Delta University Scientific Journal
Journal home page: https://dusj.journals.ekb.eg

Hallmarks of cancer: Guided research toward cancer prevention and potential limitations in recent therapeutic interventions

Mohamed M. Salama [a*], Yasmin A. Salama [a], Rania M. Khalil[a]

[a] *Department of pharmacology and biochemistry, Faculty of Pharmacy, Delta University for Science and Technology, Gamasa, Dakahlia, 35712, Egypt.*
* *Corresponding author: [Mohamed M. Salama]; Tel: [+2 01069536521]; E-mail address: [dr.mohamed.salama@deltauniv.edu.eg]*

Abstract:

Cancer remains one of the biggest global health issues today due to the disease's complexity and mutability. Moreover, despite the major advances in understanding its etiology and pathogenesis to improve prevention and treatment methods, the disease remains a major cause of natural death worldwide. Regardless of the cause or genotype of cancer, the malignancy phenotype at the cellular level results in observable physicochemical modifications. In this review, we will get focus on ten hallmarks of cancer acquired by most and perhaps all types of human malignancies, as a successful approach to combat cancer along with enhancing cancer prevention and revealing potential limitations in recent therapeutic interventions.

Keywords: *Cancer, Proliferative signaling, Apoptosis, Angiogenesis, Metastasis.*

Introduction:

Cancer is a major public health concern, which is ranked as the second most common cause of worldwide morbidity and mortality among non-communicable diseases after cardiovascular diseases (Madia et al., 2019). According to global cancer statistics (GLOBOCAN 2020) estimates, there were approximately 19.3 million new cancer cases and 10.0 million cancer deaths worldwide (Sung et al., 2021), which were significantly higher than the last statistics in 2018 (Bray et al., 2018). Besides, the cancer incidence rate is projected to increase to 24.1 million annually by 2030 and to 29.5 million by 2040 (Madia et al., 2019; Sung et al., 2021).

Classical hallmarks of cancer

Cancer refers to the rapid replication of abnormal cells with the potential to overgrow, invade the adjacent tissue, and metastasize to other organs (Wu et al., 2021). Regardless of the cause or genotype of cancer, the malignancy phenotype at the cellular level results in observable physicochemical modifications (Souho et al., 2018). The six classical hallmarks characterizing neoplasia, delineated in Hanahan and Weinberg (2000), were described as “acquired capabilities shared by most and perhaps all types of human cancers”. .

1. **Sustaining proliferative signaling**

Normal cells depend on mitogenic growth signals before they can enter a proliferative phase that transmitted to the cell *via* transmembrane receptors, binding three classes of signaling molecules: extracellular matrix components, cell-to-cell adhesion molecules, and mostly diffusible growth factors (Kim et al., 2011; Perrimon et al., 2012). Deregulation of mitogenic signaling to support proliferation is considered the chief hallmark of malignant transformation (Caon et al., 2020; Ruiz-Casado et al., 2017).

Various alterations can lead to the autonomy of growth signals. Cells may start to secrete their growth factors or stimulate a neighboring cell within their microenvironment to provide the growth factors. Also, receptors can be over-expressed above physiological levels or truncated in a way that regulatory elements are missing.

Subsequently, minute amounts of ligand or no ligand at all are sufficient to trigger proliferation. Another frequent mechanism is the constitutive activation of the intracellular signal transduction circuitry (Sever et al., 2015; Witsch et al., 2010).

2. Insensitivity to growth inhibition

Anti-growth signals ensure homeostasis in healthy tissues by counteracting signals that induce proliferation. Some of the signaling pathways blocking entry into the proliferative phase of the cell cycle are relayed *via* the retinoblastoma (Rb) protein and p53. Transforming growth factor-β (TGF-β) is a ligand that leads to the blockade of Rb protein phosphorylation and subsequent inactivation of E2 transcription factor (E2F). E2F control the expression of groups of genes essential for cell progression from the G_1 into the S phase. Loss of a functional TGF-β receptor or mutations in downstream signaling molecules makes the cell resistant to growth inhibition (Amin et al., 2015; Tarasewicz et al., 2012).

3. Evasion of programmed cell death (Apoptosis)

Apoptosis is an organized process that leads to programmed self-destruction (Menyhárt et al., 2016). Two main apoptotic pathways are recognized. The extrinsic pathway is mediated by cell surface death receptors activation while the intrinsic pathway is triggered by internal damage leading to mitochondrial cytochrome c release (Souho et al., 2018). The activation of apoptotic pathways lead to cell shrinkage, chromatin condensation, DNA fragmentation, and formation of cytoplasmic blebs and apoptotic bodies, containing the contents of the dead cell, which is phagocytosed by the surrounding cells (Xu et al., 2019).

However, deregulated apoptotic signaling in cancer, particularly the activation of anti-apoptotic systems, allows cancer cells to escape apoptosis leading to uncontrolled proliferation resulting in tumor survival, therapeutic resistance, and recurrence of cancer (Mohammad et al., 2015). An important inducer of apoptosis is p53, one of the most commonly affected tumor suppressors and mutated in more than 50% of human cancers (Aubrey et al., 2018). Besides, many tumors also overexpress endogenous inhibitors of apoptosis, such as members of the B-cell Lymphoma-2 (Bcl-2) protein family (Knight et al., 2019).

4. Limitless replicative potential

Cells division stops when their telomeres are critically short. Telomeres are structures at the ends of chromosomes that protect the termini of chromosomes from premature fusion resulting in karyotypic disarray (aneuploidy) and cell death (Aksenova et al., 2019). During DNA replication in each cell cycle, 50–100 base pair of telomeric DNA are lost, before they are eroded and lose their protective function, causing irreversible, non-proliferative state (replicative senescence) and finally death (Shammas et al., 2008; van Deursen, 2014).

Telomerase, a specific DNA polymerase, adds telomere hexanucleotide repeats at the termini of telomeric DNA. It is nearly absent in normal cells, but its expression is up-regulated to significant levels in highly proliferative cells, such as stem cells and germ cells, as well as in almost all types of malignant cells. With active telomerase, a cell can divide infinitely (Low et al., 2013; Menyhárt et al., 2016).

5. Sustained angiogenesis

The growth of solid tumors is limited by the availability of oxygen and nutrients. Hypoxic tissue conditions at the beginning of tumor growth trigger local angiogenesis (Ramjiawan et al., 2017), and lymph-angiogenesis (Ji, 2014). This hypoxic response is essentially mediated by the hypoxia-inducible factor-1α (HIF-1α) *via* nuclear factor-κB (NF-κB) signaling (Caon et al., 2020). HIF-1α initiates a signaling cascade that activates the transcription of growth factors [like vascular endothelial growth factor (VEGF), fibroblast growth factor, and angiopoietin], cytokines, and extracellular matrix remodelers to generate new vasculature (Muz et al., 2015).

6. Tissue invasion and metastasis

Tumor metastasis is a multistage process that generally includes the malignant tumor cells leaving the primary lesion, penetrating through the vessels and entering the host blood and lymphatic circulation, or directly spreading through the body cavity, reaching the distant site and continuing to proliferate and grow, eventually forming the same type of tumor as the primary lesion **(**Das et al., 2020**;** Mierke, 2019**)**. The invasion and metastasis of cancer cells are closely related to poor prognosis and patient survival and account for 90% of all cancer deaths **(**Caon et al., 2020**;** Wang et al., 2021**)**.

The invasion-metastatic cascade requires cancer cells to undergo epithelial-to-mesenchymal transition. This makes tumor cells acquire some characteristics including the loss of cell adherence proteins, alteration of cell morphology, increased motility, expression of matrix-degrading proteinases, and resistance to apoptosis. Therefore, the transformed tumor cells have a stronger ability to metastasize and invade and are more likely to survive in the

blood. These tumor cells reach a distant organ, return to their epithelial phenotype (mesenchymal-to-epithelial transition), seed in their new location, and resume proliferation to generate secondary tumors (Karlsson et al., 2017; Ribatti et al., 2020).

Revised concepts and new hallmarks

Significant advances in understanding malignant conversion have led to revealing further features of cancer. Hanahan and Weinberg (2011) extended their original six hallmarks adding four more new hallmarks.

1. **Genome instability and mutation**

Cancer involves the gradual accumulation of genomic changes and mutations. Changes may arise through direct DNA mutations or through epigenetic modifications that can change protein expression levels and affect genomic integrity. DNA-repair pathways including base excision repair, nucleotide excision repair, mismatch repair, non-homologous end joining, and homology-directed repair, play a critical role in maintaining genomic integrity (Kagohara et al., 2018; Yao et al., 2014).

A deficiency of these pathways may therefore lead to genomic instability which is a hallmark of almost all types of human malignancies. These types of genomic instability have been characterized in tumor cells, in form of chromosomal instability, such as copy number variation and aneuploidy, microsatellite instability manifested by the expansion or reduction of short nucleotide repeats present in microsatellite sequences, and base-pair mutations, including small-scale insertions, deletions, substitutions, and point mutations in oncogenes and tumor-suppressor genes which play an important role in the initiation of tumorigenesis **(**Iengar, 2012**;** Soca-Chafre et al., 2019**)**.

2. **Tumor-promoting inflammation**

There are two types of inflammation associated with cancer; tumor-promoting inflammation, which promotes cell survival, aggressiveness, and metastasis and is associated with chronic inflammation and T helper 2 cells responses. The other type is tumor-destroying inflammation, which induces cancer cell destruction and is related to acute inflammation and T helper type 1 cells responses. Tumor-promoting inflammation is characterized by a tumor microenvironment with increased levels of growth factors, angiogenic factors, and tissue-remodeling enzymes secreted from infiltrating immune cells. As a result, all these factors can aid malignant cells to proliferate, survive, and even metastasize (Cho et al., 2020; Palucka et al., 2016).

Tumor-associated macrophages (TAMs) are essential drivers of tumor-promoting inflammation and are associated with an unfavorable prognosis in several types of cancers (Mantovani et al., 2017). TAMs have the potential ability to differentiate into either M1 or M2 macrophages, which have opposing effects on tumor progression. Activated M1 macrophages release pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β), whereas M2 macrophages lack the function of phagocytizing tumor cells, produce proteolytic enzymes and growth factors, suppress the immune response, and contribute to hypoxia-induced angiogenesis, thus promoting tumor cell proliferation and migration (Mwafy et al., 2020; Zhou et al., 2020).

3. **Reprogramming of energy metabolism**

Normal cells maximize ATP availability by using glycolysis, tricarboxylic acid cycle, and aerobic mitochondrial oxidative phosphorylation (Bonora et al., 2012). In contrast, cancer cells focus on sustaining rapid cell growth and division which requires maximization of the synthesis of macromolecules, nucleotides, proteins, lipids, and glycans. Therefore, rather than ATP, cancer cells need carbon skeletons, nitrogen, and cytosolic reduced nicotinamide adenine dinucleotide phosphate (NADPH) for anabolic reactions (Porporato et al., 2018).

With this last concept and considering the limited availability of oxygen in tumors, the mitochondria in cancer cells do not work to produce ATP but to supply the cells with substrates for biosynthesis. Dividing cancer cells have increased glucose uptake rates and by simultaneously increasing the rate of glycolysis while limiting oxidative phosphorylation, cells enter a state termed aerobic glycolysis, also known as the Warburg effect. Increased glycolysis can allow the diversion of glycolytic intermediates into biosynthetic pathways required for new cell assembly (Schwartz et al., 2017; Vaupel et al., 2019).

4. **Avoiding immune destruction**

Tumor cells adopt a variety of mechanisms to avoid immune recognition and immune-mediated destruction. Inflammatory immune cells include TAMs, cytotoxic T lymphocytes, T helper lymphocytes, natural killer cells, regulatory T (Treg) cells, and myeloid-derived suppressor cells (MDSCs). Among them, Treg cells, MDSCs, and macrophages, recruited by tumor-derived chemokines, are mainly involved in the immunosuppressive

action *via* the secretion of key molecules, such as TGF-β, prostaglandin E2, and IL-10 (Argyle et al., 2018; Nicolini et al., 2018).

Most cancer cells express a large number of inhibitory checkpoint proteins that bind programmed cell death1 (PD1) and cytotoxic T lymphocyte associated protein 4 (CTLA4). Both are inhibitory checkpoint receptors expressed on the surface of activated T cells that downregulate immune responses, and trigger a cascade of signals that inhibit T cell activation, proliferation, survival, and cytotoxic secretion within cancer cells (Han et al., 2020; Seidel et al., 2018). Moreover, cancer cells may lose the expression of tumor antigens on the cell surface, thus avoiding the recognition by cytotoxic T cells (Gonzalez et al., 2018).

In summary, Cancer initiation and progression are modulated through genomic mutations, metabolic dysfunction, tumor-promoting inflammation, immune response modulation, and sustained proliferative capabilities along with its ability to induce angiogenesis and metastasis. We hope this review help as a guide for cancer prevention and potential limitations in recent therapeutic interventions.

Disclosure

The authors declare that there are no conflicts of interest.

References

Aksenova, A. Y., & Mirkin, S. M. (2019). At the Beginning of the End and in the Middle of the Beginning: Structure and Maintenance of Telomeric DNA Repeats and Interstitial Telomeric Sequences. *Genes, 10*(2), 118. doi:10.3390/genes10020118

Amin, A. R. M. R., Karpowicz, P. A., Carey, T. E., Arbiser, J., Nahta, R., Chen, Z. G., . . . Shin, D. M. (2015). Evasion of anti-growth signaling: A key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds. *Seminars in Cancer Biology, 35 Suppl*, S55-S77. doi:10.1016/j.semcancer.2015.02.005

Argyle, D., & Kitamura, T. (2018). Targeting Macrophage-Recruiting Chemokines as a Novel Therapeutic Strategy to Prevent the Progression of Solid Tumors. *Front Immunol, 9*, 2629. doi:10.3389/fimmu.2018.02629

Aubrey, B. J., Kelly, G. L., Janic, A., Herold, M. J., & Strasser, A. (2018). How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? *Cell death and differentiation, 25*(1), 104-113. doi:10.1038/cdd.2017.169

Bonora, M., Patergnani, S., Rimessi, A., De Marchi, E., Suski, J. M., Bononi, A., . . . Pinton, P. (2012). ATP synthesis and storage. *Purinergic signalling, 8*(3), 343-357. doi:10.1007/s11302-012-9305-8

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin, 68*(6), 394-424. doi:10.3322/caac.21492

Caon, I., Bartolini, B., Parnigoni, A., Caravà, E., Moretto, P., Viola, M., . . . Passi, A. (2020). Revisiting the hallmarks of cancer: The role of hyaluronan. *Seminars in Cancer Biology, 62*, 9-19. doi:https://doi.org/10.1016/j.semcancer.2019.07.007

Cho, S.-Y., Oh, Y., Jeong, E. M., Park, S., Lee, D., Wang, X., . . . Lee, C. (2020). Amplification of transglutaminase 2 enhances tumor-promoting inflammation in gastric cancers. *Experimental & Molecular Medicine, 52*(5), 854-864. doi:10.1038/s12276-020-0444-7

Das, S. S., Alkahtani, S., Bharadwaj, P., Ansari, M. T., Alkahtani, M. D. F., Pang, Z., . . . Aminabhavi, T. M. (2020). Molecular insights and novel approaches for targeting tumor metastasis. *International Journal of Pharmaceutics, 585*, 119556. doi:https://doi.org/10.1016/j.ijpharm.2020.119556

Gonzalez, H., Hagerling, C., & Werb, Z. (2018). Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes & development, 32*(19-20), 1267-1284. doi:10.1101/gad.314617.118

Han, Y., Liu, D., & Li, L. (2020). PD-1/PD-L1 pathway: current researches in cancer. *American journal of cancer research, 10*(3), 727-742.

Hanahan, D., & Weinberg, R. A. (2000). The Hallmarks of Cancer. *Cell, 100*(1), 57-70. doi:https://doi.org/10.1016/S0092-8674(00)81683-9

Hanahan, D., & Weinberg, Robert A. (2011). Hallmarks of Cancer: The Next Generation. *Cell, 144*(5), 646-674. doi:https://doi.org/10.1016/j.cell.2011.02.013

Iengar, P. (2012). An analysis of substitution, deletion and insertion mutations in cancer genes. *Nucleic acids research, 40*(14), 6401-6413. doi:10.1093/nar/gks290

Ji, R. C. (2014). Hypoxia and lymphangiogenesis in tumor microenvironment and metastasis. *Cancer Lett, 346*(1), 6-16. doi:10.1016/j.canlet.2013.12.001

Kagohara, L. T., Stein-O'Brien, G. L., Kelley, D., Flam, E., Wick, H. C., Danilova, L. V., . . . Fertig, E. J. (2018). Epigenetic regulation of gene expression in cancer: techniques, resources and analysis. *Briefings in functional genomics, 17*(1), 49-63. doi:10.1093/bfgp/elx018

Karlsson, M. C., Gonzalez, S. F., Welin, J., & Fuxe, J. (2017). Epithelial-mesenchymal transition in cancer metastasis through the lymphatic system. *Mol Oncol, 11*(7), 781-791. doi:10.1002/1878-0261.12092

Kim, S. H., Turnbull, J., & Guimond, S. (2011). Extracellular matrix and cell signalling: the dynamic cooperation of integrin, proteoglycan and growth factor receptor. *J Endocrinol, 209*(2), 139-151. doi:10.1530/joe-10-0377

Knight, T., Luedtke, D., Edwards, H., Taub, J. W., & Ge, Y. (2019). A delicate balance – The BCL-2 family and its role in apoptosis, oncogenesis, and cancer therapeutics. *Biochemical Pharmacology, 162*, 250-261. doi:https://doi.org/10.1016/j.bcp.2019.01.015

Low, K. C., & Tergaonkar, V. (2013). Telomerase: central regulator of all of the hallmarks of cancer. *Trends in Biochemical Sciences, 38*(9), 426-434. doi:https://doi.org/10.1016/j.tibs.2013.07.001

Madia, F., Worth, A., Whelan, M., & Corvi, R. (2019). Carcinogenicity assessment: Addressing the challenges of cancer and chemicals in the environment. *Environment International, 128*, 417-429. doi:https://doi.org/10.1016/j.envint.2019.04.067

Mantovani, A., Marchesi, F., Malesci, A., Laghi, L., & Allavena, P. (2017). Tumour-associated macrophages as treatment targets in oncology. *Nature reviews. Clinical oncology, 14*(7), 399-416. doi:10.1038/nrclinonc.2016.217

Menyhárt, O., Harami-Papp, H., Sukumar, S., Schäfer, R., Magnani, L., de Barrios, O., & Győrffy, B. (2016). Guidelines for the selection of functional assays to evaluate the hallmarks of cancer. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1866*(2), 300-319. doi:https://doi.org/10.1016/j.bbcan.2016.10.002

Mierke, C. T. (2019). The matrix environmental and cell mechanical properties regulate cell migration and contribute to the invasive phenotype of cancer cells. *Rep Prog Phys, 82*(6), 064602. doi:10.1088/1361-6633/ab1628

Mohammad, R. M., Muqbil, I., Lowe, L., Yedjou, C., Hsu, H.-Y., Lin, L.-T., . . . Azmi, A. S. (2015). Broad targeting of resistance to apoptosis in cancer. *Seminars in Cancer Biology, 35*, S78-S103. doi:https://doi.org/10.1016/j.semcancer.2015.03.001

Muz, B., de la Puente, P., Azab, F., & Azab, A. K. (2015). The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckland, N.Z.), 3*, 83-92. doi:10.2147/HP.S93413

Mwafy, S. E., & El-Guindy, D. M. (2020). Pathologic assessment of tumor-associated macrophages and their histologic localization in invasive breast carcinoma. *Journal of the Egyptian National Cancer Institute, 32*(1), 6. doi:10.1186/s43046-020-0018-8

Nicolini, A., Ferrari, P., Rossi, G., & Carpi, A. (2018). Tumour growth and immune evasion as targets for a new strategy in advanced cancer. *Endocr Relat Cancer, 25*(11), R577–r604. doi:10.1530/erc-18-0142

Palucka, A. K., & Coussens, L. M. (2016). The Basis of Oncoimmunology. *Cell, 164*(6), 1233-1247. doi:10.1016/j.cell.2016.01.049

Perrimon, N., Pitsouli, C., & Shilo, B.-Z. (2012). Signaling mechanisms controlling cell fate and embryonic patterning. *Cold Spring Harbor perspectives in biology, 4*(8), a005975-a005975. doi:10.1101/cshperspect.a005975

Porporato, P. E., Filigheddu, N., Pedro, J. M. B., Kroemer, G., & Galluzzi, L. (2018). Mitochondrial metabolism and cancer. *Cell Res, 28*(3), 265-280. doi:10.1038/cr.2017.155

Ramjiawan, R. R., Griffioen, A. W., & Duda, D. G. (2017). Anti-angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? *Angiogenesis, 20*(2), 185-204. doi:10.1007/s10456-017-9552-y

Ribatti, D., Tamma, R., & Annese, T. (2020). Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. *Translational Oncology, 13*(6), 100773. doi:https://doi.org/10.1016/j.tranon.2020.100773

Ruiz-Casado, A., Martín-Ruiz, A., Pérez, L. M., Provencio, M., Fiuza-Luces, C., & Lucia, A. (2017). Exercise and the Hallmarks of Cancer. *Trends in Cancer, 3*(6), 423-441. doi:https://doi.org/10.1016/j.trecan.2017.04.007

Schwartz, L., Supuran, C. T., & Alfarouk, K. O. (2017). The Warburg Effect and the Hallmarks of Cancer. *Anticancer Agents Med Chem, 17*(2), 164-170. doi:10.2174/1871520616666161031143301

Seidel, J. A., Otsuka, A., & Kabashima, K. (2018). Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Frontiers in oncology, 8*, 86-86. doi:10.3389/fonc.2018.00086

Sever, R., & Brugge, J. S. (2015). Signal transduction in cancer. *Cold Spring Harbor perspectives in medicine, 5*(4), a006098. doi:10.1101/cshperspect.a006098

Shammas, M. A., Koley, H., Bertheau, R. C., Neri, P., Fulciniti, M., Tassone, P., . . . Munshi, N. C. (2008). Telomerase inhibitor GRN163L inhibits myeloma cell growth in vitro and in vivo. *Leukemia, 22*(7), 1410-1418. doi:10.1038/leu.2008.81

Soca-Chafre, G., Montiel-Dávalos, A., Rosa-Velázquez, I. A. D. L., Caro-Sánchez, C. H. S., Peña-Nieves, A., & Arrieta, O. (2019). Multiple Molecular Targets Associated with Genomic Instability in Lung Cancer. *International journal of genomics, 2019*, 9584504-9584504. doi:10.1155/2019/9584504

Souho, T., Lamboni, L., Xiao, L., & Yang, G. (2018). Cancer hallmarks and malignancy features: Gateway for improved targeted drug delivery. *Biotechnology Advances, 36*(7), 1928-1945. doi:https://doi.org/10.1016/j.biotechadv.2018.08.001

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin, 71*(3), 209-249. doi:10.3322/caac.21660

Tarasewicz, E., & Jeruss, J. S. (2012). Phospho-specific Smad3 signaling: impact on breast oncogenesis. *Cell cycle (Georgetown, Tex.), 11*(13), 2443-2451. doi:10.4161/cc.20546

van Deursen, J. M. (2014). The role of senescent cells in ageing. *Nature, 509*(7501), 439-446. doi:10.1038/nature13193

Vaupel, P., Schmidberger, H., & Mayer, A. (2019). The Warburg effect: essential part of metabolic reprogramming and central contributor to cancer progression. *Int J Radiat Biol, 95*(7), 912-919. doi:10.1080/09553002.2019.1589653

Wang, K., Chen, Q., Shao, Y., Yin, S., Liu, C., Liu, Y., . . . Yu, H. (2021). Anticancer activities of TCM and their active components against tumor metastasis. *Biomedicine & Pharmacotherapy, 133*, 111044. doi:https://doi.org/10.1016/j.biopha.2020.111044

Witsch, E., Sela, M., & Yarden, Y. (2010). Roles for growth factors in cancer progression. *Physiology (Bethesda, Md.), 25*(2), 85-101. doi:10.1152/physiol.00045.2009

Wu, J., Zhang, Y., Ye, L., & Wang, C. (2021). The anti-cancer effects and mechanisms of lactic acid bacteria exopolysaccharides in vitro: A review. *Carbohydrate Polymers, 253*, 117308. doi:https://doi.org/10.1016/j.carbpol.2020.117308

Xu, X., Lai, Y., & Hua, Z.-C. (2019). Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Bioscience reports, 39*(1), BSR20180992. doi:10.1042/BSR20180992

Yao, Y., & Dai, W. (2014). Genomic Instability and Cancer. *Journal of carcinogenesis & mutagenesis, 5*, 1000165. doi:10.4172/2157-2518.1000165

Zhou, J., Tang, Z., Gao, S., Li, C., Feng, Y., & Zhou, X. (2020). Tumor-Associated Macrophages: Recent Insights and Therapies. *Frontiers in oncology, 10*, 188-188. doi:10.3389/fonc.2020.00188