Ouyang DY (2019) Chemotherapeutic paclitaxel and cisplatin differentially induce pyroptosis in A549 lung cancer cells via caspase-3/GSDME activation. *Apoptosis* 24:312–325
22. Chen L, Weng B, Li H, Wang H, Li Q, Wei X, Deng H, Wang S, Jiang C, Lin R, Wu J (2019) A thiopyran derivative with low murine toxicity with therapeutic potential on lung cancer acting through a NF-kappaB mediated apoptosis-to-pyroptosis switch. *Apoptosis* 24:74–82
23. Chen S, Lv X, Hu B, Zhao L, Li S, Li Z, Qing X, Liu H, Xu J, Shao Z (2018) Critical contribution of RIPK1 mediated mitochondrial dysfunction and oxidative stress to compression-induced rat nucleus pulposus cells necroptosis and apoptosis. *Apoptosis* 23:299–313
24. Bergamaschi D, Vossenkamper A, Lee WYJ, Wang P, Bochukova E, Warnes G (2019) Simultaneous polychromatic flow cytometric detection of multiple forms of regulated cell death. *Apoptosis* 24:453–464

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.