International Journal of Inflammation, Cancer and Integrative Therapy

Mini Review Open Access

Review of Breast Cancer and the Implications of Programmed Cell Death

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Abstract

Cell death is an inevitable part of life and is essential for controlling disease situations, ageing, and organismal growth. Cell death can occur in both controlled and unregulated ways. In recent years, programmed cell death (PCD)-induced cell death has drawn more and more attention. The improper regulation of PCD is crucial to tumour development. For instance, current contemporary chemotherapeutic drugs' ability to treat tumours by inducing cell death is crucial given that tumour cells are comparatively resistant to apoptosis. Non-coding RNAs (ncRNAs) have recently come to light as being involved in the regulation of several biological processes in breast cancer, including PCD.

Keywords: Cell death; Dysregulation; Cancer; Tumour; Malignancy; Breast cancer

Introduction

The most prevalent malignancy and the cause of tumor-related deaths in women is breast cancer [1]. Breast tissue can grow into cancer in cases of breast cancer. Breast lumps, altered breast form, dimpling of the skin, fluid flowing from the nipple, an inverted nipple, and red or scaly patches of skin are all indications of breast cancer. Symptoms of distant illness spread include yellow skin, shortness of breath, enlarged lymph nodes, and bone discomfort. Although there are several high-risk variables connected to the onset and spread of breast cancer, the exact cause of the disease is still unknown. Breast cancer develops as a result of mammary epithelial cells' uncontrolled proliferation in response to many oncogenic stimuli [2,3]. The most aggressive subtype of breast cancer is triple-negative breast cancer (TNBC), which has a significant likelihood of local recurrence and distant metastasis. Surgical treatments, radiation, chemotherapy, endocrine therapy, and targeted therapy are all used in the treatment of breast cancer. The fact that breast cancer patients' overall survival is still poor, however, indicates that new treatment targets must be developed for these patients [4,5]. The biomarkers ER, PR, and HER2 are frequently examined in breast cancer tissue to aid with therapy selection. Any gene, protein, or other item that can be detected in the blood, tissues, or other bodily fluids is referred to as a biomarker.

When cancer cells die, DNA known as circulating tumour DNA (ctDNA) is released into the circulation. A fast expanding field of inquiry is the identification and testing of ctDNA in blood for biomarkers. The growth and homeostasis of cells in the human body are influenced by both the regulation of cell proliferation and the removal of aberrant cells to minimise risk to the organism. While programmed cell death (PCD) is the main method by which organisms destroy these aberrant cells, this biological process also involves the removal of damaged cells that are at risk of tumorigenicity [6]. By activating membrane-bound and cytosolic proteins that result in complicated transcriptional cascade reactions and protein posttranslational modifications, PCD can be triggered by organismal development and stress signals. Apoptosis is a relatively "mild" cell death modality that typically does not cause immune or inflammatory responses, whereas pyroptosis and necroptosis refer to relatively "drastic" cell death characterised by rupture of the cell membrane and the subsequent release of inflammation-inducing factors [7]. For cancer patients, PCD control may offer considerable therapeutic advantages. Numerous illnesses, including autoimmune conditions, neurodegenerative disorders, and malignancies are linked to PCD dysregulation [8]. Current anticancer research has shifted its attention to how to activate PCD in cancer cells. Recent studies have shown that noncoding RNAs (ncRNAs) are involved in the regulation of PCD in breast cancer. As a result, developing ncRNA-based medicines that specifically target PCD may be an effective treatment for breast cancer.

Molecular mechanisms

Apoptosis

Apoptosis is an energy-dependent intracellular death mechanism that is activated during the active phase of cell death. It is a genetically regulated, autonomous, and orderly process. A cell begins the apoptotic stage after perceiving the appropriate signal stimulation, and the process of cell apoptosis may be loosely split into many stages. Caspases are essential enzymes that trigger apoptosis and are a subset of the cysteine proteases. Caspase-mediated cascade activation of irreversibly limited hydrolytic substrates is triggered by a variety of upstream cell death signals, which in turn results in cell morphological and biochemical changes like DNase-mediated DNA fragmentation, chromatin condensation, cell membrane activation, cellular crinkling, and ultimately the formation of apoptotic bodies encapsulated by cell membranes. The subsequent engulfment of these apoptotic bodies by other cells is known as phagocytosis, which completes the apoptotic cycle [9,10]. The biological evolution of organisms and the stability of their interior environments depend on apoptosis. Inhibiting the apoptotic process of tumour cells might lead to an increase in the amount of tumour cells as tumorigenesis is also correlated with defective apoptosis. Numerous studies have demonstrated that several chemotherapeutic drugs cause apoptosis in order to exert their anticancer effects. For instance, lapatinib inhibits Akt activation and decreases CIP2A expression to cause apoptosis in triple-negative breast cancer cells. Additionally, exogenous siRNA introduction can

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Received: 01-Oct-2022, Manuscript No. ijm-22-77747; **Editor assigned:** 03-Oct-2022, PreQC No. ijm-22-77747(PQ); **Reviewed:** 17-Oct-2022, QC No. ijm-22-77747; **Revised:** 21-Oct-2022, Manuscript No. ijm-22-77747(R); **Published:** 28-Oct-2022, DOI: 10.4172/2381-8727.1000200

Citation: Lowe A (2022) Review of Breast Cancer and the Implications of Programmed Cell Death. Int J Inflam Cancer Integr Ther, 9: 200.

greatly increase paclitaxel (PTX) or epirubicin sensitivity and trigger death in MCF-7 cells by silencing the survival protein gene [11]. The development of the apoptotic pathway in the treatment of breast cancer will be aided by further study on the use of anticancer medicines in combination to trigger apoptosis.

Autophagy

In eukaryotic cells under stress circumstances such hunger, inflammation, and an insufficient energy metabolism, autophagy is a dynamic cellular self-degradation process that is intimately associated to cancer. Through lysosomes, autophagic cells may break down molecules and subcellular elements such as proteins, lipids, nucleic acids, and self-damaged organelles. The PI3K-AKT-mTOR signalling route and the AMPK-TSC1/2-mTOR signalling circuit are the two primary mTOR pathway-dependent autophagy regulation mechanisms, respectively. The Class IIIPI3 complex, which controls autophagy, also involves additional signalling pathways, including the positive regulators beclin1 and UVRAG and the negative regulator bcl-2. The emergence of cancer is a double-edged sword for autophagy. Autophagy, a kind of PCD, on the one hand encourages precancerous cell death and prevents carcinogenesis. Researchers discovered that autophagy abnormalities are crucial to TNBC cells' ability to evade T-cell immunological assault [12]. On the other side, by promoting cellular autophagy, tumour cells can also block stress reactions brought on by hypoxia, metabolites, and therapeutic medicines [13]. For instance, P62, a crucial autophagy regulator, through the TRIM family member TRIM59, stimulates the growth and spread of breast cancer. Enhancing normal cell autophagy and inhibiting tumour cell autophagy are thought to be effective treatment options for advanced cancer [14].

Pyroptosis

Pyroptosis is a more rapid kind of cell death than apoptosis that is triggered by inflammasomes. The production of inflammatory bodies, activation of caspase and gasdermin, and the release of several proinflammatory substances are the primary symptoms of pyroptosis.

Necroptosis

In contrast to apoptosis, which is a process of self-destruction that occurs when apoptosis is halted, necroptosis is a unique type of planned necrotic cell death. Organelle enlargement, cell membrane rupture, and cytoplasm and nucleus disintegration can all be seen during necroptosis. Contrary to other types of PCD, necroptosis needs RIPK3-regulated phosphorylation of MLKL but is independent of caspase activation. The creation of pore complexes in the plasma membrane by MLKL as a result of this phosphorylation event causes DAMP release, cell swelling, and membrane rupture.

Ferroptosis

A form of cell death known as ferroptosis is brought on by the buildup of intracellular iron and lipid reactive oxygen species (ROS). Intracellular glutathione is depleted when intracellular cysteine transporters are blocked (such as by erastin), which ultimately results in the inactivation of Glutathione peroxidase 4 (GPX4), which causes a buildup of lipid peroxidation that can cause ferroptosis. Ferroptosis cells are distinguished from other cell types by their smaller size, denser membrane, diminished or absent cristae, and damaged outer membrane [15].

Cuproptosis

Another unique mechanism of cell death that depends on metal ions is called cuproptosis. The loss of iron-sulfur cluster proteins and the aggregation of lipid acylated proteins caused by copper's direct binding to the tricarboxylic acid cycle (TCA) components ultimately result in proteotoxic stress and cell death. Copper has both benefits and drawbacks for cells. Living things require the cofactor copper, and copper homeostasis keeps intracellular copper concentrations very low to avoid the buildup of intracellular free copper, which is bad for cells [16]. However, even low levels of intracellular copper can be poisonous and cause cell death.

Discussion

The FDA has authorised Fomivirsen, the first antisense medication, since 1998 for the treatment of CMV retinitis in immunocompromised individuals [17-20]. There are now a number of RNA-based treatments that have been given the go-ahead for clinical usage with the intention of altering the genes in the liver, muscles, or central nervous system. In immunotherapy research, RNA-based treatments are increasingly popular. These treatments promote innate and acquired immunity by silencing or upregulating immune-related genes, controlling the release of cytokines, and serving as tumour antigen vaccines. For instance, the FDA authorised Nusinesen, an ASO medication and splicing modulator, in 2016 to treat paediatric spinal muscular atrophy.

Conclusions

Breast cancer start and progression are significantly influenced by PCD dysregulation. Existing research has demonstrated the importance of ncRNAs in controlling PCD in breast cancer. As a result, understanding the interactions between ncRNAs, PCD, and their regulatory mechanisms in breast cancer will help illuminate its genesis and progression and offer fresh perspectives on its detection and therapy. Notably, research on ncRNAs in breast cancer using innovative PCD techniques like pyroptosis and necroptosis is still substantially limited and needs to be done.

Acknowledgement:

Not applicable.

Conflict of interest:

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249.
2. Sun YS, Zhao Z, Yang ZN, Xu F, et al. (2017) Risk factors and preventions of breast cancer. Int J Biol Sci 13: 1387-1397.
3. Key TJ, Verkasalo PK, Banks E (2001) Epidemiology of breast cancer. Lancet Oncol 2: 133-140.
4. Park YH, Senkus-Konefka E, Im SA, Pentheroudakis G, Saji S, et al (2020) Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with early breast cancer: a KSMO-ESMO initiative endorsed by CSCO, ISMPO, JSMO, MOS, SSO and TOS. Ann Oncol 31: 451-469.
5. Park JH, Anderson WF, Gail MH (2015) Improvements in US breast cancer survival and proportion explained by tumor size and estrogen-receptor status. J Clin Oncol 33: 2870-2876.
6. Nagata S (2005) DNA degradation in development and programmed cell death. Annu Rev Immunol 23: 853-875.
7. Bozhkov PV, Lam E (2011) Green death: revealing programmed cell death in plants. Cell Death Differ 18: 1239-1240.
8. Khan I, Yousif A, Chesnokov M, Hong L, Chefetz I, et al. (2021) A decade of cell death studies: breathing new life into necroptosis. Pharmacol Ther 220: 107717.

9. Van Opdenbosch V, Lamkanfi M (2019) Caspases in cell death, inflammation, and disease. Immunity 50: 1352-1364.

10. Nagata S (2018) Apoptosis and clearance of apoptotic cells. Annu Rev Immunol 36: 489-517.

11. Dong H, Yao L, Bi W, Wang F, Song W, et al. (2015) Combination of survivin siRNA with neoadjuvant chemotherapy enhances apoptosis and reverses drug resistance in breast cancer MCF-7 cells. J Cancer Res Therapeut 11: 717-722.

12. Yang Q, Qiu X, Zhang X, Yu Y, Li N, et al. (2021) Optimization of beclin 1-targeting stapled peptides by staple scanning leads to enhanced antiproliferative potency in cancer cells. J Med Chem 64: 13475-13486.

13. Levy JMM, Towers CG, Thorburn A (2017) Targeting autophagy in cancer. Nat Rev Cancer 17: 528-542.

14. Amaravadi R, Kimmelman AC, White E (2016) Recent insights into the function of autophagy in cancer. Genes Dev 30: 1913-1930.

15. Du T, Gao J, Li P, Wang Y, Qi Q, et al. (2021) Pyroptosis, metabolism, and tumor immune microenvironment. Clin Transl Med 11: 492.

16. Ge EJ, Bush AI, Casini A, Cobine PA, Cross JR, et al. (2022) Connecting copper and cancer: from transition metal signalling to metalloplasia. Nat Rev Cancer 22: 102-113.

17. Bazhabayi M, Qiu X, Li X, Yang A, Wen W, et al. (2021) CircGFRA1 facilitates the malignant progression of HER-2-positive breast cancer via acting as a sponge of miR-1228 and enhancing AIFM2 expression. J Cell Mol Med 25: 248-256.

18. Perry CM, Balfour JA (1999) Fomivirsen. Drugs 57: 375-380.

19. Chiriboga CA (2017) Nusinersen for the treatment of spinal muscular atrophy. Expert Rev Neurother 17: 955-962.

20. Pandey PR, Young KH, Kumar D, Jain N (2022) RNA-mediated immunotherapy regulating tumor immune microenvironment: next wave of cancer therapeutics. Mol Cancer 21: 58.