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EDITORIAL

Programmed cell death lives

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Abstract
Research on cell death mechanisms gets a lot of attention. This is understandable as it underlies biology in general, as well as the insight in pathological conditions and the development of opportunities for therapeutic intervention. Over the last years a steady rise in the number of scientific reports and in the impact of this literature on the different mechanisms of programmed cell death can be observed. A number of new concepts are highlighted.

Over the last few years, a rise in the impact of *Apoptosis* was observed and Clarivate announce the 2015 Impact Factor to be 5.561. This was due to the increased submission of high-impact and high-quality manuscripts. We, as editors of *Apoptosis* are in service as of 2016 and we are determined to improve the quality of the journal. Over the last years we celebrated adulthood [1] and the quarter-century anniversary of *Apoptosis* [2]. We will continue to maintain the rigorous, fair and fast peer-review process of submitted manuscripts. We also aim to continue inviting reviews on trending topics in the field of programmed cell death, as well as ensuring that high-quality original research articles continue to be published in *Apoptosis*. We would like to thank the members of our editorial board and the outside reviewers for their invaluable support in selecting and improving the submitted manuscripts for publication in *Apoptosis*. Similarly, we thank the contributing authors for their trust in the journal to submit their best and most original research. Last but not least, we would like to thank our publisher Springer-Nature for the opportunity to serve the scientific community with the publication of *Apoptosis*.

Five years ago, we decided to select new cover art related to programmed cell death for every volume of *Apoptosis* [1]. Last year's cover was adorned with an image from a paper of co-Editor-in-Chief Dr. Nowak-Sliwinska on the process of spindle pole clustering [2, 3]. For the coming year we selected an image from the best-cited 2021 original research paper published in *Apoptosis* [4]. It shows an A375 human melanoma cell that is exposed to the vitamin E derivative δ-Tocotrienol (δ-TT) (Fig. 1). This treatment induces cytoplasmic vacuolation, dilated endoplasmic reticulum and swollen mitochondria, specific features of cells undergoing paraptosis, a non-apoptotic form of programmed cell death [5, 6]. Apoptosis is the well-known programmed cell death mediating tumor growth suppression induced by standard anti-cancer therapies. However, over the years, it has become increasingly clear that additional forms of programmed cell deaths are involved in the anti-tumor activity of different synthetic and natural compounds [7, 8]. Specifically, paraptosis is a type of non-canonical programmed cell death characterized by a peculiar cytoplasmic vacuolation, associated with endoplasmic reticulum (ER) dilatation and mitochondrial swelling [9]. It was previously demonstrated that the vitamin E derivative δ-tocotrienol (δ-TT) triggers ER stress-mediated apoptosis in human melanoma cells [10]. This article presents that paraptosis might also be involved in the anti-cancer activity of this natural compound. Interestingly, by taking advantage of the TEM analysis technique, it was observed that, in human A375 and BLM melanoma cells, δ-TT induces cell death by promoting an intense cytoplasmic vacuolation, associated with dilated ER cisternae, swollen mitochondria with rare cristae and an enlarged nuclear envelope. It was also observed that these structural organelle alterations were strictly related to ER proteostasis disruption and mitochondrial dysfunction due to the accumulation of ER-derived Ca2 + and ROS overproduction.

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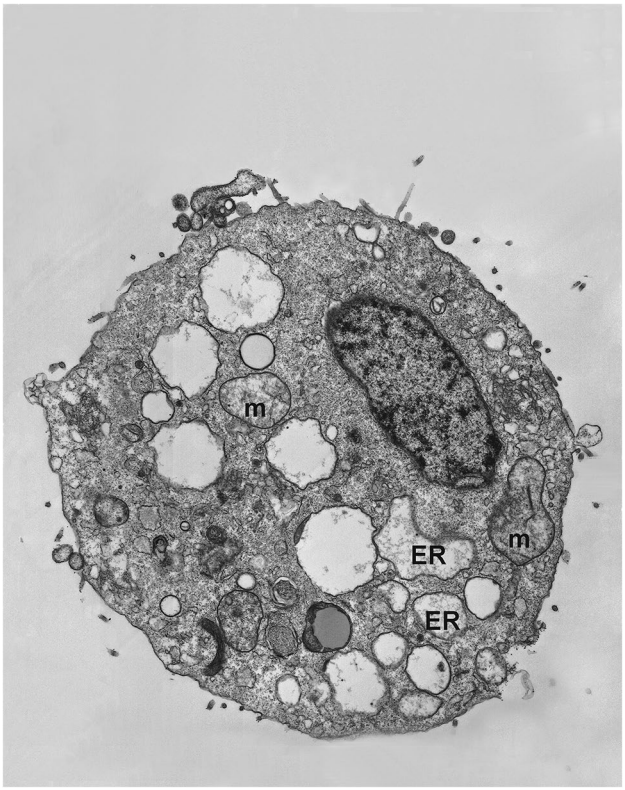

Fig. 1 Melanoma cell undergoing paraptosis after exposure to the vitamin E derivative δ-Tocotrienol (δ-TT). This TEM image shows that A375 human melanoma cells treated with δ-TT exhibit vacuolation, dilated endoplasmic reticulum (ER) cisternae and swollen mitochondria (m), as specific features of cells undergoing paraptosis. This image is taken from Raimondi M et al. Apoptosis 26(5–6):277–92, 2021 [4]

These data support that paraptosis is deeply involved in the anti-cancer activity of the natural compound δ-TT in human melanoma cells.

While science, as well as almost every other sector of society, suffered significantly from the COVID-19 pandemic, *Apoptosis* received several excellent submissions on the role of SARS-CoV-2 mediated disease. It is known that COVID-19 is primarily a vascular disease, affecting next to the (upper) airway system many other organs as well [11–13]. We have published on the disruptive effects of SARS-CoV-2 on spermatogenesis through the induction of apoptosis [14]. Another submission that we published in 2021 was on the relationship between apoptosis and COVID-19 severity, which induced the discussion whether it is possible to target the virus-induced apoptosis as a therapeutic strategy [15].

A number of excellent papers were recently published on the different mechanisms of programmed cell death. An original research paper investigated ferroptosis, a process different from apoptosis as it is known to result from iron-dependent accumulation of lipid peroxides rather than caspase activation. This study demonstrates that the BAX-associated mitochondria-dependent pathway plays a pivotal role in the interplay between ferroptosis and apoptosis [16–19]. An overview on the role of ferroptosis in cancer was provided in two comprehensive reviews [5, 20]. An original research article reported on the induction of pyroptosis, an inflammatory form of programmed cell death often associated with infection [21, 22], after ischemia reperfusion injury in fatty liver disease [23]. Necroptosis, another caspase independent mechanism of cell death [24], was investigated in infectious diseases. It was suggested that intervention in necroptosis may be helpful for combatting pathogens, prevention of lesion formation and support the remodeling of tissues [24]. Many submissions were received on the process of autophagy. Two original research papers reported on autophagy mechanisms in cancer. Berberine and icotinib synergized at induction of autophagic cell death in lung cancer [25]. A second report identified autophagy as a mechanism for therapy of acute myeloid leukemia [26]. Several comprehensive reviews on the interaction between autophagy and apoptosis [27], as well as its role in cancer were published in 2021 [28, 29].

The team of editors and publishers highly values the excellent contributions of our editorial board and external 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 submitted their manuscripts to *Apoptosis*. We highly encourage researchers to submit their exciting research to *Apoptosis* and communicate new ideas for invited reviews and special issues to further improve the journal.

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