INSIGHTS INTO THE ROLE OF ENDOLYSOSOMAL CALCIUM SIGNALLING IN EPITHELIAL-TO-MESENCHYMAL TRANSITION, AUTOPHAGY AND CHEMOSENSITIVITY OF COLORECTAL CANCER

Colorectal cancer (CRC) is a prevalent and deadly disease. In 2020, nearly 2 million cases were diagnosed globally, resulting in approximately 1 million fatalities annually [1]. The burden of CRC is projected to escalate to 3.2 million new cases and 1.6 million deaths by 2040. In Malaysia, CRC ranks as the second most common cancer and the third leading cause of cancer-related deaths [2]. The CRC treatment plan hinges on the tumour location and disease stage. Surgery is the primary approach, and radiotherapy or chemotherapy may be recommended to enhance prognosis. However, in metastatic CRC, chemotherapy often leads to drug resistance and disease progression. Two critical factors that contribute to this resistance are autophagy and epithelial-to-mesenchymal transition (EMT) [3].

Autophagy, a normal physiological process, maintains cellular vitality and homeostasis. Surprisingly, studies have revealed its significance in cancer, particularly its association with drug resistance. Metastatic cancer cells activate autophagy in response to cytotoxic drugs, thereby evading cell death. Interestingly, inhibiting autophagy can sensitise cancer cells to cell death stimuli and anticancer agents [4].

EMT is a critical process during embryogenesis that is later physiologically suppressed. However, it can be reactivated in adulthood in a variety of conditions, including wound healing, fibrosis, and cancer. In the early 1990s, a hypothesis emerged linking EMT to chemoresistance. Since then, numerous malignancies have been found to overexpress EMT markers following therapy with diverse chemotherapeutic drugs. For instance, cyclophosphamide resistance in transgenic mice with breast cancer was linked to EMT markers Zeb1 and Zeb2 expression, diminished proliferation, and apoptotic tolerance. Additionally, patients with the mesenchymal subtype of CRC (CMS4) displayed chemoresistance profiles in response to Hsp90 inhibitors in preclinical models [5] and unresponsiveness to adjuvant 5-fluorouracil therapy in a clinical cohort [6].

Endolysosomal (EL) calcium homeostasis is critical in maintaining endosomes and lysosomes physiological functions such as protein and lipid trafficking, protein degradation and autophagy. Perturbations of the homeostasis may lead to diseases such as cancer [7]. Two key calcium-permeable channels, mucolipin-1 (TRPML1) and two-pore channels (TPC), are responsible for preserving this homeostasis. Loss of TRPML1 has been shown to cause autophagy defect. Impaired lysosomal pH, accumulation of autophagosomes and abnormal mitochondria were among signs of autophagy defects observed with TRPML1 failure [8]. Interestingly, pharmacological stimulation of TRPML1 promotes autophagosome maturation [9]. TPC has also been shown to regulate autophagy as demonstrated by Sun et al [10]. Pereira and colleagues also demonstrated that calcium released via TPC induced autophagy in rat astrocytes [11]. Another group has proposed the involvement of TPC2 in leucine-richrepeatkinase-2 (LRRK2) induced autophagy [12].

Despite these findings, the functional significance of TRPML1- and TPC-mediated calcium release in autophagy and EMT in CRC remains largely unexplored. Furthermore, their potential to sensitise cancer cells to anticancer agents remains unknown, despite their proposed roles in autophagy and EL trafficking [7]. Given that inhibiting autophagy has been shown to sensitize cancer cells to chemotherapy [13], it would be intriguing to explore if TRPML1 and TPC inhibition would produce similar outcomes. In addition, the presence of functional EL calcium signalling in metastatic CRC cells and the involvement of TPC1 in modulating foetal calf serum-induced calcium signals, proliferation, and extracellular signal-regulated kinase and Akt phosphorylation suggest a potential role of EL calcium in the progression and metastasis of CRC [14]. Thus, this study is proposed to investigate the role of TRPML1 and TPC in CRC. Their potential in sensitising cancer cells to anticancer agents will also be evaluated.

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References:

1. Xi, Y. and P. Xu, Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol, 2021. 14(10): p. 101174.
2. Schliemann, D., et al., Change in public awareness of colorectal cancer symptoms following the Be Cancer Alert Campaign in the multi-ethnic population of Malaysia. BMC Cancer, 2020. 20(1): p. 252.
3. Wang, Q., et al., Drug Resistance in Colorectal Cancer: From Mechanism to Clinic. Cancers (Basel), 2022. 14(12):2928.
4. Cheng, X., et al., Targeting autophagy enhances apatinib-induced apoptosis via endoplasmic reticulum stress for human colorectal cancer. Cancer Lett, 2018. 431: p. 105-114.
5. Sveen, A., et al., Colorectal Cancer Consensus Molecular Subtypes Translated to Preclinical Models Uncover Potentially Targetable Cancer Cell Dependencies. Clin Cancer Res, 2018. 24(4): p. 794-806.
6. Roepman, P., et al., Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-tomesenchymal transition. Int J Cancer, 2014. 134(3): p. 552-62.
7. Wu, Y., P. Huang, and X.P. Dong, Lysosomal Calcium Channels in Autophagy and Cancer. Cancers (Basel), 2021. 13(6):1299.
8. Vergarajauregui, S., et al., Autophagic dysfunction in mucolipidosis type IV patients. Hum Mol Genet, 2008. 17(17): p. 2723-37.
9. Pollmanns, M.R., et al., Activated Endolysosomal Cation Channel TRPML1 Facilitates Maturation of α-Synuclein-Containing Autophagosomes. Frontiers in Cellular Neuroscience, 2022. 16:861202.
10. Sun, W. and J. Yue, TPC2 mediates autophagy progression and extracellular vesicle secretion in cancer cells. Exp Cell Res, 2018. 370(2): p. 478-489.
11. Pereira, G.J., et al., Nicotinic acid adenine dinucleotide phosphate (NAADP) regulates autophagy in cultured astrocytes. J Biol Chem, 2011. 286(32): p. 27875-81.
12. Gómez-Suaga, P., et al., Leucine-rich repeat kinase 2 regulates autophagy through a calcium-dependent pathway involving NAADP. Hum Mol Genet, 2012. 21(3): p. 511-25.
13. Aydinlik, S., et al., Enhanced cytotoxic activity of doxorubicin through the inhibition of autophagy in triple negative breast cancer cell line. Biochim Biophys Acta Gen Subj, 2017. 1861(2): p. 49-57.
14. Faris, P., et al., Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP) Induces Intracellular Ca(2+) Release through the Two-Pore Channel TPC1 in Metastatic Colorectal Cancer Cells. Cancers (Basel), 2019. 11(4):542.

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