Homeostatic Response Mechanisms in Cancer Chemotherapy

Ella Park

Abstract

This review explores the mechanisms by which cancer cells use adaptive, homeostatic responses to resist chemotherapy. This paper reviews the basic biology of cancer and the ability of cancer cells to resist and tolerate cancer treatments. Then, the discussion will examine three homeostatic mechanisms of chemotherapy resistance: antioxidant metabolism, autophagy, and the endoplasmic reticulum (ER) stress response. Additionally, the paper addresses how these mechanisms mediating cancer resistance contribute to homeostasis in healthy cells and how essential cell organelles and proteins promote tumour survival for cancer cells. Despite the advancement in cancer treatment, scientists still struggle to understand the dual role of these three mechanisms.

Introduction

Cells, the building blocks of life, are composed of various structures including the cell membrane, cytoplasm, and organelles. However, the same organelles and proteins essential for the normal function of healthy tissues can be co-opted by cancer cells to promote tumour growth and therapeutic resistance.[1] Homeostasis describes the essential mechanisms by which the body, tissues, or cells maintain a stable internal environment regardless of external changes. Cellular homeostasis is the process by which healthy cells regulate levels of nutrients, pH, and other factors to maintain optimal internal environments and support cellular function and growth.[2] This paper explores how cancer cells may exploit normal homeostatic mechanisms to promote tumour survival and progression.

Cancer is the uncontrolled growth of cells driven by genomic alterations.[3] The abnormal behaviour of cancer cells is driven by specific characteristics known as the hallmarks of cancer. These mechanisms allow cancer cells to survive and thrive in ways normal cells cannot.[4] However, the hallmarks of cancer not only drive cancer cell proliferation but may also make treating cancer more challenging.

Chemotherapy is a major cancer treatment modality that uses chemical compounds to inhibit tumour growth. Chemotherapeutic agents may also trigger cell death by interfering with the production or function of DNA, RNA, and proteins.[5] Other common modalities of treatment include: radiation therapy, which damages DNA to destroy the cancer cells; hyperthermia, where body tissues are heated up to trigger apoptosis; and targeted therapy, which uses specific molecules that selectively target the proteins controlling the growth of cancer cells.[6]

Cancer cells adapt to new environments and build resistance to chemotherapy, also called chemoresistance. Chemoresistance is a major challenge that limits the success of chemotherapy. Combining treatments may produce a synergistic effect that can delay the acquisition of chemoresistance and improve the efficacy of cancer treatment.[7] Cancer cells may develop two types of chemoresistance: intrinsic resistance and acquired resistance. Intrinsic resistance pre-exists within the cell, allowing cancer cells to resist the initial treatment and

maintain homeostasis despite the presence of therapeutic agents. Acquired resistance arises after the initiation of chemotherapy and may reduce the amount of drug transported into cancer cells, increase the export of drugs from the cell, or alter the levels or structure of drug targets.[1]

Alterations in drug metabolism or changes to the tumour microenvironment (TME) may promote chemoresistance and increase the risk of cancer relapse after treatment.[8] Multidrug resistance (MDR) mechanisms may contribute to the ability of cancer cells to resist and survive chemotherapy. MDR may arise from increased DNA repair capacity and/or enhanced efflux of xenobiotic compounds including chemotherapeutic drugs from cancer cells, allowing cancer cells to evade death or cytostasis induced by chemotherapeutic agents.[9] The common property of these mechanisms is that they all disrupt the homeostasis of the tumour cells and inhibit the efflux of drugs. Recurrent cancer cells may become more aggressive than the original tumour cells and gain an increased ability to metastasize to distant organs.

This research paper explores the mechanisms by which cancer cells hijack homeostasis to drive chemoresistance. Three mechanisms of chemoresistance—autophagy, the endoplasmic reticulum (ER) stress response, antioxidant metabolism, and senescence—can either hinder or promote tumour growth in response to chemotherapy, depending on the types and dosage of drugs used.

Homeostatic Mechanisms of Chemoresistance

1. Antioxidant Metabolism

Cells, tissues, and organs must maintain homeostasis of several types of molecules. Aerobic organisms like humans require oxygen to live and produce energy. For this reason, an environment with low oxygen levels, also known as a hypoxic environment, causes homeostatic imbalance. Hypoxia causes oxygen demands to exceed the oxygen supply available in the cell, which disrupts the homeostasis of stable oxygen levels. During hypoxic conditions, cells activate adaptive responses to maintain homeostasis with the environment by reducing energy production.[10] Cells must also maintain a stable redox balance in the levels of pro-oxidant molecules, such as reactive oxygen species (ROS), and antioxidant molecules. ROS are highly reactive molecules that contain oxygen with an unpaired valence electron. Many organelles within the cell contain varying levels of ROS.[11] Antioxidants are compounds that neutralize ROS in the cell by donating a valence electron to the reactive oxygen atom.[12] The movement of electrons may trigger a disturbance of the redox balance between ROS and antioxidants, causing a state known as oxidative stress.[13] During redox stress, excess production of ROS can lead to damage of important molecules or organelles, including proteins, lipids, and DNA, potentially leading to cell death.

Maintaining adequate levels of specific proteins and the amino acid cysteine is essential for the homeostasis of the most abundant intracellular antioxidant, glutathione (GSH).[11] GSH is an endogenous antioxidant that is responsible for detoxifying harmful external compounds and neutralizing intracellular ROS.[14] The genetic mutations in cancer cells and the hypoxic environment surrounding many tumours may lead to increased production of ROS and, consequently, cause free radical chain reactions that can damage organelles or critical

molecules like DNA. Oxygen plays a dual role in this mechanism: it is crucial for supporting aerobic life but can also be a serious threat to excess ROS production.[13] Increased ROS levels lead to increased production of GSH, which allows cells to maintain a healthy redox balance and protect against damage from free radicals. The intricate balance between GSH levels and ROS concentration is fundamental for maintaining redox balance. However, elevated glutathione levels may promote resistance to treatments like chemotherapy by preventing cancer cell apoptosis and promoting the efflux of chemotherapy drugs through the multidrug-resistant protein (MRP) transporters.[14]

MRP transporters are one of the largest branches of proteins of the human body called ABC transporters.[15] The main function of this protein family is to transport various molecules including drugs and toxins into or out of the cell.[16] MRPs are crucial in eliminating xenobiotics and maintaining cellular homeostasis within the cell. Specific MRP transporters such as MRP1 actively transport GSH and GSH conjugates to protect cells from oxidative state and free radicals.[17] MRP1 binds to GSH conjugates and transports GSH from intracellular space to extracellular medium to protect cells from foreign toxins.[18] Therefore, when xenobiotics such as chemotherapy drugs enter the cell, the levels of GSH may elevate as a result of maintaining redox balance. This also leads to the overexpression of MRP1 proteins that collaborate with GSH to pump chemotherapeutic agents out of the cell.[19] This process allows cells exposed to drugs to build multidrug resistance (MDR).

2. Autophagy

The function of autophagy is to mitigate cellular stress by removing damaged proteins and organelles. During autophagy, degraded organelles are captured by vesicles known as autophagosomes.[8] Autophagosomes fuse with lysosomes where proteolytic enzymes and a low pH environment break down the autophagosome contents. The products of lysosomal degradation are then transported back to the cytoplasm where they can be recycled and used to synthesize new molecules. Dysfunctional mitochondria or unfolded proteins in cancer cells increase ROS levels, which can cause genomic instability and increase the likelihood of mutations that may promote cancer progression.[1]

Autophagy may act as a tumour suppressive mechanism to inhibit oncogenesis and clear damaged organelles from the cell to prevent persistent tissue damage.[9] However, in advanced stages of cancer progression, autophagy can shift its role to promoting tumour survival by allowing cancer cells to scavenge essential nutrients under stressful conditions, such as chemotherapy treatment and hypoxia. Lu et al found that autophagy may promote tumour dormancy by helping cancer cells survive under stressful conditions.[10] Dormant cancer cells that utilize autophagy for survival may remain inactive for longer periods before later exiting dormancy and repopulating a tumour, leading to delayed recurrence.[10] A few dormant tumour cells might be left behind after chemotherapy and become reactivated to resume cell division and repopulate the tumour. All in all, autophagy can play a dual role in both promoting and inhibiting oncogenesis, which highlights its complexity as a mechanism driving both cancer progression and therapeutic resistance.

There are multiple mechanisms by which cancer cells can increase the expression of certain proteins or organelles that drive autophagy. For example, during cancer progression, there is an increase in the autophagy receptors such as sequestosome 1 (SQSTM1/ p62) and nuclear dot protein 52 kDa (NDP52).[20] By enabling the cancer cells to recycle damaged proteins and organelles, autophagy receptors allow a proliferation of the malignant cells even under cellular stress. Moreover, the low pH level in the cytoplasm and the cancer cell's increased metabolism may increase lysosomal transport.[21] With an increase in lysosomal function, the tumour cells release contents from the lysosome to the outside of cells, called lysosomal exocytosis.[22] This process may promote the invasion and metastasis of malignant cells as it modulates the TME to facilitate cancer progression.[21] Metastasis accounts for the cause of cancer recurrences as cancer cells travel to distant sites through the bloodstream, enabling the formation of secondary tumours.[23] The invasion of new tumours into other body parts is a major medical issue for patients because metastasis commonly occurs in vital organs such as the liver, lungs, brain, and bone.[24] All in all, cancer cells co-opt the homeostatic mechanisms needed for normal cells to drive tumour growth.

Autophagy helps cancer cells build resistance to chemotherapy by recycling damaged organelles and proteins, which allows tumours to adapt to chemotherapy.[25] For this reason, drugs that inhibit autophagy may be used in cancer treatment. Chloroquine (CQ) and hydroxychloroquine (HCQ) are the only clinically approved drugs to inhibit autophagy. In combination with other therapeutic drugs, CQ is effective in inhibiting lysosomes and overcoming drug resistance.[26] While inhibiting autophagy can enhance the efficacy of treatment by preventing cancer cells from adapting to stressful conditions caused by chemotherapy, it can also bring unintended consequences of genome instability and increased metastasic potential.

3. Endoplasmic Reticulum (ER) Stress Response

The endoplasmic reticulum (ER) is the largest organelle in the cell and plays a major role in protein synthesis and folding.[27] Cancer mutations often disrupt a cell's normal function of protein folding, which is the process where the amino acids combine to form a 3D protein structure.[28] Proper protein synthesis is crucial to maintaining ER equilibrium and may potentially contribute to cancer progression, as only correctly folded proteins can exert their function in cells.[29]

ER stress occurs when the uncontrolled growth of tumour cells overwhelms the protein-folding capacity of the ER and thus impairs the ER's ability to fold proteins. The accumulation of misfolded proteins can cause cellular damage and loss of calcium homeostasis. In response to ER stress, cells may activate the unfolded protein response (UPR) as an adaptation mechanism to reinstate ER homeostasis.[30] By expressing UPR, cancer can decrease ER stress and promote tumour survival and growth.

ER stress can alter the behaviour of cancer cells when they are exposed to the (TME), which can hinder the goal of UPR.[31] More specifically, changes in the TME may create a hostile environment characterized by hypoxia and nutrition deprivation, potentially disturbing the normal protein folding mechanism. Under the malignant TME, a balance between proteins in the cell called proteostasis can be disturbed, causing ER stress.[32] To restore ER proteostasis, cells upregulated UPR pathways through transcription.[33]

The three ER stress sensors include: inositol-requiring enzyme 1 (IRE1), pancreatic endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6).[34] These sensors are responsible for activating UPR when the cells are under ER stress by processing three different pathways for adaptive response. Specifically, IRE1 is a protein that increases the production of ER chaperones, which are calcium-binding proteins that act as sensors for the UPR and help proteins fold correctly. On the other hand, ER chaperones can also recognize the misfolded proteins and activate the ER-associated degradation (ERAD) pathway.[35] ERAD blocks protein translation and removes the misfolded proteins to maintain homeostasis and avoid cellular stress.[36]

Under ER stress, the ER chaperones such as 78 kDa glucose-regulated protein (GRP78) increase in the process of UPR, helping fold the misfolded proteins.[37] GRP78 can act as a regulator of the UPR signalling pathway and restore ER homeostasis.[38] However, the increased GRP78 protein also plays a multifunctional role in promoting tumorigenesis.[39] One of the major functions of GRP78 is to block apoptosis by inhibiting caspases, which are the enzymes essential for triggering apoptosis signals.[40] For example, the overexpression of GRP78 confers chemoresistance by increasing the cell's viability and enhancing the cellular defence mechanisms against chemotherapeutic agents.[41] Since tumour progression requires the proliferation of cells, increased activation of ER chaperones indicates that UPR promotes cancer survival. While the adaptive responses manage the unfolded proteins and allow cells to restore homeostasis, they may also play a prominent role in cancer proliferation.

Conclusion

Ultimately, cells activate various response mechanisms such as antioxidant metabolism, autophagy, and ER stress response to maintain their cellular homeostasis. When xenobiotics such as chemotherapeutic agents and other drugs enter one's body, the cells regulate response mechanisms to restore disturbed homeostasis. Specifically, antioxidant metabolism activates to neutralize the free radicals, autophagy recycles cellular components under cell stress and ER stress response UPR manages the uncontrolled folding of proteins by adjusting the protein-folding capacity. However, these same mechanisms used in cancer cells take advantage of this process to perform cancer progression. Excessive cellular mechanisms may have a dual role in cancer where they can act as a tumour suppressor or progressor. Therefore, to be considered healthy cells, they need to maintain an intricate balance between the number of proteins and organelles.

Cancer remains a leading cause of death worldwide: approximately one in five men or women develop cancer in their lifetime.[42] Despite the advancement in cancer therapies, the development of resistance to chemotherapy limits the successful treatment. For example, nearly 90% of cases of the mortality rate is attributed to chemoresistance, further resulting in the progression of metastasis.[43] There are still unanswered questions in this field. For example, it is not fully understood how the TME determines the dual role of homeostatic mechanisms in cancer progression.[44] It is also not fully understood why all three mechanisms sometimes promote tumour growth while acting as tumour suppressors in other situations. Many scientists are working to identify a way to develop specific inhibitors for the mechanisms without affecting

other normal organelles and tissues. It is essential to understand each mechanism's role in cancer promotion and its signalling pathways to develop specific inhibitors that would activate a desired response. By understanding the pathways of homeostatic responses, researchers can further develop effective therapies that can overcome chemoresistance with implications of oncology.

References

1. Chern, Y.-J. & Tai, I. T. (Dysfunctional mitochondria or unfolded protein) Adaptive response of resistant cancer cells to chemotherapy. *Cancer Biol. Med.* 17, 842–863 (2020).
2. Hu, D. *et al.* Epigenetic Modifiers in Cancer Metastasis. *Biomolecules* 14, 916 (2024).
3. Hanahan, D. & Weinberg, R. A. Hallmarks of Cancer: The Next Generation. *Cell* 144, 646–674 (2011).
4. Amjad, M. T., Chidharla, A. & Kasi, A. Cancer Chemotherapy. in *StatPearls* (StatPearls Publishing, Treasure Island (FL), 2024).
5. Wei, G., Wang, Y., Yang, G., Wang, Y. & Ju, R. Recent progress in nanomedicine for enhanced cancer chemotherapy. *Theranostics* 11, 6370–6392 (2021).
6. Rosenberg, H., Pollock, N., Schiemann, A., Bulger, T. & Stowell, K. Malignant hyperthermia: a review. *Orphanet J. Rare Dis.* 10, 93 (2015).
7. Roy, P. S. & Saikia, B. J. Cancer and cure: A critical analysis. *Indian J. Cancer* 53, 441 (2016).
8. Mizushima, N. & Komatsu, M. (The degraded organelles are captured by) Autophagy: Renovation of Cells and Tissues. *Cell* 147, 728–741 (2011).
9. Li, X., He, S. & Ma, B. (Autophagy acts as a tumour suppressor / However, excessive activation of autophagy) Autophagy and autophagy-related proteins in cancer. *Mol. Cancer* 19, 12 (2020).
10. Lu, Z. *et al.* (dormancy) The tumor suppressor gene ARHI regulates autophagy and tumor dormancy in human ovarian cancer cells. *J. Clin. Invest.* 118, 3917–3929 (2008).
11. Wu, G., Lupton, J. R., Turner, N. D., Fang, Y.-Z. & Yang, S. (maintaining adequate protein levels) - Glutathione Metabolism and Its Implications for Health. *J. Nutr.* 134, 489–492 (2004).
12. Bansal, A. & Simon, M. C. (however.. free radical chain) Glutathione metabolism in cancer progression and treatment resistance. *J. Cell Biol.* 217, 2291–2298 (2018).
13. Gosalvez, J., Tvrda, E. & Agarwal, A. (oxygen plays a dual role) - Free radical and superoxide reactivity detection in semen quality assessment: past, present, and future. *J. Assist. Reprod. Genet.* 34, 697–707 (2017).
14. Cole, S. P. C. Targeting Multidrug Resistance Protein 1 (MRP1, *ABCC1*): Past, Present, and Future. *Annu. Rev. Pharmacol. Toxicol.* 54, 95–117 (2014).
15. Sodani, K., Patel, A., Kathawala, R. J. & Chen, Z.-S. Multidrug resistance-associated proteins in multidrug resistance. *Chin. J. Cancer* 31, 58–72 (2012).
16. Müller, M., de Vries, E. G. & Jansen, P. L. Role of multidrug resistance protein (MRP) in glutathione S-conjugate transport in mammalian cells. *J. Hepatol.* 24 Suppl 1, 100–108 (1996).
17. Cole, S. P. C. & Deeley, R. G. Transport of glutathione and glutathione conjugates by MRP1. *Trends Pharmacol. Sci.* 27, 438–446 (2006).
18. Bukowski, K., Kciuk, M. & Kontek, R. Mechanisms of Multidrug Resistance in Cancer

Chemotherapy. *Int. J. Mol. Sci.* 21, 3233 (2020).
19. Rappa, G., Lorico, A., Flavell, R. A. & Sartorelli, A. C. Evidence that the multidrug resistance protein (MRP) functions as a co-transporter of glutathione and natural product toxins. *Cancer Res.* 57, 5232–5237 (1997).
20. Cerda-Troncoso, C., Varas-Godoy, M. & Burgos, P. V. Pro-Tumoral Functions of Autophagy Receptors in the Modulation of Cancer Progression. *Front. Oncol.* 10, 619727 (2021).
21. Eriksson, I. & Öllinger, K. Lysosomes in Cancer—At the Crossroad of Good and Evil. *Cells* 13, 459 (2024).
22. Buratta, S. *et al.* Lysosomal Exocytosis, Exosome Release and Secretory Autophagy: The Autophagic- and Endo-Lysosomal Systems Go Extracellular. *Int. J. Mol. Sci.* 21, 2576 (2020).
23. Seyfried, T. N. & Huysentruyt, L. C. On the Origin of Cancer Metastasis. *Crit. Rev. Oncog.* 18, 43–73 (2013).
24. Martin, T. A., Ye, L., Sanders, A. J., Lane, J. & Jiang, W. G. Cancer Invasion and Metastasis: Molecular and Cellular Perspective. in *Madame Curie Bioscience Database [Internet]* (Landes Bioscience, 2013).
25. Miller, D. R. & Thorburn, A. Autophagy and Organelle Homeostasis in Cancer. *Dev. Cell* 56, 906–918 (2021).
26. Towers, C. G. & Thorburn, A. Therapeutic Targeting of Autophagy. *EBioMedicine* 14, 15–23 (2016).
27. Schwarz, D. S. & Blower, M. D. The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell. Mol. Life Sci. CMLS* 73, 79–94 (2015).
28. Protein Folding - an overview | ScienceDirect Topics. https://www.sciencedirect.com/topics/neuroscience/protein-folding.
29. Zhang, H., Gong, W., Wu, S. & Perrett, S. Studying protein folding in health and disease using biophysical approaches. *Emerg. Top. Life Sci.* 5, 29–38 (2021).
30. Oakes, S. A. & Papa, F. R. The Role of Endoplasmic Reticulum Stress in Human Pathology. *Annu. Rev. Pathol.* 10, 173–194 (2015).
31. Chen, X. & Cubillos-Ruiz, J. R. Endoplasmic reticulum stress signals in the tumour and its microenvironment. *Nat. Rev. Cancer* 21, 71–88 (2021).
32. Valenzuela, V., Jackson, K. L., Sardi, S. P. & Hetz, C. Gene Therapy Strategies to Restore ER Proteostasis in Disease. *Mol. Ther.* 26, 1404–1413 (2018).
33. Genereux, J. C. & Wiseman, R. L. Regulating extracellular proteostasis capacity through the unfolded protein response. *Prion* 9, 10–21 (2015).
34. Corazzari, M., Gagliardi, M., Fimia, G. M. & Piacentini, M. Endoplasmic Reticulum Stress, Unfolded Protein Response, and Cancer Cell Fate. *Front. Oncol.* 7, 78 (2017).
35. Krshnan, L., van de Weijer, M. L. & Carvalho, P. Endoplasmic Reticulum–Associated Protein Degradation. *Cold Spring Harb. Perspect. Biol.* 14, a041247 (2022).
36. Krivoruchko, A. & Storey, K. B. Turtle anoxia tolerance: Biochemistry and gene regulation. *Biochim. Biophys. Acta BBA - Gen. Subj.* 1850, 1188–1196 (2015).
37. Luo, B. & Lee, A. S. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anti-cancer therapies. *Oncogene* 32, 10.1038/onc.2012.130 (2013).
38. Repges, E. The endoplasmic reticulum (ER) chaperone GRP78 is secreted during ER Stress and alleviates endothelial cell inflammation.

39. Luo, B. & Lee, A. S. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anti-cancer therapies. *Oncogene* 32, 10.1038/onc.2012.130 (2013).
40. Creagh, E. M., Conroy, H. & Martin, S. J. Caspase-activation pathways in apoptosis and immunity. *Immunol. Rev.* 193, 10–21 (2003).
41. Sozen, E. & Ozer, N. K. Impact of high cholesterol and endoplasmic reticulum stress on metabolic diseases: An updated mini-review. *Redox Biol.* 12, 456–461 (2017).
42. Bray, F. *et al.* Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* 74, 229–263 (2024).
43. Frontiers | Multidrug Resistance in Cancer: Understanding Molecular Mechanisms, Immunoprevention and Therapeutic Approaches. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.891652/full.
44. Lindqvist, L. M., Simon, A. K. & Baehrecke, E. H. Current questions and possible controversies in autophagy. *Cell Death Discov.* 1, 1–7 (2015).