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The Signaling Mechanism Of Integrin In Mammary Epithelial Cells And Mammary Neoplasia

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ABSTRACT

Breast cancer is a diverse illness that originates from genetically modified cells in the mammary epithelium. It is characterized by complex interactions between the tumor cells and the surrounding tumor microenvironment (TME). This study examines the signaling pathways of integrins in mammary epithelial cells and mammary neoplasia by doing a thorough analysis of the current literature. Integrins are transmembrane receptors that facilitate cellular interactions with extracellular matrix (ECM) proteins, including laminin, fibronectin, and collagen. They are composed of α and β subunits that combine to create heterodimers. These interactions play a vital role in the process of cell adhesion, migration, survival, and the maintenance of tissue integrity. The signaling pathways of Integrin-ECM, which involve focal adhesion complexes and kinases such as FAK and Src, govern cellular processes such as proliferation, differentiation, and survival. Integrins play a crucial role in the creation and upkeep of the ductal tree and alveoli during mammary gland development, which are necessary for lactation. Altered expression and signaling of integrins in breast neoplasia contribute to the advancement, invasion, and spread of tumors. Integrins participate in two-way communication, influencing the behavior of cancer cells and their interactions with the tumor microenvironment (TME), which consists of stromal and immune cells. Integrins such as αvβ3 and α6β4 have important functions in cell migration, the formation of new blood vessels, and the survival of cancer cells. Comprehending the dual function of integrin signaling in both promoting and inhibiting tumors is essential for the development of precise cancer treatments. Integrin-based therapies show potential for altering these pathways, thereby enhancing cancer outcomes by suppressing tumor growth and spread. Subsequent investigations should prioritize the comprehensive examination of the regulatory mechanisms governing integrins and their potential as targets for therapeutic interventions.

Keywords: Breast cancer, mammary epithelial cells, tumor microenvironment, integrins, extracellular matrix, cell adhesion, signaling pathways, tumor progression, invasion, metastasis, αvβ3 integrin, α6β4 integrin, focal adhesion kinase, Src family kinases, bidirectional signaling, cancer therapy, integrin-based treatment.

Introduction:

ECM Interaction

Cell-Extracellular Matrix (ECM) Interaction: The Role of Integrins in Mammary Epithelial Cells Integrins are membrane-spanning receptors that have a crucial function in facilitating the communication between cells and the ECM. This connection is essential for preserving tissue structure, cellular function, and overall balance in mammary epithelial cells.

1. The Architecture and Role of Integrins

- Composition: Integrins consist of α (alpha) and β (beta) subunits that join together to create heterodimers. In humans, there are a total of 18 α subunits and 8 β subunits, resulting in the formation of 24 distinct integrin receptors. The precise arrangement of these subunits dictates the integrin's ability to attach to ECM proteins with a particular strength and selectivity.

- Integrins serve the purpose of linking the extracellular matrix (ECM) to the cytoskeleton of mammary epithelial cells. They play a crucial role in providing structural support and enabling two-way communication between the cell's interior and the external environment.

2. Attachment to Extracellular Matrix Proteins

- Laminin is a prominent constituent of the basement membrane, which is a specialized kind of ECM found beneath epithelial tissues, such as the mammary gland. Integrins, specifically α6β1 and α3β1, attach to laminin, securing mammary epithelial cells to the basement membrane. This attachment promotes cell polarity, differentiation, and survival.
- Fibronectin is a large glycoprotein found in the ECM that interacts with integrins such as α5β1 and αvβ3. This interaction is involved in cell adhesion, migration, and wound healing.
- Collagen is the predominant protein found in the ECM, where it plays a crucial role in supplying both tensile strength and structural integrity. Integrins, specifically α1β1 and α2β1, have the ability to attach to different forms of collagen. This attachment plays a role in cell adhesion, movement, and the preservation of the structural framework of the mammary gland.[1]

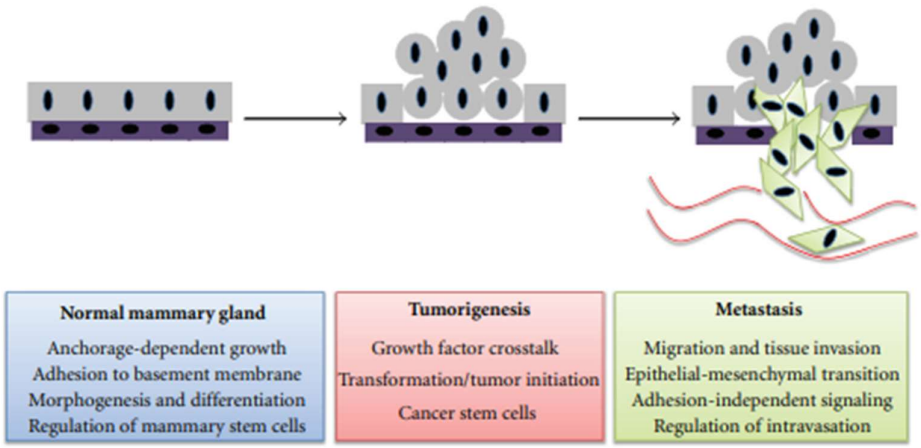

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Figure 1: Roles of integrin signaling in mammary epithelial cells and breast cancer progression.

3. Preservation of Tissue Structure and Function

- Cell adhesion is facilitated by the binding of integrins to the extracellular matrix (ECM), which promotes correct adherence of mammary epithelial cells to the ECM. This binding prevents detachment and the occurrence of anoikis, a type of programmed cell death triggered by detachment from the ECM. The adherence is crucial for preserving the structural integrity of mammary tissue.
- Cell Polarity: The engagement of integrins with the ECM is crucial for the establishment and maintenance of cell polarity, a fundamental requirement for the effective operation of epithelial cells. Cell polarity impacts functions such as the uptake of nutrients, the release of substances, and the transmission of signals inside cells.
- Signal transduction occurs when integrins attach to extracellular matrix (ECM) proteins, which then triggers a series of intracellular signaling pathways. These pathways are responsible for regulating a range of cellular functions, such as cell proliferation, differentiation, and survival. The transmission of these signals occurs via focal adhesion complexes, which connect integrins to the actin cytoskeleton and other signaling molecules like FAK and Src family kinases.
- Integrins are involved in tissue remodeling and morphogenesis in the context of mammary gland development and breastfeeding. They facilitate the coordination of the dynamic alterations in ECM

composition and structure that are necessary for the development of ductal branching, alveolar formation, and milk production.[2]

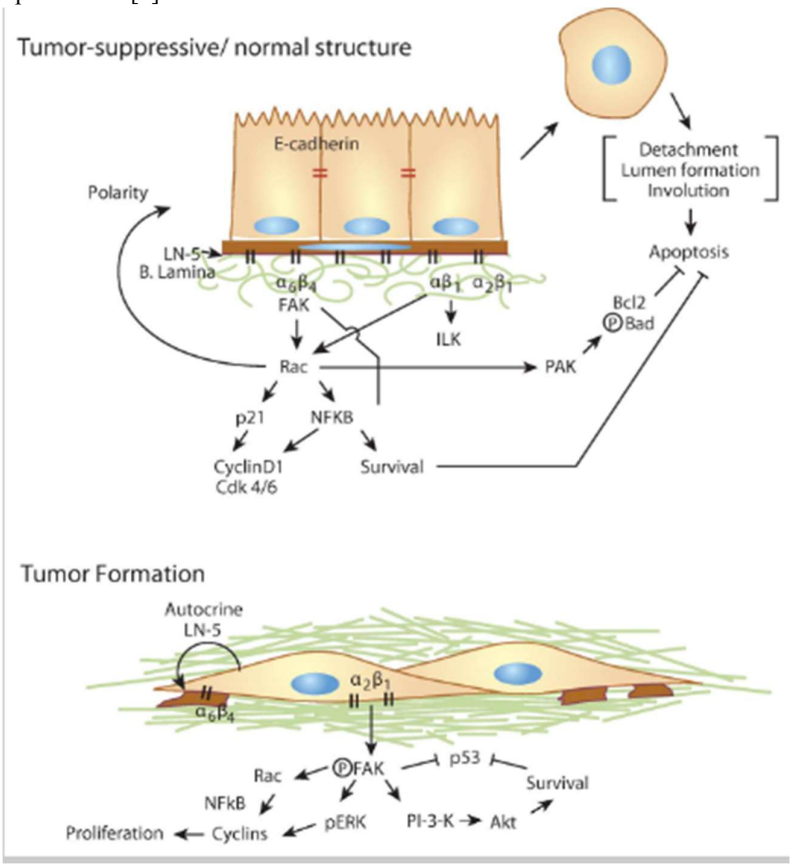

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Figure 2: Integrin-mediated signaling pathways

Integrin-mediated signaling pathways are essential for controlling epithelial polarity and differentiation. The binding of α6β4 integrin to the basal lamina triggers the activation of FAK, which in turn communicates with Rac to enhance cell proliferation and survival through the involvement of p21 and NFkB. This signaling pathway also stimulates the basal secretion of laminin-5 (LN-5), which helps to establish cell polarity. In addition, adherence to the basal lamina inhibits programmed cell death by activating PAK, which in turn activates Bcl2 and Bad. Loss of adhesion results in apoptosis, a process essential for the removal of luminal contents. During the formation of tumors, the cells of the tumor break down the layer of cells that supports and separates them from the surrounding tissue, and they infiltrate the surrounding tissue, while also releasing a substance called autocrine LN-5 to prevent programmed cell death. In addition, the binding of α2β1 integrin to collagen stimulates cell growth and survival by activating FAK, pERK, and PI-3-K signaling pathways. The activated pFAK protein counteracts p53 to inhibit cell death.

4. Role in Mammary Gland Development and Function Development:

- Integrins have a crucial role in guiding the establishment of the ductal tree during mammary gland development. They facilitate connections between epithelial cells and the ECM. These interactions are essential for the rapid increase and specialization of mammary progenitor cells.
- Lactation: Integrins have a role in controlling the process of milk production and release. They exert an influence on the arrangement of mammary epithelial cells into alveoli, which are the structures

responsible for milk production, and aid in preserving the structural integrity of the mammary gland throughout lactation.[3]

Regulation of the ECM During Normal Mammary Development

The mammary gland undergoes ductal development primarily in response to hormonal signals during adolescence, followed by alveolar development during pregnancy. Full terminal differentiation of the gland only happens if lactation, or milk production, takes place. Every stage of development has a distinct extracellular matrix (ECM) protein composition that controls the differentiation of the mammary gland and the expression of genes[4][5][6][7].

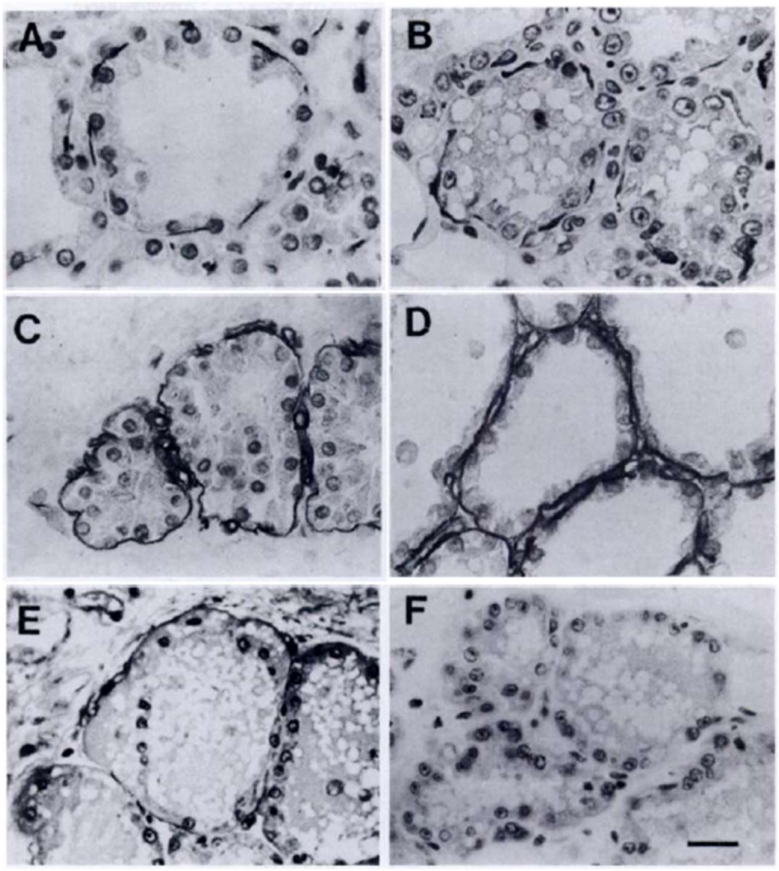

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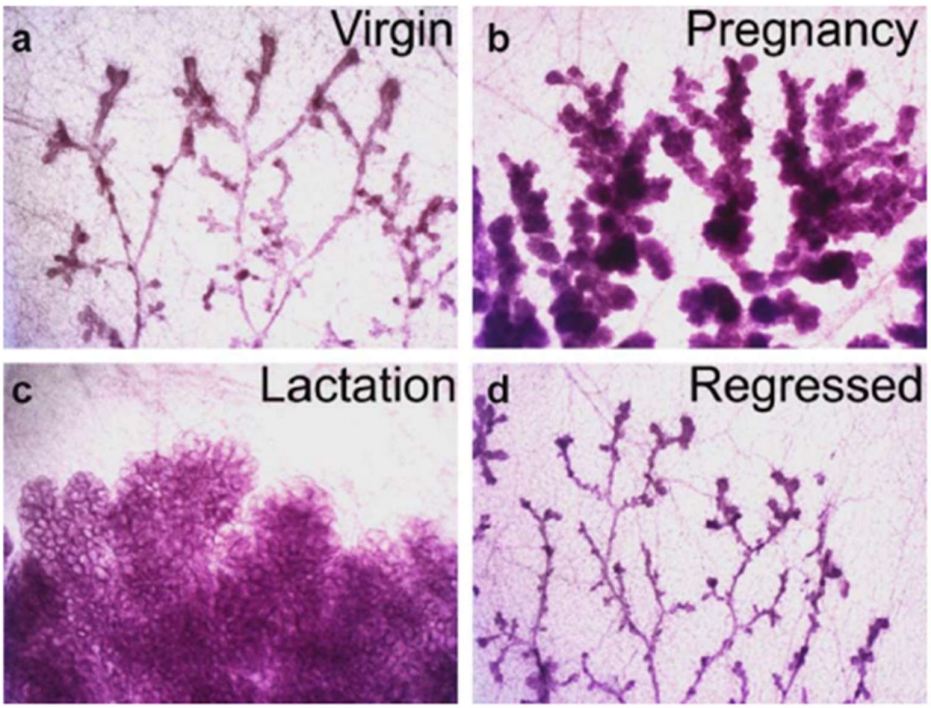
Figure 3: The arrangement of myoepithelial cells and basement membrane proteins

The arrangement of myoepithelial cells and basement membrane proteins in the mammary gland of nursing rats. The lactating rat mammary gland sections were stained using antisera to myosin (A), prekeratin (B), type IV collagen (C), laminin (D), fibronectin (E), or preimmune rabbit serum (F). The continuity of the myoepithelial cell processes (A, B) around the alveoli is no longer observed. The basement membrane can be readily distinguished using antisera specific to type IV collagen, laminin, and fibronectin (C, D, E). Observe the lack of coloration in the region treated with preimmune rabbit serum (F). The value of the bar is 14 zm. Magnification at the original level is 720 times.

The alterations in gene expression encompass various components, including laminins, fibrillar collagens of types I, III, and V, bead-filament collagen VI, collagen IX, basal lamina collagen IV, and collagen-associated proteins that are involved in cross-linking, such as elastin, fibrillin 1, decorin, lumican, and biglycan [8].



Source- doi.org/10.1007/s10911-007-9039-3

Figure 4: morphological changes in mammary gland

The study investigates the morphological changes that occur in the mammary gland of female Sprague-Dawley rats in relation to their reproductive condition. Displayed are representative whole mount pictures of MG#5 from a virgin/nulliparous (never given birth), b late-stage pregnant, c nursing day 7, d fully regressed/parous (already given birth) rats, at an original magnification of 40×.

The absence of fibronectin (FN) in the mammary epithelium leads to a loss of lobuloalveolar development and is associated with reduced integrin signaling events [9]. This indicates a fascinating self-regulation of morphogenesis through the local secretion of fibronectin by the epithelial cells. The presence of fibrillar collagen in the development of the ductal mammary tree is indicated by the observation that collagen is deposited on the sidewalls of emerging ducts, where there is limited proliferation of epithelial cells [10]. Conversely, the amount of collagen found at the terminal end buds (TEBs), which are the structures responsible for ductal extension and penetration through the fat pad, is rather small. Exogenous application of TGF-β at the tip of the growing ductal tree hinders the growth of the ducts and leads to the formation of thick fibrillar collagen around the TEBs [11]. The regulation of both the deposition and degradation of extracellular matrix (ECM) plays a crucial role in the development of the ductal tree. The presence of stromelysin-1, stromelysin-3, gelatinase, and matrilysin is necessary for the branching morphogenesis to take place [12][13][14][15]. These findings provide evidence that the expansion of the mammary ductal tree is a regulated process involving controlled cell division and infiltration at the terminal end bud (TEB). It is crucial to have strict regulations for this process, since the improper breakdown of the basal lamina components by stromely sin/MMP3 leads to the disturbance of cellular polarity and encourages the invasion of tumor cells [16]. The degradation of the basal lamina has a significant impact, as evidenced by the induction of stromelysin-1 expression in the mouse mammary gland, which leads to the development of new invasive tumors [17]. This demonstrates that the presence of an intact basal lamina inhibits tumor formation. The discovery that proteases, such as stromelysin-1, have a role in controlling both normal branching morphogenesis throughout development and tumor formation, highlights the importance of maintaining a delicate equilibrium between maintaining an intact extracellular matrix (ECM) with the right proteins and the controlled degradation of the ECM. Typically, in healthy mammary tissue, the breakdown of extracellular matrix (ECM) and the activity of proteases are associated with tissue restructuring. This includes the invasion of the ductal tree into the mammary fat pad and the creation of branching structures. Similarly, during

lactation, there is involution of the tissue. The presence of comparable deterioration during the growth of tumors implies that breast cancer cells exploit the developing program, while simultaneously restructuring and infiltrating the breast stroma and fat pad.

The role of integrins and metabolism in breast cancer

The metabolic conditions of cells have a significant impact on the maintenance of cell stability and survival. Multiple regulatory systems govern the response to metabolic stress, such as hypoxia and glucose deprivation. Hypoxia-inducible factor (HIF), mammalian target of rapamycin (mTOR), and AMP-activated protein kinase (AMPK) regulate cellular balance during metabolic stress caused by changes in diet or other environmental conditions [18]. Conversely, cancer cells exhibit a distinct metabolic profile. They exhibit a high rate of cell division and require a significant amount of metabolites, including amino acids and nucleic acids [19][20]. One significant distinction between normal cells and malignant cells is in their energy providing pathway. In healthy cells, oxidative phosphorylation is the primary mechanism for energy synthesis, whereas in cancer cells, energy is mostly obtained through aerobic glycolysis [21]. Thus, tumor cells undergo a process known as energy metabolism reprogramming (EMR), which is often regarded as a distinguishing feature of cancer cells [22]. There are multiple regulating mechanisms for electromagnetic radiation (EMR), and one significant mechanism involves the process of twisting. Twist is an EMT regulator that acts as a factor promoting EMR through the β1-integrin/FAK/PI3K/AKT/mTOR and p53 signaling pathways in breast cancer cells [23]. Integrins are well-known targets for these metabolites, as well as for metabolic signals. The metabolic alterations largely impact integrins through the regulation of gene expression and protein modification processes such as glycosylation. This includes the degradation of integrins and their movement inside the cell membrane [18]. Evidence demonstrates that metabolic circumstances regulate the expression of integrins via several mechanisms. When exposed to low oxygen circumstances or when HIF is activated, the following integrins are expressed: α5 in the SW480 cell line [24], β2 in the U937 cell line [25], β1 in the 18OC cell line [26], and α5β1 integrin in osteosarcoma cells [27]. In addition, adiponectin stimulates the production of α5β1-integrin in prostate cancer cells [28] and α2β1-integrin in chondrosarcoma SW1353 cells through an AMPK-dependent mechanism [29].

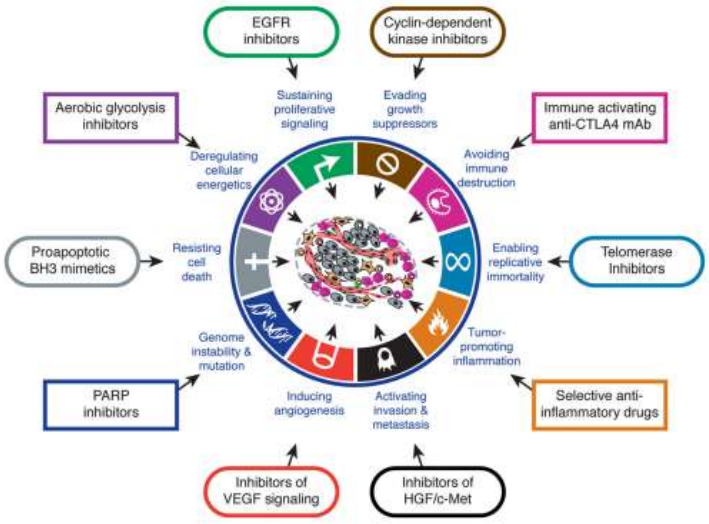


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Figure 5: Therapeutic Targeting of the Hallmarks of Cancer

The administration of medications that induce apoptosis may cause cancer cells to excessively stimulate mitogenic signaling, allowing them to counterbalance the initial reduction caused by these treatments. These considerations indicate that combining the notions of distinct functional capacities and the many metabolic

pathways that underlie them will be advantageous in drug development and treatment protocol design. Therefore, specifically, we can imagine that targeting several core and emergent hallmark capabilities and enabling traits in mechanism-guided combinations will lead to more efficient and long-lasting treatments for human cancer.

Integrins and Adhesion Mechanisms Signaling

Integrins are essential cell surface receptors that facilitate the connection between cells and the ECM. They have a crucial function in multiple physiological processes by connecting the internal cytoskeleton with the ECM. Integrins consist of alpha and beta subunits that can combine in various configurations to create unique integrin heterodimers. Each heterodimer has specialized affinities for different ECM proteins such as fibronectin, collagen, and laminin.

Bidirectional signal transduction:

- Outside-In Signaling refers to the process where integrins, upon binding to extracellular matrix (ECM) components, establish a signaling cascade. This process entails the enlistment of diverse intracellular signaling molecules to the cytoplasmic domain of the integrin. The compounds mentioned are FAK, Src family kinases, and further unidentified molecules. Cell behavior, including proliferation, differentiation, and survival, can be influenced by this signaling.
- Intracellular signaling: In contrast, integrins can also convey signals from the interior of the cell to the ECM. Integrins' affinity and avidity for their ligands are modified via inside-out signaling. Cellular adhesion qualities can be modified in response to internal cues, enabling cells to adapt. This ability is crucial for important biological processes such as cell migration and immunological responses.

Focal Adhesion Kinase

FAK is an essential non-receptor tyrosine kinase largely found at focal adhesions, which are specialized structures that facilitate the connection between the cell and the ECM. FAK has a role in various cellular processes such as cell migration, adhesion, proliferation, and survival.

Activation Mechanism:

When integrins connect with parts of the extracellular matrix (ECM), they bring FAK to focal adhesions, which starts a chain of events. FAK goes through autophosphorylation at tyrosine 397, which makes a spot for Src family kinases to attach. Once Src kinases link to phosphorylated tyrosine 397 on FAK, they phosphorylate more tyrosine residues inside FAK. These phosphorylation events make FAK's kinase activity stronger and make new docking sites for other signaling proteins. This sets off a complicated web of signaling interactions that control different cellular responses.

Cellular processes that include the activation of FAK:

FAK, or Focal Adhesion Kinase, is important for many biological processes. It helps cells stick together and spread by encouraging the creation and strengthening of focal adhesions, which makes it easier for cells to connect to the ECM. FAK controls focal adhesion dynamics and actin cytoskeleton rearrangement, which are both important for cell movement. It is also an important part of mechanotransduction, which turns mechanical forces into biochemical signals that affect how cells react to changes in the physical features of the ECM. FAK also affects cell growth and survival by working with other signaling pathways, supporting cell cycle progression, and shielding cells from messages that tell them to die.

Functional Analysis of the Genome (FAK) and Disease:

- Cancer: FAK is frequently overexpressed in many types of cancer, leading to enhanced cell motility and invasion. The active investigation of targeting FAK in cancer therapy is now underway.
- Fibrosis: Dysregulated FAK signaling is associated with fibrotic disorders, in which there is an excessive accumulation of extracellular matrix (ECM) and migration of cells, leading to tissue scarring.[30]

Integrin and the TME in breast cancer

The role of integrin and the tumor microenvironment (TME) in breast cancer. The tumor microenvironment (TME) contains a diverse range of modulatory elements, including fibroblasts, immune cells, blood vessels, stem cells, and extracellular matrix (ECM) components. These ECM components consist of molecules such as collagen, hyaluronan, fibronectin, and integrins. The cell migratory capacity of cancer cells is a crucial component of cancer controlled by the microenvironment. Studies have shown that melanoma cells have varying migratory patterns depending on the milieu they are in. For example, melanoma cells move quicker and in a more specific direction in the dermis compared to fatty connective tissues [31]. Additionally, the investigation of fibrosarcoma cells in microenvironments revealed that cell migration in the dermis differs from the migratory pattern observed in fatty connective tissue [32]. Thus, our data validate the impact of the microenvironment on the migration of cancer cells. Cancer cells are classified into three classes based on their migration mode: single-cell migration, multicellular-pattern movement, and collective migration. No cellular interaction is found in the mechanism of single-cell migration. It is presumed that each cell migrates autonomously, meaning that there is no link between the migration patterns of neighboring cells. The multicellular pattern is characterized by the movement of cells in a coordinated manner, migrating in the same direction and without strong or complete adhesion [33]. Collective migration is a phenomenon that occurs during the process of tissue regeneration and wound healing[34]. Cells exhibiting collective migration retain their intercellular adhesion capabilities and demonstrate coordinated movement with neighboring cells along their migration trajectory. MDA-MB-231 and TN1, both human breast cancer cell lines, exhibit both single-cell and multicellular arrangements [35][36].

Blood arteries have an impact on cellular migration, in addition to the characteristics of the microenvironment [33]. The proximity of blood vessels to cancer cells can enhance cellular motility. There is a direct relationship between the proximity of macrophages to blood arteries and the migration of cells. This phenomenon may be attributed to the assistance that macrophages offer to cancer cells in their efforts to access the stroma and infiltrate blood arteries. Collagen [33]is a significant element in the TME. The arrangement and abundance of collagen in the tumor microenvironment (TME) have a substantial impact on the movement of cells. Put simply, a high concentration of collagen encourages the movement of cells. Nevertheless, it is evident that the migratory profile of cells is determined by the collective involvement of signaling, genetic composition, and microenvironment, as stated in reference [33]. Integrins, which play a crucial role in cell-to-cell and cell-to-matrix interactions, are very significant among the various essential players in the extracellular matrix (ECM). They have a direct impact on cancer progression [37]. The interaction between α2β1-integrin and lumican, an extracellular matrix (ECM) protein, has a detrimental impact on tumor growth[38]. Furthermore, the combination of β1-integrin, kindlin, and EGFR promotes the movement of cells in breast cancers, leading to increased migration [39]. Tenascin-C (TNC) is an extracellular glycoprotein that integrins attach to in order to induce epithelial-mesenchymal transition (EMT). TNC acts as a ligand for αv, α2, β1, and β6-integrins, which are expressed at higher levels in some cancer cells. The binding of TNC to αvβ6 and αvβ1-integrins promotes epithelial-mesenchymal transition (EMT) [40]. Another component of the tumorigenicity generated by the microenvironment in breast cancer is the connection between integrins and VEGF. Expression of the α6β4-integrin promotes increased survival rates in breast cancer. The elevated levels of VEGF are responsible for the underlying process that enables tumor cells to survive. The α6β4-integrin deactivates the 4E-binding protein 1, which is a translational suppressor responsible for regulating the action of the elongation factor eIF-4E. This, in turn, leads to the activation of VEGF synthesis [41].

Integrins within the tumor microenvironment (TME) have crucial functions in supporting the growth of new blood vessels (angiogenesis). The αvβ3-integrin is a particular integrin found in the tumor microenvironment (TME). It forms a complex with fibronectin, fibrinogen, proteolysed collagen, and tenascin to enhance cell motility. Angiogenesis and cell migration are easily prevented if this essential organizer is absent [42]. Additional integrins that have been observed to increase in expression during angiogenesis in breast cancers include the fibronectin receptor α5β1-integrin [43] and the collagen receptor α2β1-integrin [44]. Stiffness is another characteristic of the cellular microenvironment that plays a role in determining the fate of cells. The stiffness of the microenvironment is regulated by the organization of the extracellular matrix (ECM). While there are other proteins involved in this process, we will primarily focus on the role of integrin linked kinase (ILK) because to its notable contribution to stiffness. In the case of breast cancers, there is a connection between low oxygen levels

(hypoxia) and rigidity (stiffness) in the extracellular matrix (ECM), which is utilized by tumors to interact with their surrounding surroundings. The critical stage of this process relies heavily on the crucial interaction between ILK and β1-integrin, which initiates a series of signals and leads to the adjustment of invasion, migration, and angiogenesis. Therefore, the rigid and oxygen-deprived microenvironments expedite the progression of breast cancer stem cells via the ILK/PI3K/AKT-mediated pathway [45]. The tyrosine kinase FER modulates cell adhesion linked with integrins α6 and β1, resulting in enhanced metastasis of breast carcinoma cells. Additionally, experiments conducted on mice models of human breast tumors have shown that the excessive production of FER kinase encourages the spread of cancer cells to other parts of the body.

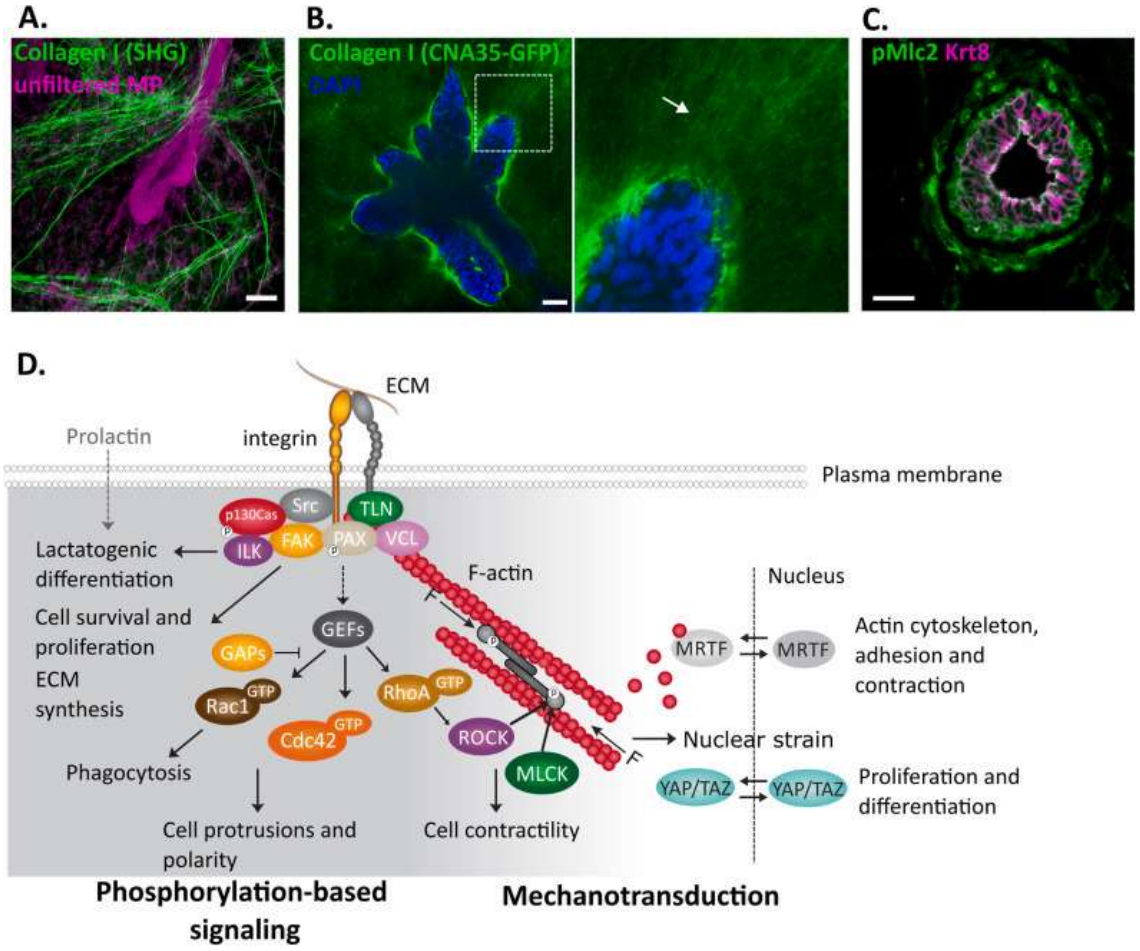
Table 1: Integrin Selectivity of SJ749

Assay type	**IC_{50}**				
	α5β1/FN	**αvβ3/VN**	**αIIbβ3/FBG**	**αvβ5/VN**	**α2β1/COL**
Purified receptor	1.8 nmol/L	1 μmol/L	>10 μmol/L	–	–
Cell adhesion	340 nmol/L*	>10 μmol/L	–	>10 μmol/L†	>10 μmol/L‡
Cell migration	2.9 μmol/L§	–	–	–	–

Source-**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1876892/**

IC_{50} determined for α5β1-positive Jurkat cell; IC_{50} for HT29 α5-positive transfectants was slightly higher (800 nmol/L).
†IC_{50} determined for SK-BR-3 as well as HT29 tumor cells.
‡IC_{50} determined for HUVEC as well as HT29 adhesion to collagen.
§IC_{50} determined for HUVEC cell migration on fibronectin.

Therefore, FER-targeted therapy is suggested as a therapeutic approach for treating invasive breast cancer. Integrins present in the tumor microenvironment (TME) can also contribute to resistance against therapy. Specifically, β1 [46][47] and αvβ3/β5-integrins have been shown to make cancer cells resistant to radiotherapy [39]. β1-integrin has been identified as a significant factor in the development of resistance to chemotherapy in solid malignancies [48]. The β1-integrin present in the tumor microenvironment (TME) might cause resistance to tamoxifen in breast cancers by interacting with the G protein-coupled estrogen receptor. As a result, it is recommended as a potential target for therapeutic interventions[49]. Ultimately, the combination of components linked with TME plays a crucial role in determining the fate of cells. Integrins play a crucial role in regulating cellular destiny within the tumor microenvironment (TME). They establish a well-established connection between signaling pathways and interactions with MMPs, VEGF, TNC, and other components of the TME. Moreover, the identification of these connections may present encouraging therapy strategies for breast cancer.



Source- www.sciencedirect.com/science/article/pii/S1084952120301671?via%3Dihub

Figure: Integrin-mediated mechanosensing and signaling

Mechanosensing and signaling through integrins play a vital role in the development and functioning of the mammary gland. Multiphoton microscopy allows for the visualization of collagen I fibers and epithelial features in pubertal mouse terminal end buds (TEBs). Tension-aligned collagen fibers can be observed in collagen gels containing collagen I and nuclei in primary human mammary epithelial organoids. The presence of phosphorylated myosin light-chain 2 (pMlc2) suggests the ability of acto-myosin to contract in both the basal and apical luminal cells. Integrin binding to extracellular matrix (ECM) ligands forms protein complexes that develop into focal adhesions. These adhesions connect to the actin cytoskeleton and activate signaling pathways involved in lactogenic differentiation, cell survival, proliferation, and ECM creation. Rho GTPases (specifically RhoA, Rac1, and Cdc42) are activated in the downstream pathway, which in turn regulates actin polymerization and contractility. These processes affect the movement of molecules into the nucleus and the functioning of transcription factors that respond to mechanical forces, such as MRTF and YAP/TAZ. These transcription factors control the fate of cells and the feedback between the cytoskeleton and the cell.

Objective:

To study on the signalling mechanism of integrin in mammary epithelial cells and mammary neoplasia

Literature Review:

(Paavolainen & Peuhu, 2021)[50] The mammary gland experienced significant restructuring during its growth after birth and reproductive cycles. The organ's innate plasticity was thought to increase its vulnerability to carcinogenesis. The morphological alterations in the mammary epithelium encompassed processes such as cell proliferation, differentiation, death, and migration. These processes were all regulated by the adherence of cells

to the extracellular matrix (ECM). Integrin adhesion receptors were involved in detecting the biochemical composition, arrangement, and mechanical characteristics of the extracellular matrix (ECM) that surrounds cells, and had a substantial impact on the destiny of the cells. This review provides a concise overview of the current research on the impact of integrin-mediated adhesion and mechanosensing on mammary gland development, function, and homeostasis. It examines the influence of factors such as extracellular matrix composition, stiffness, and topography, as well as integrin expression patterns, focal adhesion assembly, dynamic regulation of the actin cytoskeleton, and nuclear mechanotransduction. The study mostly examined studies conducted in vivo or using organoid models because to the difficulties associated with recreating the mechanical properties of a complex tissue environment in vitro. These investigations collectively showed that mechanosensing played a role in regulating the development of the mammary gland in many ways.

(Brandão-Costa et al., 2020)[51] The extracellular matrix (ECM)'s shape and make-up can change, which can affect how cancer grows and spreads. Epithelial-mesenchymal transition (EMT) changes epithelial cells into mesenchymal cells. This changes how cells stick to each other, which helps cancer spread. This research looked into how MCF-7 breast cancer cells, which don't spread easily, connect with the ECM made by MDA-MB-231 cells, which do spread easily. MDA-ECM changed the structure of MCF-7 cells by lowering the level of E-cadherin, raising the level of mesenchymal markers, and making cell motility better. These changes turned on integrin-related signaling pathways, which increased the phosphorylation of FAK, ERK, and AKT. They also turned on TGF-β receptor signaling, which increased the phosphorylation of SMAD2 and SMAD4 and their translocation to the nucleus. Kistrin (Kr), an integrin αvβ3 ligand, stopped the activation of TGF-β receptors in MCF-7 cells that had been treated with MDA-ECM. The study showed that integrin and TGF-β signaling cause MCF-7 cells to go through EMT when they contact with the extracellular matrix (ECM) of metastatic cells. This suggests possible drug targets to stop breast cancer metastasis.

(Tsirtsaki & Gkretsi, 2020)[52] Cell-extracellular matrix interactions, commonly known as focal adhesions (FA), have a significant impact on tissue homeostasis and are also associated with malignancy. Integrin-Linked Kinase (ILK), a highly expressed protein found in focal adhesions, plays a role in multiple signaling pathways. This review conducted a comprehensive analysis of the current literature on the involvement of ILK in breast cancer (BC), which included data from both laboratory experiments conducted in controlled environments (in vitro) and tests conducted on living organisms (in vivo), as well as research including samples from actual BC cases. Suppressing or pharmacologically inhibiting ILK led to apoptosis, prevention of epithelial-to-mesenchymal transition, and decreased cell invasion. In contrast, the overexpression of ILK resulted in the inhibition of anoikis and promoted tumor development and metastasis. In addition, it was discovered that ILK was increased in BC tumors, and its expression was found to be associated with tumor grade and metastasis. Therefore, ILK was suggested as a promising candidate for anti-cancer treatments.

(Romagnoli et al., 2020)[53] The integrin dimers α3/β1, α6/β1, and α6/β4 functioned as receptors for laminins in mammary epithelial cells. Laminins, which are significant constituents of the mammary basement membrane, interacted with these integrin dimers. The precise functions of basement membrane components and their integrin receptors in controlling the formation of functioning glands have not been extensively examined. In order to investigate the roles of laminin-binding integrins, we generated mutant mice with particular defects in the α3 and α6 integrin chains in mammary luminal cells using the Cre-Lox technique. During pregnancy, these genetically altered mice demonstrated decreased luminal progenitor activity and a delay in the development of lobulo-alveolar structures. While the mammary glands seemed to be working properly at the beginning of lactation, there were noticeable changes in the structure of the myoepithelial cells. These changes suggest that the cells were undergoing remodeling of their cytoskeleton as a way to compensate for any functional deficiencies. Crucially, the mutant females did not continue to produce milk, and their mammary glands experienced early shrinkage. Disabling the p53 gene improved the growth issues, but did not bring back lactation. The results indicated that the p53 pathway had a role in controlling the growth and survival of mammary cells after connecting to laminin-binding integrins. This emphasized the importance of cell contacts with laminin in the process of lactogenic differentiation.

(Karamanou, Franchi, Onisto, et al., 2020)[54] Lumican, a short leucine-rich proteoglycan, modulated estrogen receptor (ER)-related activities in breast cancer cells, impacted the expression of matrix macromolecules, and controlled the process of epithelial-to-mesenchymal transition. Nevertheless, it remained ambiguous if the effects of lumican on breast cancer cells, which are dependent on estrogen receptor (ER), were associated with

the expression of integrins and their intracellular signaling pathways. We conducted a study to examine the impact of lumican on three different breast cancer cell lines: the MDA-MB-231 cell line, which is highly metastatic and expresses ERβ, the MDA-MB-231 cell line with decreased ERβ expression (shERβMDA-MB-231), and the MCF-7/c cell line, which is less invasive and expresses ERα. Scanning electron microscopy, confocal microscopy, real-time PCR, western blot, and cell adhesion assays were employed. In addition, the impact of lumican on cell morphology was examined in 3D collagen cultures. Treatment with Lumican resulted in enhanced cellular adhesion and aggregation, while suppressing the development of microvesicles and microvilli. Furthermore, it decreased the levels of the cell membrane adhesion receptor CD44, as well as its several forms and variations, hyaluronan (HA), and HA synthases. Lumican reduced the expression of CD44 and HA synthases in MDA-MB-231 cells, emphasizing the important involvement of α1, α2, α3, αVβ3, and αVβ5 integrins in cell adhesion. This effect was not detected in MCF-7/c cells. Lumican upregulated the expression of α2 and β1 integrin subunits in both MDA-MB-231 and shERβMDA-MB-231 cells, in comparison to MCF-7/c cells. Lumican was discovered to downregulate downstream integrin signaling pathways, such as FAK, ERK 1/2 MAPK 42/44, and Akt. The findings offered a deeper understanding of the molecular pathways that drive lumican's ability to combat invasive breast cancer.

(Li et al., 2023)[55] Integrins are transmembrane sensors that can bind to specific molecules and send signals. Interestingly, integrin β4 has a long tail in the cytoplasm that can connect to the actin cytoskeleton and work with it. 'Inside-out' signaling by integrins can improve ligand affinity, allowing two-way cellular signal transfer that is important for many biological processes. Their activity and expression are connected to how tumors grow and spread, including how they start to grow, how cells move, how they invade tissue, and how they metastasize. By working with receptors, some integrins help cancer grow, while others stop it. Integrin signaling pathways, which include Ras- and Rho-GTPase, TGFβ, Hippo, Wnt, Notch, and Shh, are very important for the growth of cancer. Figuring out how integrins control things is important for stopping cancer from spreading and creating treatments based on integrins. This piece talks about integrin signaling in cancer and the possible uses of integrin agonists as cancer treatments.

(Karamanou, Franchi, Vynios, et al., 2020)[56] ERα and ERβ are estrogen receptors that play a big part in how breast cancer cells grow, change, and spread, especially when it comes to the epithelial-to-mesenchymal transition (EMT). ERα-mediated endocrine resistance makes cancer more invasive by encouraging cell growth and a mesenchymal phenotype. When ERα is turned off in MCF-7 cells and ERβ is turned off in MDA-MB-231 cells, the cells' properties and the amounts of EMT markers change. Mesenchymal cells can invade through invadopodia, which are actin-rich membrane protrusions that are important for breaking down the extracellular matrix and allowing tumors to grow. Cortactin and MMP-14 control these protrusions. Lumican can stop the production of cortactin and MMP-14, which changes mesenchymal cells into cells that look like epithelial cells. So, lumican might be able to stop EMT-related metastatic traits, which means that lumican-based cancer therapies could be a good area for further study.

(Smeland et al., 2020)[57] Cancer-associated fibroblasts (CAFs) change the tumor microenvironment in a big way. One type of CAFs has more integrin α11β1, which is an integrin that binds to collagen and helps the tumor grow. We looked at how much human integrin α11 was present in breast cancer samples using a new antibody that targets it. Ab 210F4B6A4 was chosen from a group of monoclonal antibodies to be studied further. An immunohistochemical study of 392 breast cancer samples showed that integrin α11 was found in stromal spindle-shaped cells, where it was found with αSMA and cytokeratin-14. In 66% of cases, high levels of stromal integrin α11 were found. This was linked to aggressive breast cancer features like high histologic grade, higher proliferation, lack of ER, presence of HER2, and triple-negative phenotype. At the protein or mRNA levels, however, this expression did not show a link with survival in breast cancer. To sum up, higher levels of stromal integrin α11 are linked to breast cancer that is more likely to spread.

Methodology

This study used a secondary research methodology to investigate the obstacles in INTEGRIN IN MAMMARY EPITHELIAL CELLS AND MAMMARY NEOPLASIA. Secondary research entails the gathering and examination of preexisting data and information from other sources. The approach utilized for this review study encompasses the subsequent procedures:

1. Review of existing literature:

- Sources: The study utilizes a diverse range of sources to collect thorough and extensive findings. The sources encompass academic books, peer-reviewed journals, respectable news outlets, industry magazines, websites, articles, and previously published research papers.
- The literature chosen for this review was based on its relevance to the issue, the credibility of the sources, and the recency of the articles. Only sources that offer substantial insights into THE SIGNALING MECHANISM OF INTEGRIN IN MAMMARY EPITHELIAL CELLS AND MAMMARY NEOPLASIA.

2. Data Collection:

- Scholarly publications and journals were examined to get insight into the theoretical frameworks, technological breakthroughs, and THE SIGNALING MECHANISM OF INTEGRIN IN MAMMARY EPITHELIAL CELLS AND MAMMARY NEOPLASIA.
- The study analyzed reliable news sources and industry journals to collect up-to-date trends, practical obstacles, real-world examples, and expert perspectives regarding THE SIGNALING MECHANISM OF INTEGRIN IN MAMMARY EPITHELIAL CELLS AND MAMMARY NEOPLASIA.
- Research Papers: A comprehensive analysis of existing research papers was conducted to examine the past discoveries, methodology, and conclusions made by other researchers in the field.

Discussion:

The signaling pathways of integrins are crucial for preserving the structural and functional integrity of mammary epithelial cells, as well as for the advancement of breast neoplasia. Integrins are membrane-spanning receptors that mediate cellular interactions with the extracellular matrix (ECM). The subunits α (alpha) and β (beta) combine to create heterodimers, which enable a diverse range of specialized interactions with extracellular matrix (ECM) proteins. Crucial extracellular matrix (ECM) proteins that play a role in these interactions are laminin, fibronectin, and collagen. These proteins are necessary for the attachment, movement, and viability of cells.

Integrins have a role in maintaining the structural integrity of breast tissue by facilitating the attachment of cells to the extracellular matrix (ECM), which helps avoid cell death caused by detachment (anoikis). Additionally, they have a significant function in the establishment and upkeep of cell polarity, which is vital for a range of cellular processes including nutrient absorption, secretion, and signal transmission. Integrin-ECM interactions trigger signaling pathways that control cellular activities such as proliferation, differentiation, and survival. These pathways mostly include focal adhesion complexes and related kinases, such as FAK and Src family kinases.

Integrins have a crucial role in the establishment and preservation of the ductal tree and alveoli during mammary gland development, which are essential for the production of milk. The extracellular matrix (ECM) undergoes dynamic alterations throughout several stages of mammary development, which are regulated by hormonal signals and the local release of ECM components by epithelial cells. This dynamic regulation guarantees the appropriate development and operation of tissues.

Cancer cells in breast neoplasia can use integrins and their associated signaling pathways to facilitate the advancement and spread of tumors. Cancer cells frequently display modified integrin expression and signaling, which contributes to their ability to invade and spread to other parts of the body. Integrins have the ability to impact the behavior of cancer cells by engaging in bidirectional transmission. This involves two types of signaling: outside-in signaling, which occurs when integrins bind to components of the extracellular matrix (ECM) and trigger signaling pathways within the cell, and inside-out signaling, which occurs when signals from within the cell modify the affinity and avidity of integrins for their ligands.

Integrins also engage with the tumor microenvironment (TME), which encompasses diverse stromal cells, immune cells, and extracellular matrix (ECM) components. These interactions have the ability to regulate the movement of cancer cells, their ability to invade surrounding tissues, and the formation of new blood vessels (angiogenesis). For example, the αvβ3 integrin facilitates the movement of cells and the formation of new blood vessels by binding to fibronectin, fibrinogen, and degraded collagen. The α6β4 integrin improves the survival of cancer cells by suppressing translational suppressors and boosting the synthesis of VEGF through its interaction with VEGF.

Integrins are vital transmembrane receptors that facilitate cell-extracellular matrix (ECM) interactions, which are necessary for preserving the structural and functional integrity of mammary epithelial cells. Integrins, which consist of α and β subunits, combine to create heterodimers. These heterodimers have the ability to connect with specific extracellular matrix (ECM) proteins like laminin, fibronectin, and collagen. This interaction helps in promoting cell adhesion, migration, and survival [1]. Integrins inhibit anoikis and preserve tissue integrity by facilitating cell attachment to the extracellular matrix (ECM). Additionally, they play a crucial role in establishing and sustaining cell polarity, a vital aspect of cellular processes such as nutrition absorption and signal transmission [2].

Integrins play a crucial role in directing the growth of the ductal tree and alveoli, which are essential for lactation, during the development of the mammary gland. The extracellular matrix (ECM) undergoes dynamic changes throughout several phases of development, which are regulated by hormonal signals and the release of ECM components by epithelial cells. This control guarantees the appropriate development and functioning of tissues [3]. However, in the context of breast neoplasia, cancer cells take use of integrin signaling to facilitate the advancement of tumors. Modified integrin expression and signaling intensify the invasion and spread of cancer cells through reciprocal signaling processes. Outside-in signaling refers to the process in which integrins attach to extracellular matrix (ECM) components, which then triggers intracellular signaling cascades. On the other hand, inside-out signaling refers to the process that regulates the affinity and avidity of integrins for their ligands [30].

During the tumor microenvironment (TME), integrins establish connections with stromal cells, immune cells, and extracellular matrix (ECM) components, thereby exerting an influence on the behavior of cancer cells. The αvβ3 integrin enhances movement and the formation of new blood vessels by binding to fibronectin, fibrinogen, and collagen that has been broken down by proteolysis. The α6β4 integrin increases the survival of cancer cells by connecting with VEGF, blocking translational suppressors, and boosting VEGF synthesis [42].

Conclusion:

The signaling pathways of integrins are crucial in controlling the behavior of mammary epithelial cells and the development of mammary tumors by facilitating interactions with the extracellular matrix (ECM). Integrins, which consist of α and β subunits, combine to create heterodimers that interact with extracellular matrix (ECM) proteins such as laminin, fibronectin, and collagen. This interaction facilitates cell adhesion, migration, and survival. These interactions play a crucial role in preserving the structural integrity of tissues, maintaining the orientation of cells, and ensuring the proper functioning of cells as a whole. Integrins play a crucial role in directing the growth of the ductal tree and alveoli, which are necessary for lactation, during mammary gland development. In the setting of breast cancer, cancer cells utilize integrins to augment tumor development, invasion, and metastasis by modifying signaling pathways. More precisely, integrins such as αvβ3 and α6β4 play a role in facilitating cell movement, the formation of new blood vessels, and the ability of cancer cells to stay alive. Furthermore, the tumor microenvironment (TME) has an impact on integrin signaling, which in turn affects the behavior of cancer cells and their interaction with stromal and immune cells. Comprehending the two-fold aspect of integrin signaling, which has the ability to either stimulate or hinder the development of cancer, is essential for the advancement of precise cancer treatments. Integrin-based therapies show potential for altering these pathways, which could potentially result in enhanced cancer outcomes. Further investigation should prioritize the detailed regulation mechanisms of integrins and their potential as therapeutic targets for suppressing tumor development and metastasis.

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