



18th National and 3rd International Conference of هجدهمین همایش ملی و سومین همایش Iranian Biophysical chemistry بین المللی بیوشیمی فیزیک ایران

25-26 Des, 2024, University of Hormozgan

۶-۵ دی ماه ۱۴۰۳، دانشگاه هرمزگان

## Beyond Apoptosis: The Diverse Roles of Caspase-9 in Cancer Cell Fate Determination

Shiva Akbari-Birgani\*, Mehrnaz Amjadi, Mohammad Borna Amirian, Mohammad Hossein Saeedi Moghadam

Institute for Advanced Studies in Basic Sciences, Zanjan, Iran. <u>sh.akbari@iasbs.ac.ir</u>, me.amjadi@iasbs.ac.ir, borna.amirian@iasbs.ac.ir, <u>saeidi.m@iasbs.ac.ir</u>

## Abstract

Apoptosis is a complex and highly regulated process, involving numerous signaling pathways and molecular mechanisms. Here are some key steps and components in apoptosis, including activation of caspases a family of proteases that play a crucial role in apoptosis. Their activation triggers a cascade of events leading to cell death. In recent studies, caspase-9, an initiator caspase in the intrinsic apoptotic pathway, has been found to play non-apoptotic roles in cellular processes such as differentiation and migration. This study investigated the non-apoptotic functions of caspase-9 and its putative contribution to molecular mechanisms in cancer cells. Activation of caspase-9 and its effects were studied in glioblastoma, neuroblastoma, leukemia, and breast cancer cell lines and their corresponding organoids, evaluating its impact on molecular signatures and pathological features. This study found diverse effects of caspase-9 activation in various cancer cell lines and organoids. In luminal breast cancer, it triggered apoptosis, while in tamoxifen-resistant cells it did not induce cell death. In triple-negative breast cancer, it exhibited anti-metastatic properties. In glioblastoma, it induced cellular senescence; in leukemic and neuroblastoma cells, it promoted differentiation signatures. Interestingly, all organoid models displayed reduced pathological features associated with the aggressive epithelial-mesenchymal transition (EMT). Moreover, our data mining survey on breast cancer transcriptomic data revealed an association between the downregulation of caspase-9 and the aggressive features of breast cancer. These findings suggest that activating caspase-9 could alter cell fate in different cancers. This work highlights the potential for targeted activation of caspase-9 as a novel therapeutic strategy for cancer treatment, particularly for aggressive cancers with EMT characteristics. Further studies are needed to explore the mechanisms underlying the non-apoptotic functions of caspase-9 in cancer cells and to evaluate the therapeutic potential of this approach.

**Key words:** Caspase-9; Cell fate; Apoptosis; Senescence; Differentiation; Cancer cells; Organoid models **References** 





## 18th National and 3rd International Conference of مجدهمین همایش ملی و سومین همایش Iranian Biophysical chemistry بین المللی بیوشیمی فیزیک ایران

25-26 Des, 2024, University of Hormozgan

۶-۵ دی ماه ۱۴۰۳، دانشگاه هرمزگان

- 1. Rihova, K., et al., *Caspase-9 Is a Positive Regulator of Osteoblastic Cell Migration Identified by diaPASEF Proteomics*. J Proteome Res, 2024. **23**(8): p. 2999-3011.
- 2. Shalini, S., et al., *Old, new and emerging functions of caspases*. Cell Death Differ, 2015. **22**(4): p. 526-39.
- 3. Akbari-Birgani, S., et al., *Delay in apoptosome formation attenuates apoptosis in mouse embryonic stem cell differentiation*. J Biol Chem, 2014. **289**(24): p. 16905-13.
- 4. Madadi, Z., et al., *The effect of caspase-9 in the differentiation of SH-SY5Y cells*. Eur J Pharmacol, 2021. **904**: p. 174138.