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Purpose of Intracellular Communication Connexin 43 in Breast Cancer Cells

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Abstract--- *Intracellular communication is a vital process that supports cellular activities in both normal breast cells and cancer embedded cells. The procedure is eased by gap junctions; a cluster of aqueous pathways that bond the interior of two neighboring cells. Gap junctions are composed of several connexins that sustain intracellular communication amid adjacent cells. The process entails an exchange of metabolites, ions and electric signals which support cell processes. The channels comprised of connexins support cell to cell association through diffusion. Unlike in normal breast cells, cancer cells have faults in gap junctions, caused by poorly expressed connexins. While there exists several types of connexins, connexin 43 is a special gap junction that functions independently and plays integral roles as far as intracellular communication amid cancerous cells is concerned. Such roles include gene transcription and signal transduction. As such, connexin 43 is associated with breast cancer pathogenesis. Based on the above findings, this paper highlights the major roles of gap junctions and connexin 43 intracellular communication, particularly in breast cancer development. Moreover, connexin 43 also enhances metastasis and invasion which are vital in cancer cell dormancy and regeneration of cancer stem cells. Therefore, the paper also features inclusive knowledge regarding functional dynamics and discrepancy expression of connexin 43 the pathogenesis of breast cancer.*

Keywords--- *Tumor Microenvironment, Connexin 43, Intracellular Communication, Cancer Stem Cells, Gap Junctions, Cancer Dormancy.*

I. INTRODUCTION

Gap junctions include a family of connexins made of intracellular membrane channels that sustain intercellular communication amid normal and breast cancerous cells. Gap junctions and connexin 43 to be particular are developed at the basolateral surfaces of adjacent cells to directly link their cytoplasm. Presently scientists suppose that these connexins isoforms constitute approximately four hydrophobic transmembrane helices, an amino-terminal as well as a carboxyl-terminal. Although significance evidence shows that there is a high degree of sequence diversity amid these components they all operate as a family for appropriate docking interaction of connexins in adjacent breast cells. The sole purpose of gap junctions and connexins is to facilitate cross-communication amid cells by controlling the intercellular interchange of inorganic ions, as well as other cellular metabolites in a procedure, referred to as gap junction intracellular communication. The process enables cancerous cells to cumulate cancer prognosis.

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II. INTRACELLULAR COMMUNICATION IN BREAST CANCER CELLS

Comprehensive studies suggest that connexin 43 play a vital role in determining breast cancer sternness in terms of cancer cells regeneration. As such examining the purpose of gap junctions could help identify the distinction between malignant breast cells and normal cells. However, the studies that support both the pro and anti-metastatic roles for connexin 43 suggest that the levels of function are somehow elevated in breast cancer cells (Banerjee, 2016). Other studies analyze the existing debates of whether connexin 43 inhibits or promotes breast cancer metastasis and progression. Whileconnexin 43 among other gap junction components support intracellular communication it is not clear whether the consequences are similar for both normal and breast cancer cells (Phillips et al., 2017). In breast tumors, the overallconnexin 43 expressions can either be increased or decreased depending on the kind of mutation projected with analterationofthe proteins ordinary migration through the plasma membrane of one cell to the gap junctions to the cytoplasm of neighboring cells.

A majority of studies examining the tenacity of connexin 43 in breast cells affected by cancer declare that intracellular communication tends to be altered in tumor cells that lack connexin 43.During the prognosis of breast cancer, connexin 43 may be ineffective affecting the restoration of gap junction intracellular communication. Although the same studies suggest that with primary tumors, in particular, the primary role of connexin 43 remains elusive (Phillips et al., 2017).The countenance of connexin proteins differs in breast cells as cells habitually express numerous forms of the connexin. As such since the role of gap junction intracellular communication is less observable in cancerous cells as equated to ordinary cells. Meaning the function of connexin 43 is also limited. Connexin 43 is a principal element studied in different cancers comprising liver, prostate, and lung (Banerjee, 2016). Though all these studies affirm that connexin 43 has a tumor progressive responsibility, its role in breast cancer progression is least explored. It is unclear whether connexin 43 purpose decreases or increased with breast cancer stages.

Another study by Beckmann, Hainz, Tschernig& Meier (2019), suggest that tumor cell accretion regulation entails cell to cell bonding proteins. Aggregation regulation includes several members of the cadherin family and cell-surface proteins including galectin. In individuals with breast cancer, connexin 43 is over expressed as compared to normal breast cells. In such cases, another cell junction element, plakoglobin is released to accelerate the expression of connexin 43.Plakoglobin in conjunction with connexin 43 limit the formation of abrogates and suppresses cancer metastasis in breast cells. The same studies suggest that the aggravated expression level tends to be linked to cancer cell aggregation. A microscopic-based quantification approach was deployed to analyze the bundling effect in cancerous cells in the deficiency of substrates responsible for cellular binding. Deploying the methodology researchers demonstrated how connexin 43 in cancerous cells contribute to cell aggregation and proliferation (Ribeiro-Rodrigues et al., 2017). Gap junctions including connexin 43 connect two adjacent cells through establishing a continuous flow of cellular metabolites that accelerate the proliferation of breast cancerous cells.

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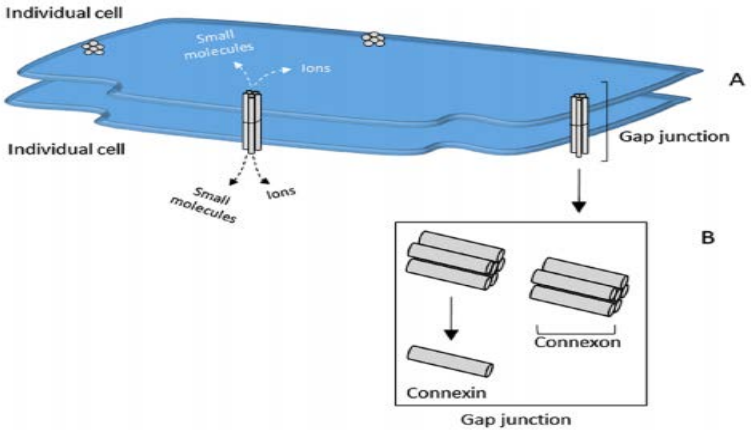

Figure 1: Showing the Ideal Structure of Gap Junctions that Facilitate Intracellular Communication Amid Breast Cancerous Cells(Ribeiro-Rodrigues et al., 2017).

Connexin 43 action is linked with the aptitude to establish gap junction intercellular movement of metabolites. The process requires close monitoring of cellular assays founded on the relocation of probes amid cells. While this is the case, a study by Banerjee, (2016) supports these findings ascertaining that connexin 43 has functions in autocrine diffusion especially when hemichannels are active amid the extracellular medium and the cytoplasm. Gap junctions support various signaling pathways through their communication with terminal domains of connexin 43. Meaning communication sustenance between cancerous cells requires the presence of an actin cytoskeleton that aids in specificity for membrane delivery. Notably, the sequences of different connexinisotypes may be variable but collectively allow transmission of ions and other metabolites between breast cancerous cells (Beckmann et al., 2019), As such with all these differing findings this report identifies and presents three vital roles of gap junctions and connexin 43 in mammary cells affected by cancer.

III. INTRACELLULAR COMMUNICATION ROLES OF CONNEXIN43 IN MAMMARY SUBJECTED TO CANCER.

Tumor Suppression

Connexin 43 functions as a tumor suppressor in the process of facilitating intracellular communication amid breast cancerous cells. Literally, the gap junction component assumes a tumor-suppressive role contributing to breast. Over expression of connexin 43 in mammary cells affected by cancer significantly lessens cell proliferation and unclear levels of β-catenin proteins. In a servey by Ribeiro-Rodrigues et al., (2017) the outcomes advocate that the process of tumor development in breast cells is directly related to an increased production of connexin 43. The process favors the epithelial transition which is responsible of silencing movement of cancer-related molecules from one cell to another. As such the connexin 43 acts to silence the proliferation of cancerous cells that ideally result in breast tumorigenesis. On the other hand, the proliferation of normal breast cells is enhanced due to loss of apical polarization and, mitotic support in cancerous cells (Grek et al., 2016). The tumor suppression role also includes activation of signaling channels that enhance infiltration in non-cancerous breast epithelium.

In addition, the ability of breast cancerous cells to proliferate is limited in the presence of connexin 43. Connexin

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43 gap junction components are able to safeguard normal breast cells by causing an immediate death of cancerous cells. This is made possible through their communicative ability. The element is integral in the transmission of complementary proteins that reduce the growth of tumors in cancer affected cells (Grek et al., 2016). Connexin 43's inhibitory role in tumorigenesis lessens the association of cancerous cells, therefore, altering their prognosis. Most importantly, cell surface connexin 43 enables the localization of β-catenin proteins that reduce the binding effect amid breast cancerous cells. The binding effect of cells' connexin 43 and β-catenin proteins increase the quantity of transport factors such as cytoplasm produced in the signaling process that subsequently reduce cell proliferation. The loss of gap junction intracellular communication is facilitated by the down-regulation of connexin expression (Ribeiro-Rodrigues et al., 2017). In tumors where connexin 43 is distinguished at the top of the the cell, the increased levels of β-catenin proteins were directly associated with lymph node prognosis and metastasis, suggesting the function of connexin 43 in suppressing tumor regeneration in breast cells.

Connexin43 Role in Cancer Stem Cells Proliferation

Literally, different types of breast tumors include an assorted family of turmeric cells reiterating subcategory at their classified peak referred to as stem cancer cells. As such connexin 43 also has a function in the proliferation of cancer stem cells used to replace breast cancerous cells in cancer therapy. Connexin 43 proliferates and sustains stem cells' self-renewal through the transmission of cellular metabolites such as exosomes and non-coding RNA (Stoletov et al., 2013). Hepatocellular carcinoma is an essential element embed in connexin 43 that enables the development of stem cells. In stem cells, significant studies demonstrate that connexin 43 is capable of maintaining a continuous propagation of stem cells in a gap junction intercellular communication. While other forms of gap junction elements significantly decrease in stem cells due to the presence of hypermethylation, in promoter regions of connexin 43 stem cells are likely to proliferate rapidly (Bazzoun, Lelièvre&Talhouk, 2015). As such the proliferation of stem cells requires increased expression of connexin 43, while at the same time prohibiting the regeneration of breast cancerous cells.

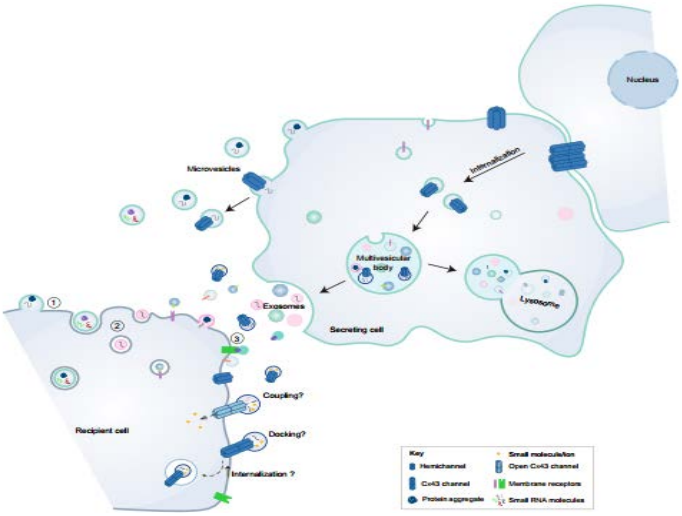

Figure 2: Showing the Role of Connexin 43 in Vesicle-Mediated Intercellular Communication, Including the Transfer of Exomes, Ions and Other Cellular Metabolites in Breast Cancerous Cells (Stoletov et al., 2013).

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Similarly, the expression of connexin 43 components is higher in stem cells when compared against normal cells. The signaling complex is accountable for the sustainability of stem cell regeneration and consequent activation of cytoplasmic accumulation (Bazzoun, Lelièvre&Talhouk, 2015). Although the exact mechanism remains unexplored the connexin-protein interactions in stem cells are critical to determining whether certain gap junction subunits are responsible for tumor dominance and stem cells regeneration in breast cancerous cells. Captivatingly, cancer stem cells express connexins as well which enable gap junction intercellular communication. Although their capacity to support active regeneration of tumors is limited, they help in upheaving the survival rate of existing cancerous cells (Stoletov et al., 2013). Some stem cell-related functions are based upon their interaction with transcription factors. As such connexin 43 is integral in sustaining stem cell properties and active proliferation.

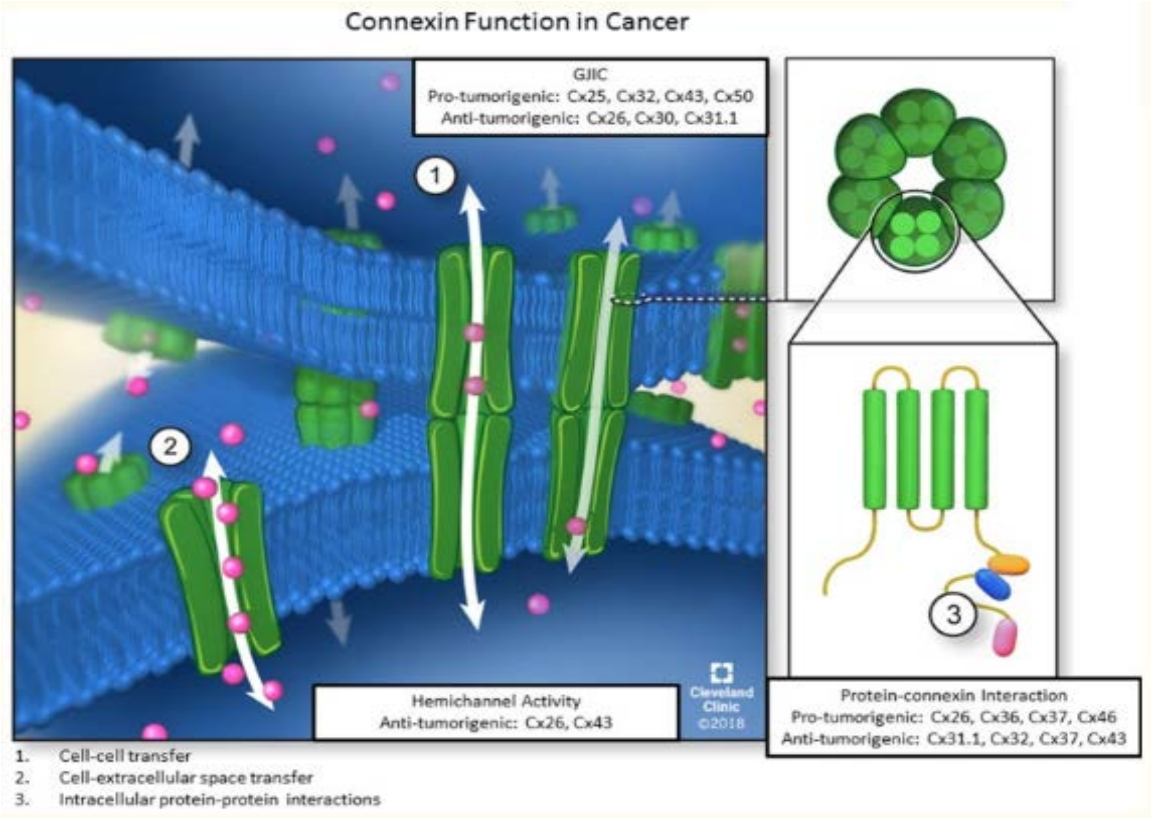

Figure 3: Showing the Major Intracellular Communication Roles of Connexins; Tumor Suppression, Tumor Cell Adhesion and Stem Cell Proliferation in Breast Cells (Grek et al., 2016).

Tumor Cells Adhesion

Arguably, connexin 43 facilitates signaling through the cell to cell connection to enable tumor cell adhesion. It is another approach that connexin 43 supports tumor cells' communication with endothelial cells. Gap junctions across the endothelial barrier arbitrate the exchange of cellular metabolites and organic ions in tumor cells. connexin 43 pathwayss are located at the cell membrane and include hemichannels which facilitate the association of tumor cells (Gava et al., 2018). Although endothelial membranes of tumor cells are heterogeneous based on the vessel sizes, connexin 43 facilitates adhesion of the cells for inorganic molecules exchange. As such, connexin 43 increases the

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union and assembly of tumor cells. In a study investigating gap junction intercellular communication amid breast cancer cells, the findings suggest the connexin 43 is a primary factor in tumor cell bonding particularly in early stages of diapedesis (Sinyuk, Mulkearns-Hubert, Reizes&Lathia, 2018). Since endothelial cells abundantly express connexin 43, the increased adhesion observed in tumor cells is likely a result of over expression of gap junction elements.

IV. CONCLUSION

Precisely, it is evident that gap junction elements and connexin 43 in particular play a significant intracellular communication role in breast cancerous cells. Connexin gap junctions allow interaction through an increased intercellular migratory ability. The major communication roles are embedded in tumor suppression, a proliferation of stem cells as well as tumor cells adhesion. Connexin 43 improves the ability of cancerous cells to metastasize through increasing the movement of ions and other cellular metabolites between cells. Regardless of the stages of breast cancer connexin 43 acts as a tumor suppressor and tumor inducer respectively.

Over expression of connexin 43 also increases the adhesion of tumor cells in pulmonary endothelium. Overall, the expression of gap junction elements including connexin 43 is required for sustainable communication amid cancerous cells. As a result, it aids in proliferation, metastasis and overall prognosis of breast cancer. Notably, the knowledge regarding communicative functions of connexin 43 is limited. As such further studies must establish various signals and mechanisms that are behind the alteration nature of connexin 43 in enabling intercellular communication between cancerous cells.

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