How to Cite:
Gupta, A., Sati, P., Acharya, K., Shingadia, H., Joseph, A. S. M., Jaganathan, R., & Mukherjee, S. (2022). Understanding cell to cell communication in tumor microenvironment: Translating the present knowledge to therapeutics. *International Journal of Health Sciences*, *6*(S6), 9721–9731.
https://doi.org/10.53730/ijhs.v6nS6.12539

Understanding cell to cell communication in tumor microenvironment: Translating the present knowledge to therapeutics

Akshita Gupta
Department of Microbiology, University of Nirwan
*Corresponding author email: 24akshitagupta@gmail.com

Pallavi Sati
High Altitude Plant Physiology, Research Center Hemwati Nandan,Bahuguna Garhwal University, Srinagar
Email: pallavisati45@gmail.com

Kirtish Acharya
Department of Physiology, MKCG Medical College, Berhampur University
Email: kirtish97@gmail.com

Hitesh Shingadia
Department of Zoology,SVKM'S Mithibai College of Arts, Chauhan Institute of Science and Amrutben Jivanlal College of Commerce and Ecnomics,University of Mumbai
Email: hiteshshingadia26@gmail.com

Anto Simon Joseph M.
Research Scholar, Department of Biotechnology,Sri Krishna Arts and Science College, Coimbatore
Email: simonbscbt@gmail.com

Ravindran Jaganathan
Microbiology Unit, Preclinical Department, Royal college of Medicine Perak, Universiti Kuala Lumpur
Email: jravimicro@gmail.com

Supriyo Mukherjee
Department of Microbiology, University of Kalyani
Email: supriyom00@gmail.com

Abstract---The tumor microenvironment is an atmosphere that covers a tumor withinside the body. It consists of the extracellular matrix, immune cells, blood vessels, and different cells, like fibroblasts. Cell-

to-cell communication is a vital procedure that continues the organic features and hemostasis of cells in microenvironmental, organs, and intact systems. The cell-to-cell communication complexity has been studied for many years and is now well-known because a part of the molecular mechanisms of complexity, organ disorder, and developmental biology. A tissue microenvironment of a growing tumor is constituted of the tumor stroma, proliferating tumor cells, infiltrating inflammatory cells, blood vessels, and quite a few related tissue cells. The tumor microenvironment offers all the vitamins, it desires to the tumor and also makes an area for the tumor to expand. Researchers are running to recognize its position in most cancer risk, improvement, and treatment. While therapeutically focused on the tumor microenvironment is an appealing method for the remedy of most cancers, current FDA-permitted remedies have restrained efficacy. Immune checkpoint blockade remedy changed into the primary era of antibody-primarily based cures to target immune cells withinside the microenvironment of tumor (PD1 and CTLA4). As we maintain to recognize the way of tumor microenvironment contributes to new healing objectives, tumorigenesis, and techniques might be identified. The article additionally gives a top-level view of the tumor microenvironment and its properties. The article aims to symbolize the prevailing have a look at with admire its healing implementations

Keywords---tumor microenvironment, cell-to-cell communication, cell signaling, carcinogenesis, cancer therapy.

Introduction

Communication is the process of sharing records or information via different ways of extraordinary mechanisms of signaling [1]. Intercellular communications may be regulated via way of means of extraordinary flexible signaling pathways. The intracrine communication is the process that relies upon the chemical nature of the signaling molecule and the production of a particular target withinside the target cell, and itself targeted by the autocrine communication target cells [2]. The direct communication is a process of self to self (autocrine or intracrine) or among the close cells, and nearby indirect communication is exercised over a quick distance (synaptic signaling and paracrine) or an extended distance (endocrine) [3]. Cell-to-cell communication process is critical for homeostasis, morphogenesis, cell growth, cell differentiation, and cell-to-cell interplay [4]. McCrea defined cell-to-cell communication as “the song that the nucleus hears” and, while dissonant, aberrant cell-to-cell communications can also additionally harm the fitness of the organism [1].

Different forms of junctions, that are responsible microenvironmental joining of cells, are a part of a communication community crucial for cell signaling [5]. The lack of cell-to-cell adhesion may be related to the next discount of hole junctions or may with the nearby modifications withinside the surroundings and then in neighboring cells, those modifications can set off ion-associated receptors [6]. Such activities reveal that extraordinary stimuli will have massively extraordinary

effects. However, it's miles daunting to use the understanding of communication among cells and cell surrounding regions to the particular scenario of the tumor microenvironment and most cancers cell improvement, in addition to later activities of dissemination, migration, and invasion through organs or tissues and, lastly, to its utility in cancer treatments and therapies [7].

The tumor microenvironment is the type of atmosphere that covers a tumor withinside the body [8]. It consists of the blood vessels, extracellular matrix, immune cells, and different cells (fibroblasts) [9]. A tumor and tumor microenvironment continuously engage and affect every different, both undoubtedly or negatively [10]. The additives of the microenvironment engage with every different and with the tumor to allow most cancers to grow. The tumor microenvironment offers all the vitamins, it desires to the tumor and also makes an area for the tumor to expand [11]. Researchers are running to recognize its position in most cancer risk, improvement, and treatment [12]. Despite the modern-day knowledge of stromal composition and organ microstructure, the need for complicated models' incorporation of heterocellular interactions stays critical in most cancer-related research, in particular, to delineate the importance thing causative relationships and molecular pathways concerned withinside the tumor dissemination, tumor microenvironment, and usual carcinogenesis [13].

A key mission of studying cell communication is signaling pathways delineation that is concerned in most cancers' regulation. A range of research proposes that signaling pathways can modify every different via way of means of sequential signaling triggering activities in the cells [14]. For example, the protein Wnt can mediate the stability of proliferation and differentiation, especially withinside the niches of stem cells. The latest Drosophila study has elucidated a process in which an acyl institution is covalently connected to Wnt, different ways can mediate the Porcupine of transmembrane protein to minimize Wnt pastime [15]. Although, in maximum cases, temporal and spatial interactions among pathways are described by integrative signaling. It is yet to be determined.

Chemical Signaling is usually used in cell communication [16]. These chemical alerts, which are usually the different types of molecules produced or proteins via way of means of a sending cell, are regularly secreted or released by the cell and launched into the extracellular area [17]. There, they float over to neighboring cells like messages in a bottle. All cells cannot be able to "hear" a specific chemical message. To hit upon a sign (that is, to be a target cell), the proper receptor for that sign is required in neighbor cells [18]. The signaling molecule binding to its receptor can alter the activity or shape of the receptor, triggering cells an extruded interior [19]. Signaling molecules are regularly known as ligands, a popular period for bind of molecules in particular to different molecules (including receptors) [20]. The message carried via way of means of a ligand is regularly followed by a series of chemical messengers withinside the cell. As a result, it ends in a extrude withinside the cell, including the process of alteration withinside the pastime of a gene or maybe an entire procedure induction, including the cell division process [21].

Thus, the authentic intercellular (among-cells) sign is transformed into an intracellular sign (inside-cell) that triggers a reaction. Forms of signaling cell to

cell signaling include the transmission of a sign to a receiving cell from a sending cell. However, now no longer all receiving and sending cells are next-door neighbors, nor do all cell pairs trade alerts withinside an equal way. There are 4 fundamental classes of chemical signaling that are determined in multicellular organisms which include autocrine signaling, paracrine signaling, endocrine signaling, and signaling via way of means of direct contact [22]. The primary variation among the extraordinary classes of signaling is the space that the sign travels thru the organism to attain the goal cell. This has a look at makes a specialty of knowledge the decision to cell communication and sports generally takes place in the tumor microenvironment. The article additionally gives a top-level view of the tumor microenvironment and its properties. The article aims to symbolize the prevailing have a look at with admire its healing implementations.

Basics of Cell Communication

Cell-to-cell communication process is a vital procedure that continues the microenvironmental hemostasis and organic features of cells, different organs, and intact systems [23]. The complex nature of cell-to-cell communication has been studied for many years and it is now well-known because molecular mechanisms are part of organ disorder, carcinogenesis, and developmental biology [24]. The interactions among heterogeneous cells and the remote cells or connecting cells encompass the complexity, which allows you to preserve the hemostasis of the microenvironment inside a unique place [25]. For example, melanocytes were advised as a connecting cell at once communicates with different forms of cells, e.g., fibroblasts, epithelia, myocytes, immune cells, different organ cells, and neurocytes, through secreted connectors, different organ cells, or mediators' interactions [26]. Several latest articles have centered on the position of cell-to-cell communication in heterogeneity, and tumor microenvironment complexity mediation, in addition to metastasis and tumor recurrence. The retinal homeostasis can be compromised by the breakdown of cell-to-cell communication via way of means of converting gene expression of connexin and hole junction intercellular communication, main to the breakdown of the blood-retinal barrier and cell apoptosis. It continues to be wondered whether or not cell-to-cell communication may be a brand-new opportunity to deeply recognize molecular mechanisms of cell-to-cell interplay, outline profiles of intercellular sign networks, and perceive cell function-particular biomarkers and healing goals [27].

Cell-to-Cell Communication in Microenvironment and Carcinogenesis

A microenvironment of tissue in a growing tumor is constituted of tumor cell proliferation, infiltrating inflammatory cells, the tumor stroma, quite a few related tissue cells, and blood vessels [28]. It is unique surroundings that emerge withinside the path of tumor development due to its host interactions. It is created via way of means and always fashioned and ruled via way of means of the tumor, which affects cell activities taking vicinity in surrounding tissues and orchestrates molecular [29]. Tumors broaden in complicated and stronges microenvironments that affect their growth, metastasis, and invasion. In this area, tumor cells and the adjoining microenvironments of tumor cells are in common communication [30]. The interplay of most cancer cells with their

microenvironment is bidirectional and dynamic and it consists of cell-free contacts and cell-to-cell contacts, or (regarding ECM), and the mediators that allow those contacts [31]. Mediators are the secreted soluble vesicles that can be answerable for the horizontal switch of genetic records among cell/non-cell speaking cells.

Tumor cells can hijack extraordinary cell and non-cell non-malignant additives of TME to sell their very own growth and their survival below adverse conditions. Along with that, for such contacts the mediators may be soluble factors (cytokines/ chemokines/growth factors, etc.), or people who allow horizontal biomaterial or genetic switch together with cfDNA, CTCs, apoptotic bodies, and exosomes [32]. A study of the tumor microenvironment can also additionally assist enhance most cancer treatments. The organization of various cell sorts withinside the tumor microenvironment can be extraordinary for every character tumor; however extraordinary most cancers sorts tend to have comparable microenvironments [33]. For example, the microenvironment of many cancers may be stiff or very fibrotic. This makes it greater hard for tablets to penetrate and attain the middle of the tumor. The microenvironment can surround many different cancers sorts tend to be greater vascular, and packed with blood vessels. In those cases, it can be less complicated for tablets to attain the ones of most cancer cells [34]. The tumor microenvironment additionally includes many extraordinary immune cells. Understanding those is critical to high-quality make use of immunotherapy and broadening new treatments [35].

Components of Tumor Microenvironment

Tumors are composed of various additives similar to neoplastic cells. The term non-cancerous additives consist of cells including endothelial cells, and fibroblasts in addition to cells of immune system [36]. This set of the cells is known by the name tumor stroma and is a player withinside the tumor microenvironment. This microenvironment performs a vital position in lots of components of tumorigenesis, including tumor vasculature production, which is extraordinarily implicated withinside the development of metastasis [37]. Recently, it has ended up clean that the microenvironment of the tumor additionally impacts the reaction to remedies. In addition, the modulation of tumor stroma can enhance the activity and applicability of current remedies and represents new possibilities for healing targeting [38]. The stromal cells and primary additives are related to the immune system most cancer cells, cells of the vascular system, capillaries, and supporting mesenchymal cells including adipocytes, fibroblasts, and the ECM, which covers most cancers cells. Besides cells, the stroma additionally accommodates chemokines, growth factors, antibodies, and cytokines. A rising tumor microenvironment is a complicated and constantly evolving entity [39].

A brief explanation of tumor cell interaction and microenvironment

A brief rationalization of tumor cell interplay and microenvironment. Several elements are expressed through distinct tumor microenvironment additives that make contributions to strategies associated with tumorigenesis, due to the fact they're intently associated with most cancer cells [36]. Extracellular matrix allows

metastasis, tumor development, and invasion, with the help of angiogenesis increment and matrix transformation. There is likewise the space of the immune cells to the tumor microenvironment, which produces immunosuppressive surroundings in addition to the neoplastic cells output into the lymph circulation and blood [40]. Angiogenesis is crucial for the improvement method of the latest vessels into the tumor, happens below the impact of the molecules of pro-angiogenic produced through VEGF and endothelial cells, that can also be generated through different microenvironmental and neoplastic cells together with fibroblasts and macrophages. The macrophages are the foremost tumor immunity associated with the cells because of their massive amount. During the start of the tumor, the method is not unusual to place antitumor activity by the presence of M1 macrophages. However, extra superior tiers have a comparable phenotype to Tumor-associated macrophages (TAM) cells and M2 macrophages having protumorigenic activity, specifically for excessive manufacturing of IL-10. Cancer-associated fibroblasts (CAFs) may also sell angiogenesis, tumor growth, and invasion. The Cancer-associated adipocytes (CAAs) selling invasion, persistent inflammatory surroundings, and malignant development with IL-6 manufacturing [41].

Table 1
Leading Components of Tumor Microenvironment concerning their active roles [41]

Components of the tumor microenvironment	Role
Cancer-associated fibroblasts (CAFs)	Protumorigenic activity, specifically for excessive manufacturing of IL-10.
Tumor-associated macrophages (TAMs)	May also sell invasion, tumor growth, and angiogenesis
Cancer-associated adipocytes (CAAs)	Selling invasion, persistent inflammatory surroundings, and malignant development with IL-6 manufacturing

*CAFs- Cancer-associated fibroblasts, TAMs- Tumor-associated macrophages, CAAs- Cancer-associated adipocytes, IL- Interleukins

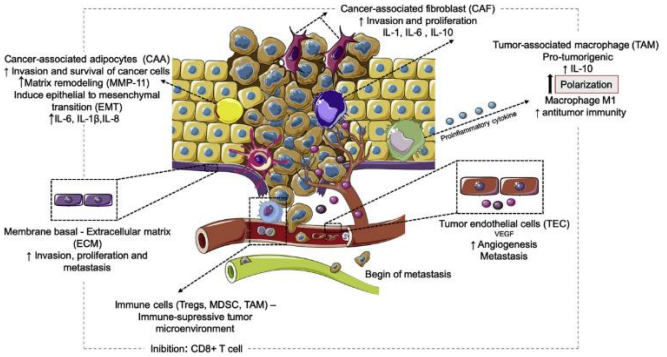

Figure 1. Tumor Microenvironment concerning the various components of it and their roles and cell communication [42].

Therapeutic Application of the Study

Over the ultimate decade, most cancers remedy has passed through a revolution. Traditionally, the drugs of chemotherapy focused on tumors extra broadly; however, now, the new healing technique's goal is unique cells in the tumor microenvironment. Immune checkpoint blockade remedy changed into the primary era of antibody-primarily based cures to targeted cell of immune system withinside the microenvironment of tumor (PD1 and CTLA4). These cures work by the blocking off interactions of receptor-ligand, dulling T-cell function and activation. Patients who reply to immune check-factor blockade remedy have a great scientific advantage, however, at this factor in time, maximum sufferers will be resistant [43]. The identity of applicable biomarkers is needed to understand sufferers who're anticipated to advantage from the factors of immune check blockade remedy. Therapeutically focused on activation of the dendritic cell by using vaccination of dendritic cell has been correctly used withinside the remedy of most of the prostate cancers.

The 'Provenge' procedure entails the harvesting of the monocytes from prostate most cancers sufferers, differentiation of them into the dendritic cells, and their activation with phosphate antigen of prostatic acid, after which they are returned re-introducing returned to the sufferers. Provenge remedy can bring about a great discount on the burden of tumors in sufferers of prostate cancers. Formation of the latest vessels of blood to alleviate deprivation of oxygen and amassing metabolic wastages is a growing requirement of tumors; therefore, focusing on angiogenesis changed into an appealing method. Antiangiogenic remedy has targeted focused on the signaling axis of VEGF–VEGF receptor and it has collaborated with a VEGF (Bevacizumab) neutralizing antibody, VEGF (Aflibercept) decoy receptor, (Sorafenib) tyrosine kinase inhibitor, VEGF binding blocking antibodies to its receptor (Ramucirumab) [44]. As a single agent, maximum sufferers both do immediate or no longer reply to antiangiogenic remedies or resistance broadening.

Antiangiogenic remedy's successful integration into the clinics will probably require a mixture of different approaches or retailers. Like, Bevacizumab in mixture with PDL1 has proven a few fulfillments for the remedy of renal cancers and hepatocellular carcinoma [45]. While therapeutically focused on the microenvironment of tumors is an appealing method for the remedy of most cancers, current FDA-permitted remedies have restrained efficacy [43]. As we maintain to recognize the way of contribution of the tumor microenvironment to tumorigenesis, the latest healing objectives and techniques might be studied. Promising preclinical research has proven capability for using chimeric antigen receptor liver stellate cells, natural killer cells, and fibroblasts.

Conclusion

Several elements are expressed through distinct tumor microenvironment additives that make contributions to strategies associated with tumorigenesis, due to the fact they're intently associated with most cancer cells. Likewise, there is the passage to the tumor microenvironment of immune cells, that produces immunosuppressive surroundings in addition to the output of the neoplastic cell

into the lymph circulation and blood circulation. In this area, tumor cells and the adjoining microenvironments of the tumor cells are in common communication. The interplay of most cancer cells with their microenvironment is bidirectional and dynamic. Tumor cells can hijack extraordinary cell and non-cell non-malignant additives of TME to sell their very own growth and survival below adverse conditions. The tumor microenvironment additionally includes many extraordinary immune cells. Understanding those is critical to high-quality make use of immunotherapy and broadening new treatments. This study focused on understanding the cell-to-cell communication and activities that usually occur in the tumor microenvironment. The article also provided an overview of the tumor microenvironment and its properties. The article aimed to represent the present study concerning its therapeutic implementations.

References

1. AlMusawi, S., Ahmed, M., & Nateri, A. S. (2021). Understanding cell-cell communication and signaling in the colorectal cancer microenvironment. *Clinical and Translational Medicine*, *11*(2), e308.
2. AlMusawi, S., Ahmed, M., & Nateri, A. S. (2021). Understanding cell-cell communication and signaling in the colorectal cancer microenvironment. *Clinical and Translational Medicine*, *11*(2), e308.
3. Alnagmy, A., Zaghloul, M. S., Mahmoud, M., Aboelkasem, H., Mokhtar, M. H., & Awad, A. (2022). Dosimetric comparison between intensity modulated radiotherapy and three-dimensional conformal radiotherapy in adjuvant setting after radical cystectomy in high-risk urothelial bladder cancer . International Journal of Health Sciences, 6(S6), 7366–7375. https://doi.org/10.53730/ijhs.v6nS6.11819
4. Ancey, P. B., Contat, C., & Meylan, E. (2018). Glucose transporters in cancer–from tumor cells to the tumor microenvironment. *The FEBS journal*, *285*(16), 2926-2943.
5. Baghban, R., Roshangar, L., Jahanban-Esfahlan, R., Seidi, K., Ebrahimi-Kalan, A., Jaymand, M., & Zare, P. (2020). Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Communication and Signaling*, *18*(1), 1-19.
6. Baghban, R., Roshangar, L., Jahanban-Esfahlan, R., Seidi, K., Ebrahimi-Kalan, A., Jaymand, M., & Zare, P. (2020). Tumor microenvironment complexity and therapeutic implications at a glance. *Cell Communication and Signaling*, *18*(1), 1-19.
7. Barari, A. (2021). *Targeted Combination Treatment in Renal Cell Carcinoma* (Doctoral dissertation, Wayne State University).
8. Bassler, B. L. (2002). Small talk: cell-to-cell communication in bacteria. *Cell*, *109*(4), 421-424.
9. Bhalla, U. S., & Iyengar, R. (1999). Emergent properties of networks of biological signaling pathways. *Science*, *283*(5400), 381-387.
10. Block, K. I., Gyllenhaal, C., Lowe, L., Amedei, A., Amin, A. R., Amin, A., & Sidransky, D. (2015, December). Designing a broad-spectrum integrative approach for cancer prevention and treatment. In *Seminars in cancer biology* (Vol. 35, pp. S276-S304). Academic Press.

11. Briscoe, J., & Thérond, P. P. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nature reviews Molecular cell biology*, *14*(7), 416-429.
12. Brücher, B. L., & Jamall, I. S. (2014). Cell-cell communication in the tumor microenvironment, carcinogenesis, and anticancer treatment. *Cellular Physiology and Biochemistry*, *34*(2), 213-243.
13. Brücher, B. L., & Jamall, I. S. (2014). Cell-cell communication in the tumor microenvironment, carcinogenesis, and anticancer treatment. *Cellular Physiology and Biochemistry*, *34*(2), 213-243.
14. Cambi, A., de Lange, F., van Maarseveen, N. M., Nijhuis, M., Joosten, B., van Dijk, E. M., & Figdor, C. G. (2004). Microdomains of the C-type lectin DC-SIGN are portals for virus entry into dendritic cells. *The Journal of cell biology*, *164*(1), 145-155.
15. Castells, M., Thibault, B., Delord, J. P., & Couderc, B. (2012). Implication of tumor microenvironment in chemoresistance: tumor-associated stromal cells protect tumor cells from cell death. *International journal of molecular sciences*, *13*(8), 9545-9571.
16. Danhier, F., Feron, O., & Préat, V. (2010). To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of controlled release*, *148*(2), 135-146.
17. Davis, T. C., Williams, M. V., Marin, E., Parker, R. M., & Glass, J. (2002). Health literacy and cancer communication. *CA: a cancer journal for clinicians*, *52*(3), 134-149.
18. Dominiak, A., Chełstowska, B., Olejarz, W., & Nowicka, G. (2020). Communication in the cancer microenvironment as a target for therapeutic interventions. *Cancers*, *12*(5), 1232.
19. Ebbesen, P., Pettersen, E. O., Gorr, T. A., Jobst, G., Williams, K., Kieninger, J., & Scozzafava, A. (2009). Taking advantage of tumor cell adaptations to hypoxia for developing new tumor markers and treatment strategies. *Journal of enzyme inhibition and medicinal chemistry*, *24*(sup1), 1-39.
20. Espinosa-Rivero, J., Bañuelos, C., & Betanzos, A. (2022). Impact of cell–cell interactions on communication and collectiveness. In *Cell Movement in Health and Disease* (pp. 51-65). Academic Press.
21. Fane, M., & Weeraratna, A. T. (2020). How the ageing microenvironment influences tumour progression. *Nature Reviews Cancer*, *20*(2), 89-106.
22. Fantl, W. J., Johnson, D. E., & Williams, L. T. (1993). Signalling by receptor tyrosine kinases. *Annual review of biochemistry*, *62*(1), 453-481.
23. Filomeni, G., Rotilio, G., & Ciriolo, M. R. (2002). Cell signalling and the glutathione redox system. *Biochemical pharmacology*, *64*(5-6), 1057-1064.
24. Franco, P. I. R., Rodrigues, A. P., de Menezes, L. B., & Miguel, M. P. (2020). Tumor microenvironment components: Allies of cancer progression. *Pathology-Research and Practice*, *216*(1), 152729.
25. Goel, S., Duda, D. G., Xu, L., Munn, L. L., Boucher, Y., Fukumura, D., & Jain, R. K. (2011). Normalization of the vasculature for treatment of cancer and other diseases. *Physiological reviews*, *91*(3), 1071-1121.
26. Hanahan, D., & Coussens, L. M. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer cell*, *21*(3), 309-322.
27. Hervé, J. C., & Derangeon, M. (2013). Gap-junction-mediated cell-to-cell communication. *Cell and tissue research*, *352*(1), 21-31.

28. Jurj, A., Zanoaga, O., Braicu, C., Lazar, V., Tomuleasa, C., Irimie, A., & Berindan-Neagoe, I. (2020). A comprehensive picture of extracellular vesicles and their contents. Molecular transfer to cancer cells. *Cancers*, *12*(2), 298.
29. Kim, B. S., Das, S., Jang, J., & Cho, D. W. (2020). Decellularized extracellular matrix-based bioinks for engineering tissue-and organ-specific microenvironments. *Chemical Reviews*, *120*(19), 10608-10661.
30. Kirberger, M. (2011). Defining a Molecular Mechanism for Lead Toxicity via Calcium-Binding Proteins.
31. Li, I., & Nabet, B. Y. (2019). Exosomes in the tumor microenvironment as mediators of cancer therapy resistance. *Molecular cancer*, *18*(1), 1-10.
32. Lim, W. A., & Pawson, T. (2010). Phosphotyrosine signaling: evolving a new cellular communication system. *Cell*, *142*(5), 661-667.
33. Mattes, B., & Scholpp, S. (2018). Emerging role of contact-mediated cell communication in tissue development and diseases. *Histochemistry and cell biology*, *150*(5), 431-442.
34. Ögmundsdóttir, H. M., Pétursdóttir, I., Gudmundsdóttir, I., Ámundadóttir, L., Rønnov-Jessen, L., & Petersen, O. W. (1993). Effects of lymphocytes and fibroblasts on the growth of human mammary carcinoma cells studied in short-term primary cultures. *In Vitro Cellular & Developmental Biology-Animal*, *29*(12), 936-942.
35. Pedersen, M. H., Hood, B. L., Beck, H. C., Conrads, T. P., Ditzel, H. J., & Leth-Larsen, R. (2017). Downregulation of antigen presentation-associated pathway proteins is linked to poor outcome in triple-negative breast cancer patient tumors. *Oncoimmunology*, *6*(5), e1305531.
36. Piferrer, F., Beaumont, A., Falguière, J. C., Flajšhans, M., Haffray, P., & Colombo, L. (2009). Polyploid fish and shellfish: production, biology and applications to aquaculture for performance improvement and genetic containment. *Aquaculture*, *293*(3-4), 125-156.
37. Schmitz, S., & Machiels, J. P. (2016). Targeting the tumor environment in squamous cell carcinoma of the head and neck. *Current treatment options in oncology*, *17*(7), 1-16.
38. Siernicka, M., Winiarska, M., Bajor, M., Firczuk, M., Muchowicz, A., Bobrowicz, M., & Zagozdzon, R. (2015). Adenanthin, a new inhibitor of thiol-dependent antioxidant enzymes, impairs the effector functions of human natural killer cells. *Immunology*, *146*(1), 173-183.
39. Solinas, G., Germano, G., Mantovani, A., & Allavena, P. (2009). Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. *Journal of leukocyte biology*, *86*(5), 1065-1073.
40. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, *5*(3), x-xv. https://doi.org/10.53730/ijhs.v5n3.2938
41. Suryatika, I. B. M., Poniman, S., Manuaba, I. B. P., Yasa, I. W. P. S., & Sutapa, G. N. (2021). The potential cancer risk on body organs as abdomen CT-scan exposure result. International Journal of Life Sciences, 5(3), 171–178. https://doi.org/10.53730/ijls.v5n3.1721
42. Tse, J. C., & Kalluri, R. (2007). Mechanisms of metastasis: epithelial-to-mesenchymal transition and contribution of tumor microenvironment. *Journal of cellular biochemistry*, *101*(4), 816-829.
43. Vail, D. M., Thamm, D. H., & Liptak, J. (2019). *Withrow and MacEwen's Small Animal Clinical Oncology-E-Book*. Elsevier Health Sciences.

44. Vlodavsky, I., Bar-Shavit, R., Ishar-Michael, R., Bashkin, P., & Fuks, Z. (1991). Extracellular sequestration and release of fibroblast growth factor: a regulatory mechanism? *Trends in biochemical sciences*, *16*, 268-271.
45. Weinberg, R. A. (1996). How cancer arises. *Scientific American*, *275*(3), 62-70.
46. Willert, K., & Nusse, R. (2012). Wnt proteins. *Cold Spring Harbor perspectives in biology*, *4*(9), a007864.
47. Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell research*, *30*(6), 492-506.
48. Zhou, S., Gravekamp, C., Bermudes, D., & Liu, K. (2018). Tumour-targeting bacteria engineered to fight cancer. *Nature Reviews Cancer*, *18*(12), 727-743.