Epithelial–Mesenchymal Transition for Breast Carcinogenesis

Subjects: Medicine, General & Internal

Contributor: Chia-Jung Li

The transforming growth factor-β (TGF-β) signaling pathway plays multiple regulatory roles in the tumorigenesis and development of cancer. TGF-β can inhibit the growth and proliferation of epithelial cells and induce apoptosis, thereby playing a role in inhibiting breast cancer. Therefore, the loss of response in epithelial cells that leads to the inhibition of cell proliferation due to TGF-β is a landmark event in tumorigenesis. As tumors progress, TGF-β can promote tumor cell invasion, metastasis, and drug resistance. At present, the above-mentioned role of TGF-β is related to the interaction of multiple signaling pathways in the cell, which can attenuate or abolish the inhibition of proliferation and apoptosis-promoting effects of TGF-β and enhance its promotion of tumor progression.

breast cancer transforming growth factor-β epithelial-to-mesenchymal transition signaling pathway

1. Introduction

Breast cancer is a common cancer in women worldwide with increasing incidence and mortality rates. In Latin America, 200,000 women are diagnosed with breast cancer per year, with more than 52,000 deaths annually [1][2][3]. The high incidence and mortality rate of this disease have led to an increase in research meant to combat this public health issue. In order to accurately predict the clinical outcome of breast cancer, several types of scoring systems are used, based on histopathological appearance, anatomical location, molecular alterations, disease presentation, and clinical features. Moreover, in a recent study, molecular classification was revealed to be especially important in predicting clinical outcome, as it was associated with drug resistance [4]. According to current information, breast cancer can be divided into six major subgroups based on their molecular portrait including normal-like, HER-2 positive, luminal A and B type, basal-like, and claudin-low. The normal-like subgroup has an expression profile similar to that of noncancerous breast tissue. The overexpression of ErbB2, a receptor-like tyrosine kinase oncogene also known as human epidermal growth factor receptor 2 (HER-2), influences several signaling pathways and promotes dysregulated growth, oncogenesis, metastasis, and chemoresistance in breast cancer. The HER2 overexpression has been reported with poor prognosis, especially in patients without chemotherapy and target therapy [5]. The luminal A and B breast cancer subtypes generally express luminal cytokeratin 8/18 and the estrogen receptor, but at different levels. The luminal A subtype is generally characterized by higher estrogen receptor (ER) expression and lower HER-2 expression. In contrast with the luminal A subtype, luminal B breast cancer is usually characterized by lower ER expression and a higher Ki67 index, leading to advanced breast cancers with high proliferation rates and a worse prognosis. The basal-like subtype is

characterized by the expression of biomarkers in the basal/myoepithelial cells of normal breast tissue such as cytokeratin 5/6, cytokeratin 14, cytokeratin 17, vimentin, P-cadherin, and p63 [6][7][8][9]. The claudin-low subtype is characterized by the low expression of cell–cell adhesion molecules including claudins 3, 4, and 7, occludin, and E-cadherin [10][11]. This subtype is also characterized by the presence of epithelial-to-mesenchymal transition (EMT) processes and stem cell-associated features [12]. The basal-like and claudin-low subtypes are commonly found in triple-negative breast cancer (TNBC), which is characterized by the lack of hormone receptors such as PR, ER, and HER-2, and is associated with higher recurrence and distant metastasis rates. The expression of estrogen receptor (ER) and the progesterone receptor (PR) are important predictive markers for hormone therapy [13]. These receptors can be used as targets for adjuvant endocrine therapy in order to regulate breast carcinogenesis. Patients who receive this type of therapy have been shown to have a better prognosis including overall survival, disease-free survival, and time to treatment failure [14]. On the other hand, the lack of PR expression in breast cancer leads to a more aggressive progression and a poorer prognosis. Due to the emergence of molecular analysis methods, the detailed mechanisms of tumorigenesis in undifferentiated phenotypes are essential in providing novel targets for treatment.

2. Epithelial-to-Mesenchymal Transition in Breast Cancer

Breast carcinogenesis is a complex, multiple step process, involving several mechanisms that mediate cell proliferation, differentiation, apoptosis, epithelial-to-mesenchymal transition, and angiogenesis [15]. In breast cancers with a poorly differentiated phenotype, the tumor cell is characterized by stem cell-like features, which arise due to the EMT process. This promotes the process of dedifferentiation and leads to a worse prognosis [16]. For example, EMT markers such as vimentin, N-cadherin, and cadherin-11, have been reported to be upregulated in triple-negative breast cancer (TNBC), thereby promoting extracellular matrix remodeling via matrix metallopeptidases (MMPs) and decreasing the expression of epithelial markers, finally leading to a poor clinical outcome [17]. In previous studies, invasion and metastasis were shown to be the major risk factors associated with a poor clinical outcome, which are also related to the EMT process [18][19][20][21]. The transcription factors that are involved in the EMT process such as SNAIL1/2, ZEB1/2, TWIST1/2, and FOXC1/2 play an important role in mediating embryogenesis and carcinogenesis by regulating the expression of E-cadherin (**Table 1**) [22]. Currently, the EMT program is divided into three types: embryogenesis, fibrosis, and tumorigenesis. Type 1 and 2 EMT contribute to organ development and tissue regeneration [23]. Type 3 EMT is involved in breast carcinogenesis and has been reported to be significantly associated with local invasion and distant metastasis [24][25]. It is also involved in regulating several cellular functions including cellular adhesion, migration, proliferation, differentiation, survival, and metastasis through several processes such as loss of epithelial polarity, detachment of the basement membrane, and acquisition of mesenchymal features [18][19][26]. Advanced breast cancer is often characterized as having stem cell-like features, which appear due to the EMT process. This includes loss of hormone receptors and cell–cell interaction proteins. In vitro, the estrogen knockdown reporter model of MCF-7 showed that the loss of ER expression was significantly associated with the EMT process, thereby promoting cell proliferation and migration by increasing the extracellular matrix and reducing matrix metalloproteases [27]. As such, EMT was thought to be an important step in carcinogenesis and the formation of distant metastasis [28][29]. In addition, the stem cell-like

features induced by EMT were shown to contribute to drug resistance [30]. Several EMT-related signaling pathways play an important role in drug resistance in breast cancer cells. Cells undergoing EMT show similar cancer stem cell function including an increase in drug efflux pumps and anti-apoptotic effects. The two features increase drug resistance in cancer cells. Aggressive TNBC tumors such as metaplastic breast cancer are usually characterized by resistance to chemotherapy due to the activation of the EMT process, which is associated with worse outcomes [31]. The claudin-low subtype is also linked to metaplastic breast cancer due to the low expression of GATA3-regulated genes, which are involved in both the EMT process and cell adhesion. Notably, six critical components including TGF-β signaling, PI3K/AKT/mTOR signaling, regulatory factors, exosomes, and angiogenesis, were reported to regulate EMT by genetic or epigenetic alterations, thereby altering interaction with the extracellular matrix in breast carcinogenesis.

Table 1. List of epithelial-to-mesenchymal transition regulators in cancer progression.

Family	Transcription Factor	Role	Ref.
Zinc-finger domain	SNAIL	Snail blocks the cell cycle and confers resistance to cell death.	[32]
	SLUG	Downregulation of E-cadherin expression occurs during the EMT, a process also exploited by invasive cancer cells.	[33]
	ZEB1	Represses E-cadherin promoter and induces EMT by recruiting SMARCA4/BRG1.	[34]
	ZEB2	ZEB2 protein is involved in chemical signaling pathways that regulate early growth and development.	[35]
bHLH	TWIST1	Overexpression of TWIST1 induces EMT, a key process in the metastasis formation of cancer.	[36]
FOX	FOXC1	FOXC1 partially promotes tumor metastasis by regulating EMT programs to support microvascular invasion, thereby increasing angiogenesis.	[37]
	FOXC2	Transcriptional activator that are upregulated in breast cancer.	[38]
Homeobox	SIX1	Six1 can promote the metastasis of human tumors, and the increased expression of Six1 can be used as an indicator for predicting breast cancer metastasis.	[39]
	LBX1	LBX1 is upregulated in the unfavorable estrogen receptor (ER)/progesterone (PR)/HER2 triple-negative basal-like subtype.	[40]
cadherin	E-cadherin	E-cadherin an active suppressor of invasion and growth of many epithelial cancers.	[41] [42]
	N-cadherin	It is dependent on its association with the actin-cytoskeleton and is mediated through interactions with catenin proteins.	[43]

3. The Role of the TGF-β Pathway in Breast Cancer

Transforming growth factor-β (TGF-β), a multifunctional cytokine, directly regulates cell development, differentiation, homeostasis, proliferation, and transformation. TGF-β signaling plays an important role in the activation of the EMT and interacts with downstream signaling pathways in breast tumorigenesis [44]. The activation of TGF-β induces both canonical SMAD2/3-dependent signaling and non-SMAD signaling in order to promote the EMT process. In SMAD-mediated signaling, TGF-β directly binds to the membrane receptors, leading to the formation of the SMAD complex by activating SMAD2/3/4. In non-SMAD signaling pathways, TGF-β triggers the AKT/PI3K pathway, Ras/Raf/MEK/ERK signaling pathway, and Wnt/β-catenin signaling pathway in order to induce the expression of epithelial proteins [45][46]. Moreover, the TGF-β type I receptor interacts with the Src homology 2 domain-containing transforming protein 1 (SHC1) to activate the growth factor receptor-bound protein 2 (GRB2) and son of sevenless (SOS) in order to induce Ras/Raf/MEK/ERK signaling. In addition, TGF-β may phosphorylate Par6 directly via the type II receptor, thereby promoting the degeneration of RhoA via Smurf1 and inducing the dissolution of the tight junctions [47]. Par6 plays an important role in stress fiber formation, thereby regulating cell polarity and junction stability. In breast carcinogenesis, the partitioning defective 6 (PAR6) promotes the loss of polarity via TGF-β-dependent signaling and induces mesenchymal-like invasive mammary tumor cells. Notably, studies have shown that by blocking Par6 signaling, the EMT process can be curbed [48]. These results were confirmed by the formation of ZO-1-positive epithelium-like structures in breast carcinogenesis. Moreover, distant metastasis was also suppressed [20][48]. The TGF-β receptor also induced the expression of three Ras-related GTP-binding proteins, namely RhoA, RAC1, and CDC42, leading to cytoskeletal changes by regulating the actin cytoskeleton in response to extracellular signals [49]. In addition, TGF-β interacts with the PI3K/AKT pathway for translational regulation. In the study by Fei Huang et al. [50], HER2/EGFR signaling switched the TGF-β function in breast cancer to activate phosphorylation of Smad3 through AKT, promoting epithelial–mesenchymal transition and migration. TGF-β also interacts with Wnt signaling via β-catenin. In the study by Anders Sundqvist et al. [51], TGF-β triggered Wnt7a/7b via Smad2/3, enhancing TGF-β-induced EMT of the mammary epithelial cells, and the components of the WNT signaling pathway were enriched within the late TGF-β target genes. Moreover, glycogen synthase kinase-3β (GSK3β) inhibits the β-catenin in the nucleus and activates the lymphoid enhancer-binding factor 1 (LEF) and T cell factor (TCF), thereby inducing the EMT process [52]. In an inducible c-fos estrogen receptor (FosER) cell model, β-catenin and TGF-β signaling cooperated to induce a mesenchymal phenotype during the EMT process. Inhibition of both signaling pathways in FosER cells led to a reversion from a mesenchymal phenotype to a polarized epithelial phenotype [53].

References

1. Barrios, C.H.; Reinert, T.; Werutsky, G. Access to High-Cost Drugs for Advanced Breast Cancer in Latin America, Particularly Trastuzumab. Ecancermedicalscience 2019, 13, 898.
2. Pinto, J.A.; Pinillos, L.; Villarreal-Garza, C.; Morante, Z.; Villaran, M.V.; Mejia, G.; Caglevic, C.; Aguilar, A.; Fajardo, W.; Usuga, F.; et al. Barriers in Latin America for the Management of Locally Advanced Breast Cancer. Ecancermedicalscience 2019, 13, 897.

3. Pinto, J.A.; Saravia, C.H.; Flores, C.; Araujo, J.M.; Martinez, D.; Schwarz, L.J.; Casas, A.; Bravo, L.; Zavaleta, J.; Chuima, B.; et al. Precision Medicine for Locally Advanced Breast Cancer: Frontiers and Challenges in Latin America. Ecancermedicalscience 2019, 13, 896.
4. Caparica, R.; Lambertini, M.; Ponde, N.; Fumagalli, D.; de Azambuja, E.; Piccart, M. Post-Neoadjuvant Treatment and the Management of Residual Disease in Breast Cancer: State of the Art and Perspectives. Ther. Adv. Med. Oncol. 2019, 11.
5. Rossi, L.; McCartney, A.; Risi, E.; Malorni, L.; Biganzoli, L.; Di Leo, A. Managing Advanced Hr-Positive, Her2-Negative Breast Cancer with Cdk4/6 Inhibitors in Post-Menopausal Patients: Is There a Best Sequence? Ther. Adv. Med. Oncol. 2018, 10.
6. Sorlie, T.; Perou, C.M.; Tibshirani, R.; Aas, T.; Geisler, S.; Johnsen, H.; Hastie, T.; Eisen, M.B.; van de Rijn, M.; Jeffrey, S.S.; et al. Gene Expression Patterns of Breast Carcinomas Distinguish Tumor Subclasses with Clinical Implications. Proc. Natl. Acad. Sci. USA 2001, 98, 10869–10874.
7. Nielsen, T.O.; Hsu, F.D.; Jensen, K.; Cheang, M.; Karaca, G.; Hu, Z.; Hernandez-Boussard, T.; Livasy, C.; Cowan, D.; Dressler, L.; et al. Immunohistochemical and Clinical Characterization of the Basal-Like Subtype of Invasive Breast Carcinoma. Clin. Cancer Res. 2004, 10, 5367–5374.
8. Matos, I.; Dufloth, R.; Alvarenga, M.; Zeferino, L.C.; Schmitt, F. P63, Cytokeratin 5, and P-Cadherin: Three Molecular Markers to Distinguish Basal Phenotype in Breast Carcinomas. Virchows Arch. 2005, 447, 688–694.
9. Van de Rijn, M.; Perou, C.M.; Tibshirani, R.; Haas, P.; Kallioniemi, O.; Kononen, J.; Torhorst, J.; Sauter, G.; Zuber, M.; Kochli, O.R.; et al. Expression of Cytokeratins 17 and 5 Identifies a Group of Breast Carcinomas with Poor Clinical Outcome. Am. J. Pathol. 2002, 161, 1991–1996.
10. Prat, A.; Parker, J.S.; Karginova, O.; Fan, C.; Livasy, C.; Herschkowitz, J.I.; He, X.; Perou, C.M. Phenotypic and Molecular Characterization of the Claudin-Low Intrinsic Subtype of Breast Cancer. Breast Cancer Res. 2010, 12, R68.
11. Dias, K.; Dvorkin-Gheva, A.; Hallett, R.M.; Wu, Y.; Hassell, J.; Pond, G.R.; Levine, M.; Whelan, T.; Bane, A.L. Claudin-Low Breast Cancer; Clinical & Pathological Characteristics. PLoS ONE 2017, 12, e0168669.
12. Herschkowitz, J.I.; Simin, K.; Weigman, V.J.; Mikaelian, I.; Usary, J.; Hu, Z.; Rasmussen, K.E.; Jones, L.P.; Assefnia, S.; Chandrasekharan, S.; et al. Identification of Conserved Gene Expression Features between Murine Mammary Carcinoma Models and Human Breast Tumors. Genome Biol. 2007, 8, R76.
13. Pernas, S.; Tolaney, S.M. Her2-Positive Breast Cancer: New Therapeutic Frontiers and Overcoming Resistance. Ther. Adv. Med. Oncol. 2019, 11.
14. Bartlett, J.M.; Brookes, C.L.; Robson, T.; van de Velde, C.J.; Billingham, L.J.; Campbell, F.M.; Grant, M.; Hasenburg, A.; Hille, E.T.; Kay, C.; et al. Estrogen Receptor and Progesterone

Receptor as Predictive Biomarkers of Response to Endocrine Therapy: A Prospectively Powered Pathology Study in the Tamoxifen and Exemestane Adjuvant Multinational Trial. J. Clin. Oncol. 2011, 29, 1531–1538.

15. Lin, S.C.; Chu, P.Y.; Liao, W.T.; Wu, M.Y.; Tsui, K.H.; Lin, L.T.; Huang, C.H.; Chen, L.L.; Li, C.J. Glycyrrhizic Acid Induces Human Mda-Mb-231 Breast Cancer Cell Death and Autophagy Via the Ros-Mitochondrial Pathway. Oncol. Rep. 2018, 39, 703–710.
16. Hao, Y.; Baker, D.; Dijke, P.T. Tgf-Beta-Mediated Epithelial-Mesenchymal Transition and Cancer Metastasis. Int. J. Mol. Sci. 2019, 20, 2767.
17. Micalizzi, D.S.; Ford, H.L. Epithelial-Mesenchymal Transition in Development and Cancer. Future Oncol. 2009, 5, 1129–1143.
18. Felipe Lima, J.; Nofech-Mozes, S.; Bayani, J.; Bartlett, J.M. Emt in Breast Carcinoma—A Review. J. Clin. Med. 2016, 5, 65.
19. Chiu, H.C.; Li, C.J.; Yiang, G.T.; Tsai, A.P.; Wu, M.Y. Epithelial to Mesenchymal Transition and Cell Biology of Molecular Regulation in Endometrial Carcinogenesis. J. Clin. Med. 2019, 8, 439.
20. Chiu, H.C.; Wu, M.Y.; Li, C.H.; Huang, S.C.; Yiang, G.T.; Yen, H.S.; Liu, W.L.; Li, C.J.; Kao, W.Y. Epithelial-Mesenchymal Transition with Malignant Transformation Leading Multiple Metastasis from Disseminated Peritoneal Leiomyomatosis. J. Clin. Med. 2018, 7, 207.
21. Wu, M.Y.; Li, C.J.; Yiang, G.T.; Cheng, Y.L.; Tsai, A.P.; Hou, Y.T.; Ho, Y.C.; Hou, M.F.; Chu, P.Y. Molecular Regulation of Bone Metastasis Pathogenesis. Cell. Physiol. Biochem. 2018, 46, 1423–1438.
22. Moreno-Bueno, G.; Portillo, F.; Cano, A. Transcriptional Regulation of Cell Polarity in Emt and Cancer. Oncogene 2008, 27, 6958–6969.
23. Kent, C.N.; Reed, I.K.G. Regulation of Epithelial-Mesenchymal Transition in Endometrial Cancer: Connecting Pi3k, Estrogen Signaling, and Micrornas. Clin. Transl. Oncol. 2016, 18, 1056–1061.
24. Kalluri, R.; Weinberg, R.A. The Basics of Epithelial-Mesenchymal Transition. J. Clin. Investig. 2009, 119, 1420–1428.
25. Lamouille, S.; Xu, J.; Derynck, R. Molecular Mechanisms of Epithelial-Mesenchymal Transition. Nat. Rev. Mol. Cell Biol. 2014, 15, 178–196.
26. Makker, A.; Goel, M.M. Tumor Progression, Metastasis, and Modulators of Epithelial-Mesenchymal Transition in Endometrioid Endometrial Carcinoma: An Update. Endocr. Relat. Cancer 2016, 23, R85–R111.
27. Al Saleh, S.; Al Mulla, F.; Luqmani, Y.A. Estrogen Receptor Silencing Induces Epithelial to Mesenchymal Transition in Human Breast Cancer Cells. PLoS ONE 2011, 6, e20610.

28. Ye, X.; Brabletz, T.; Kang, Y.; Longmore, G.D.; Nieto, M.A.; Stanger, B.Z.; Yang, J.; Weinberg, R.A. Upholding a Role for Emt in Breast Cancer Metastasis. Nature 2017, 547, E1–E3.
29. Fischer, K.R.; Altorki, N.K.; Mittal, V.; Gao, D. Fischer Et Al. Reply. Nature 2017, 547, E5–E6.
30. Mani, S.A.; Guo, W.; Liao, M.J.; Eaton, E.N.; Ayyanan, A.; Zhou, A.Y.; Brooks, M.; Reinhard, F.; Zhang, C.C.; Shipitsin, M.; et al. The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells. Cell 2008, 133, 704–715.
31. Hennessy, B.T.; Giordano, S.; Broglio, K.; Duan, Z.; Trent, J.; Buchholz, T.A.; Babiera, G.; Hortobagyi, G.N.; Valero, V. Biphasic Metaplastic Sarcomatoid Carcinoma of the Breast. Ann. Oncol. 2006, 17, 605–613.
32. Vega, S.; Morales, A.V.; Ocana, O.H.; Valdes, F.; Fabregat, I.; Nieto, M.A. Snail Blocks the Cell Cycle and Confers Resistance to Cell Death. Genes Dev. 2004, 18, 1131–1143.
33. Medici, D.; Hay, E.D.; Olsen, B.R. Snail and Slug Promote Epithelial-Mesenchymal Transition through Beta-Catenin-T-Cell Factor-4-Dependent Expression of Transforming Growth Factor-Beta3. Mol. Biol. Cell 2008, 19, 4875–4887.
34. Stemmler, M.P.; Eccles, R.L.; Brabletz, S.; Brabletz, T. Non-Redundant Functions of Emt Transcription Factors. Nat. Cell Biol. 2019, 21, 102–112.
35. Di Gennaro, A.; Damiano, V.; Brisotto, G.; Armellin, M.; Perin, T.; Zucchetto, A.; Guardascione, M.; Spaink, H.P.; Doglioni, C.; Snaar-Jagalska, B.E.; et al. A P53/Mir-30a/Zeb2 Axis Controls Triple Negative Breast Cancer Aggressiveness. Cell Death Differ. 2018, 25, 2165–2180.
36. Zhu, Q.Q.; Ma, C.; Wang, Q.; Song, Y.; Lv, T. The Role of Twist1 in Epithelial-Mesenchymal Transition and Cancers. Tumour Biol. 2016, 37, 185–197.
37. Yang, Z.; Jiang, S.; Cheng, Y.; Li, T.; Hu, W.; Ma, Z.; Chen, F.; Yang, Y. Foxc1 in Cancer Development and Therapy: Deciphering Its Emerging and Divergent Roles. Ther. Adv. Med. Oncol. 2017, 9, 797–816.
38. Hollier, B.G.; Tinnirello, A.A.; Werden, S.J.; Evans, K.W.; Taube, J.H.; Sarkar, T.R.; Sphyris, N.; Shariati, M.; Kumar, S.V.; Battula, V.L.; et al. Foxc2 Expression Links Epithelial-Mesenchymal Transition and Stem Cell Properties in Breast Cancer. Cancer Res. 2013, 73, 1981–1992.
39. Radisky, D.C. Defining a Role for the Homeoprotein Six1 in Emt and Mammary Tumorigenesis. J. Clin. Investig. 2009, 119, 2528–2531.
40. Yu, M.; Smolen, G.A.; Zhang, J.; Wittner, B.; Schott, B.J.; Brachtel, E.; Ramaswamy, S.; Maheswaran, S.; Haber, D.A. A Developmentally Regulated Inducer of Emt, Lbx1, Contributes to Breast Cancer Progression. Genes Dev. 2009, 23, 1737–1742.
41. Christofori, G. Changing Neighbours, Changing Behaviour: Cell Adhesion Molecule-Mediated Signalling During Tumour Progression. EMBO J. 2003, 22, 2318–2323.

42. Hazan, R.B.; Qiao, R.; Keren, R.; Badano, I.; Suyama, K. Cadherin Switch in Tumor Progression. Ann. N. Y. Acad. Sci. 2004, 1014, 155–163.
43. Mrozik, K.M.; Blaschuk, O.W.; Cheong, C.M.; Zannettino, A.C.W.; Vandyke, K. N-Cadherin in Cancer Metastasis, Its Emerging Role in Haematological Malignancies and Potential as a Therapeutic Target in Cancer. BMC Cancer 2018, 18, 939.
44. Wendt, M.K.; Allington, T.M.; Schiemann, W.P. Mechanisms of the Epithelial-Mesenchymal Transition by Tgf-Beta. Future Oncol. 2009, 5, 1145–1168.
45. Yu, L.; Hu, R.; Sullivan, C.; Swanson, R.J.; Oehninger, S.; Sun, Y.P.; Bocca, S. Mfge8 Regulates Tgf-Beta-Induced Epithelial Mesenchymal Transition in Endometrial Epithelial Cells in Vitro. Reproduction 2016, 152, 225–233.
46. Bokhari, A.A.; Lee, L.R.; Raboteau, D.; Hamilton, C.A.; Maxwell, G.L.; Rodriguez, G.C.; Syed, V. Progesterone Inhibits Endometrial Cancer Invasiveness by Inhibiting the Tgfbeta Pathway. Cancer Prev. Res. 2014, 7, 1045–1055.
47. Izzi, L.; Attisano, L. Ubiquitin-Dependent Regulation of Tgfbeta Signaling in Cancer. Neoplasia 2006, 8, 677–688.
48. Viloria-Petit, A.M.; David, L.; Jia, J.Y.; Erdemir, T.; Bane, A.L.; Pinnaduwage, D.; Roncari, L.; Narimatsu, M.; Bose, R.; Moffat, J.; et al. A Role for the Tgfβ-Par6 Polarity Pathway in Breast Cancer Progression. Proc. Natl. Acad. Sci. USA 2009, 106, 14028–14033.
49. Liu, F.; Gu, L.N.; Shan, B.E.; Geng, C.Z.; Sang, M.X. Biomarkers for Emt and Met in Breast Cancer: An Update. Oncol. Lett. 2016, 12, 4869–4876.
50. Huang, F.; Shi, Q.; Li, Y.; Xu, L.; Xu, C.; Chen, F.; Wang, H.; Liao, H.; Chang, Z.; Liu, F.; et al. Her2/Egfr-Akt Signaling Switches Tgf-B from Inhibiting Cell Proliferation to Promoting Cell Migration in Breast Cancer. Cancer Res. 2018, 78, 6073–6085.
51. Sundqvist, A.; Morikawa, M.; Ren, J.; Vasilaki, E.; Kawasaki, N.; Kobayashi, M.; Koinuma, D.; Aburatani, H.; Miyazono, K.; Heldin, C.H.; et al. Junb Governs a Feed-Forward Network of Tgfβ Signaling That Aggravates Breast Cancer Invasion. Nucleic Acids Res. 2018, 46, 1180–1195.
52. Wu, M.Y.; Yiang, G.T.; Cheng, P.W.; Chu, P.Y.; Li, C.J. Molecular Targets in Hepatocarcinogenesis and Implications for Therapy. J. Clin. Med. 2018, 7, 213.
53. Eger, A.; Stockinger, A.; Park, J.; Langkopf, E.; Mikula, M.; Gotzmann, J.; Mikulits, W.; Beug, H.; Foisner, R. Beta-Catenin and Tgfbeta Signalling Cooperate to Maintain a Mesenchymal Phenotype after Foser-Induced Epithelial to Mesenchymal Transition. Oncogene 2004, 23, 2672–2680.