# Cancer Stem Cells in Cancer

Subjects: Immunology

Contributor: Na Kyeong Lee

Cancer stem cells (CSCs), which have the capacity to self-renew and differentiate into various types of cells, are notorious for their roles in tumor initiation, metastasis, and therapy resistance. Thus, underlying mechanisms for their survival provide key insights into developing effective therapeutic strategies. A more recent focus has been on exosomes that play a role in transmitting information between CSCs and non-CSCs, resulting in activating CSCs for cancer progression and modulating their surrounding microenvironment. The field of CSC-derived exosomes (CSCEXs) for different types of cancer is still under exploration. A deeper understanding and further investigation into CSCEXs' roles in tumorigenicity and the identification of novel exosomal components are necessary for engineering exosomes for the treatment of cancer.

Keywords: cancer stem cell ; cancer stem cell-derived exosome ; immunotherapy ; exosome engineering

## 1. Introduction

The majority of human cancers display heterogeneity in morphology, expression of cell surface markers, and proliferative or angiogenic potential [1]. During tumor progression, intrinsic mechanisms, including acquired mutations and the "cells of origin", drive a heterogeneous population of tumor cells, and extrinsic factors from the microenvironment influence the fate of the cells [2]. This results in tumor cells with genetically distinct molecular signatures and therapy resistance [3]. Intravital microscopy studies have shown that tumor cells dynamically interact with their microenvironment, leading to metastasis from the primary tumor [4]. Lineage-retracing experiments in cancer models revealed a subpopulation of cancer cells displaying stem cell-associated characteristics, called cancer stem cells (CSCs), driving tumor growth [5].

## 2.Cancer Stem Cells

CSCs or cancer-initiating cells, which are masked in tumors and have the capacity to self-renew and differentiate into various types of cells, are known to contribute to tumorigenesis [6][7]. Since the CSC concept emerged in the 1990s, it has been one of the most popular cancer research models. The clonal evolution model postulates that malignancies result from the accumulation of genetic instability and sequential selection within the original clone, leading to intra-tumoral heterogeneity [8]. Markers and properties of CSCs have been identified in hematological malignancies, including leukemia, as well as solid tumors, including brain tumors, breast, colorectal, ovarian, pancreatic, and prostate cancers, multiple myeloma, and melanoma [9][10][11][12][13][14]. CSCs exhibit chemo- or radio-resistance, which is attributed to the epithelial–mesenchymal transition (EMT), the signaling pathways, and the DNA damage checkpoint activation, along with the upregulation of CSC markers, including aldehyde dehydrogenase [15][16]. It has been reported that signaling pathways, such as Wnt, transforming growth factor (TGF)-β, Notch, Hedgehog, JAK-STAT (Janus-activated kinase/signal transducer and activator of transcription), and platelet-derived growth factor receptor (PDGFR), are employed by CSCs. Thus, CSCs are highly sought-after as therapeutic targets for the battle against treatment resistance and tumor relapse.

Localized tumor microenvironments as CSC niches have been investigated using 3-D tissue models and microfluidics [17]. Mesenchymal stem cells (MSCs) in the microenvironment secrete proteins, including cytokines and growth factors, which play roles in the differentiation of MSCs [18]. The more recent focus has been on the role of the exosomes secreted from CSCs in modulating CSC niches. Exosomes containing a wide range of RNAs, DNAs, and proteins are released outside of the originating cells through the fusion of multivesicular endosomes or multivesicular bodies (MVBs) with the plasma membrane [19]. The involvement of exosomes in the phenotype transformation from non-CSC to CSC has been recently evidenced by the presence of exosomal FMR (fragile X mental retardation) 1-AS (antisense RNA) 1, the X chromosome long non-coding RNA (lncRNA), which is overexpressed in malignant tumor tissues and activates TLR (Toll-like receptor) 7-NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling [20].

Exosomes have been reported to interact with the immune cells modulating the host's immune response and tumor progression [21]. Tumor-derived exosomes (TEXs) induce apoptosis of the activated cluster of differentiation (CD) $8^+$ T cells, suppress natural killer (NK) cell activity, promote the induction of regulatory T cells (Tregs) and myeloid-derived

suppressor cells, and interfere with monocyte differentiation. While TEXs form the immunosuppressive environment, Treg-derived exosomes inhibit the induction of cytotoxic T lymphocytes. Furthermore, exosomes released from the NK cells have shown strong cytotoxicity against tumor cells; this finding has been substantiated by the FasL expressed on the membrane of NK cell-derived exosomes as well as its role in the killing of $Fas^+$ tumor cells [22][23]. In addition, a cell-free cancer vaccine candidate using α-fetoprotein-enriched exosomes derived from dendritic cells (DCs) can contribute to adoptive immunotherapy [24]. This stimulates the production of interferon-γ and interleukin (IL)-2 and reduces the expression of TGF-β and IL-10 at the tumor site. The feasibility and safety of DC-derived exosomes and autologous TEXs for the treatment of cancer have been tested in clinical trials [25][26][27][28].

Hence, a deeper understanding and further investigations of the role of CSC-derived exosomes (CSCEXs) in tumorigenicity and the identification of exosomal components could aid in the engineering of exosomes to enhance therapeutic efficacy [29]. The physiological and functional properties of CSCEXs are still under exploration. The immunosuppressive and pro-tumoral capacity of CSCEXs has been studied [30][31]. The CSCEXs induce EMT through the transfer of microRNAs (miRs) to cancer cells and elevate the level of metastasis mediators [32][33]. As cellular expression levels and paracrine or juxtacrine signaling, changed through the transportation of CSCEXs' miRs into the recipient cells, also contribute to drug resistance, the chemotherapeutic effects, such as cell cycle arrest and apoptosis of cancer cells, can be inhibited by CSCEXs [34][35].

## 3. Potential for Exploiting CSCEXs

Stem and progenitor cells mediate regenerative properties through paracrine factors, including cytokines and exosomes [30]. The impact of CSCs and CSCEXs on tumor progression can be inferred from the differential expression of several miRNAs in ductal carcinoma in situ stem-like cells. Non-invasive breast CSCs with downregulated miR-140 and upregulated miR-21 and miR-29a show tumorigenicity and a migratory capacity [36][37]. Thus, the specific targeting of RNAs that are aberrantly expressed in CSCs could help in designing CSC-based therapeutics. We can target CSCs using DNA vaccines or mRNA vaccines, but mutagenicity, short half-life, and autoimmunity are the limitations of conventional DNA vaccines or mRNA vaccines [38]. Cell-to-cell transport of exosomal circular noncoding RNAs is involved in the regulation of CSC phenotypes and can influence the tumor microenvironment [39]. So far, the clinical use of circular noncoding RNAs as cancer vaccines has not yet been proven.

### 3.1. Effects of Exosomes on Cancer Stem Cells

Exosomes mediate various effects on CSCs by stimulating the Wnt, Notch, Hippo, Hedgehog, NF-κB, and TGF-β pathways, among others [40]. It follows that exosomes can exert numerous downstream effects involving differentiation, tumorigenesis, and other crucial endogenous functions of CSCs [41].

In breast cancer, $CD44^-$ cell proportions were observed to increase from $CD44^{high}/CD24^{low}$ CSCs through cell cycle inhibitory miRNA delivery by exosomes [42]. Moreover, in ovarian cancer, the exosomal release of miRNA-454 was observed to sustain the stemness phenotype of cancer cells [43]. Another example of prostate CDEXs with the surface expression of caveolin-1 was observed to transform CSCs into a metastatic phenotype via NF-κB signaling [44]. Furthermore, the interactions of CSCs with CAFs have been observed by using CAF-derived exosomes and their miRNA content, such as miR-21, miR-378e, and miR-143 [45]. These were also observed to promote tumor progression, except for miR-320, which antagonized the premetastatic niche formation [45].

Recent studies have proposed superior tumor growth inhibitory effects by targeting CSCs rather than the whole tumor [46]. Thus, potential strategies for targeting CSCs by delivering miRNAs to inhibit the EMT or the formation of premetastatic niches have been thoroughly researched [47]. Neutralizing antibodies, or antibody-mediated CSC therapies, aim to target CSCs in various cancers to attenuate the stemness phenotype of these cells [47]. Exosome signaling is also known to induce the production of CSCs, ameliorate treatment resistance, and prevent tumor relapse [48]. There is also a growing interest in exosome engineering to target specific signaling pathways by miR or siRNA inhibitors for CSC modulation [40].

### 3.2. Targeting Cancer Stem Cells through Engineered Exosomes

The identification of various potential markers of CSCs expressed in different cancer types provides a possible means for targeting CSCs specifically using engineered exosomes. Targeting the CD44 expressed in hepatocellular carcinoma in metastatic hepatocellular CSCs using anti-CD44 antibody-coated exosomes could directly induce CSC death. Likewise, the CSC markers of different cancers, such as $CD24^+$, CD133, $CD90^+$, $ESA^+$ ($EpCAM^+$), CD166, CD44, CD49f, integrins a2/b1, BCL-2, β-catenin, BMI-1, BrdU, Ki67, CD44, CD133, CD49f (integrin a6), CK5/14, CK8/18, GST-p, ABCG2/Hoechst 33342, OCT3/4, P63, P27, SCA-1, SMO, and CD200, can be targeted using engineered anti-antibody-

coated exosomes. In addition, exosomes engineered for targeting different signaling pathways that contribute to self-renewal, differentiation, tumor initiation, and drug resistance in CSCs could aid in the effective design of engineered exosomes for cancer treatment [49][50].

According to the differential roles of surface markers/cargo in exosomes derived from CSCs and non-stem cells, exosomes engineered with surface markers/cargo unique to CSCs are expected to have potential for the treatment of cancer. CSCEXs contain multiple stemness marker proteins, such as CD44v6 and Notch1, which generate transient or dynamic tumor heterogeneity in the tumor microenvironment compared to non-cancer exosomes [51]. CSCEXs' RNA cargo, such as miR-19b-3p, playing a unique role in metastasis can also be envisaged as a therapeutic target. The exosomal miR-210-3p isolated from lung CSCs contributed to the pro-metastatic niche of lung cancer, while miR-210-3p in non-stem TEXs mainly promoted tumor angiogenesis. Triphosphate RNAs unique to CSCEXs, which facilitate the pro-tumoral phenotype of neutrophils, can be targeted for cancer immunotherapy [52].

## 4. Conclusions and Future Directions

CSCs, or cancer-initiating cells, are tumorigenic and give rise to local and distal tumor recurrence. A subpopulation of cancer cells possessing self-renewing and multipotent properties is a potent hindrance to conventional cancer therapies that solely target the existing malignant cells. Many investigations have focused on gaining insights into the biological properties of CSCs and their secretions for the development of novel therapeutic interventions specifically targeting CSCs. Recent investigations have established the significance of exosomes in cell-to-cell communication and the formation of a unique niche for the homeostasis of CSCs and non-stem cancer cells; this makes CSCs an ideal target in disrupting this balance. We can focus on targeting and exploiting Evs, including the exosomes released from CSCs, as a potential strategy for eliminating CSCs [53].

Further efforts are needed to elucidate the complex biological effects of CSCEXs on tumorigenesis, metastasis, and cancer immunity. Thus, a better and more thorough understanding of the characteristics and contents of these CSCEXs and other EVs may give way to the development of new clinical diagnostic/prognostic tools and therapies to prevent tumor resistance and relapse [54].

### References


1. Marusyk, A.; Polyak, K. Tumor heterogeneity: Causes and consequences. Biochim. Biophys. Acta 2010, 1805, 105–117.
2. Sutherland, K.D.; Visvader, J.E. Cellular Mechanisms Underlying Intertumoral Heterogeneity. Trends Cancer 2015, 1, 15–23.
3. Dagogo-Jack, I.; Shaw, A.T. Tumour heterogeneity and resistance to cancer therapies. Nat. Rev. Clin. Oncol. 2018, 15, 81–94.
4. Scheele, C.L.; Maynard, C.; van Rheenen, J. Intravital Insights into Heterogeneity, Metastasis, and Therapy Responses. Trends Cancer 2016, 2, 205–216.
5. Schepers, A.G.; Snippert, H.J.; Stange, D.E.; van den Born, M.; van Es, J.H.; van de Wetering, M.; Clevers, H. Lineage Tracing Reveals Lgr5+ Stem Cell Activity in Mouse Intestinal Adenomas. Science 2012, 337, 730–735.
6. Batlle, E.; Clevers, H. Cancer stem cells revisited. Nat. Med. 2017, 23, 1124–1134.
7. Yu, Z.; Pestell, T.G.; Lisanti, M.P.; Pestell, R.G. Cancer stem cells. Int. J. Biochem. Cell Biol. 2012, 44, 2144–2151.
8. Nowell, P.C. The clonal evolution of tumor cell populations. Science 1976, 194, 23–28.
9. Mimeault, M.; Hauke, R.; Mehta, P.P.; Batra, S.K. Recent advances in cancer stem/progenitor cell research: Therapeutic implications for overcoming resistance to the most aggressive cancers. J. Cell. Mol. Med. 2007, 11, 981–1011.
10. Singh, S.K.; Clarke, I.D.; Terasaki, M.; Bonn, V.E.; Hawkins, C.; Squire, J.; Dirks, P.B. Identification of a cancer stem cell in human brain tumors. Cancer Res. 2003, 63, 5821–5828.
11. Al-Hajj, M.; Wicha, M.S.; Benito-Hernandez, A.; Morrison, S.J.; Clarke, M.F. Prospective identification of tumorigenic breast cancer cells. Proc. Natl. Acad. Sci. USA 2003, 100, 3983–3988.
12. Zhang, S.; Balch, C.; Chan, M.W.; Lai, H.-C.; Matei, D.; Schilder, J.M.; Yan, P.S.; Huang, T.H.-M.; Nephew, K.P. Identification and Characterization of Ovarian Cancer-Initiating Cells from Primary Human Tumors. Cancer Res. 2008, 68, 4311–4320.

13. Schatton, T.; Murphy, G.F.; Frank, N.Y.; Yamaura, K.; Waaga-Gasser, A.M.; Gasser, M.; Zhan, Q.; Jordan, S.; Duncan, L.M.; Weishaupt, C.; et al. Identification of cells initiating human melanomas. Nature 2008, 451, 345–349.

14. Matsui, W.; Huff, C.A.; Wang, Q.; Malehorn, M.T.; Barber, J.; Tanhehco, Y.; Smith, B.D.; Civin, C.I.; Jones, R.J. Characterization of clonogenic multiple myeloma cells. Blood 2004, 103, 2332–2336.

15. Kaur, G.; Sharma, P.; Dogra, N.; Singh, S. Eradicating Cancer Stem Cells: Concepts, Issues, and Challenges. Curr. Treat. Options Oncol. 2018, 19, 20.

16. Pattabiraman, D.R.; Weinberg, R.A. Tackling the cancer stem cells—What challenges do they pose? Nat. Rev. Drug Discov. 2014, 13, 497–512.

17. Sreepadmanabh, M.; Toley, B.J. Investigations into the cancer stem cell niche using in-vitro 3-D tumor models and microfluidics. Biotechnol. Adv. 2018, 36, 1094–1110.

18. Wang, K.-X.; Xu, L.-L.; Rui, Y.-F.; Huang, S.; Lin, S.-E.; Xiong, J.-H.; Li, Y.-H.; Lee, W.Y.-W.; Li, G. The Effects of Secretion Factors from Umbilical Cord Derived Mesenchymal Stem Cells on Osteogenic Differentiation of Mesenchymal Stem Cells. PLoS ONE 2015, 10, e0120593.

19. Van Der Goot, F.G.; Gruenberg, J. Intra-endosomal membrane traffic. Trends Cell Biol. 2006, 16, 514–521.

20. Li, W.; Zhang, L.; Guo, B.; Deng, J.; Wu, S.; Li, F.; Wang, Y.; Lu, J.; Zhou, Y. Exosomal FMR1-AS1 facilitates maintaining cancer stem-like cell dynamic equilibrium via TLR7/NFκB/c-Myc signaling in female esophageal carcinoma. Mol. Cancer 2019, 18, 1–15.

21. Taylor, D.D.; Gercel-Taylor, C. Exosomes/microvesicles: Mediators of cancer-associated immunosuppressive microenvironments. Semin. Immunopathol. 2011, 33, 441–454.

22. Seo, N.; Akiyoshi, K.; Shiku, H. Exosome-mediated regulation of tumor immunology. Cancer Sci. 2018, 109, 2998–3004.

23. Lugini, L.; Cecchetti, S.; Huber, V.; Luciani, F.; Macchia, G.; Spadaro, F.; Paris, L.; Abalsamo, L.; Colone, M.; Molinari, A.; et al. Immune surveillance properties of human NK cell-derived exosomes. J. Immunol. 2012, 189, 2833–2842.

24. Lu, Z.; Zuo, B.; Jing, R.; Gao, X.; Rao, Q.; Liu, Z.; Qi, H.; Guo, H.; Yin, H. Dendritic cell-derived exosomes elicit tumor regression in autochthonous hepatocellular carcinoma mouse models. J. Hepatol. 2017, 67, 739–748.

25. Escudier, B.; Dorval, T.; Chaput, N.; André, F.; Caby, M.-P.; Novault, S.; Flament, C.; Leboulaire, C.; Borg, C.; Amigorena, S.; et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: Results of thefirst phase I clinical trial. J. Transl. Med. 2005, 3, 10.

26. Morse, M.A.; Garst, J.; Osada, T.; Khan, S.; Hobeika, A.; Clay, T.M.; Valente, N.; Shreeniwas, R.; Sutton, M.A.; Delcayre, A.; et al. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. J. Transl. Med. 2005, 3, 9.

27. Besse, B.; Charrier, M.; Lapierre, V.; Dansin, E.; Lantz, O.; Planchard, D.; Le Chevalier, T.; Livartoski, A.; Barlesi, F.; Laplanche, A.; et al. Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC. OncoImmunology 2016, 5, e1071008.

28. Dai, S.; Wei, D.; Wu, Z.; Zhou, X.; Wei, X.; Huang, H.; Li, G. Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. Mol. Ther. 2008, 16, 782–790.

29. Wang, J.; Zheng, Y.; Zhao, M. Exosome-Based Cancer Therapy: Implication for Targeting Cancer Stem Cells. Front. Pharmacol. 2017, 7, 533.

30. Al-Sowayan, B.S.; Al-Shareeda, A.T.; Alrfaei, B.M. Cancer Stem Cell-Exosomes, Unexposed Player in Tumorigenicity. Front. Pharmacol. 2020, 11, 384.

31. Gabrusiewicz, K.; Li, X.; Wei, J.; Hashimoto, Y.; Marisetty, A.L.; Ott, M.; Wang, F.; Hawke, D.; Yu, J.; Healy, L.M.; et al. Glioblastoma stem cell-derived exosomes induce M2 macrophages and PD-L1 expression on human monocytes. OncoImmunology 2018, 7, e1412909.

32. Wang, L.; Yang, G.; Zhao, D.; Wang, J.; Bai, Y.; Peng, Q.; Wang, H.; Fang, R.; Chen, G.; Wang, Z.; et al. CD103-positive CSC exosome promotes EMT of clear cell renal cell carcinoma: Role of remote MiR-19b-3p. Mol. Cancer 2019, 18, 1–15.

33. Cheng, Z.; Lei, Z.; Yang, P.; Si, A.; Xiang, D.; Tang, X.; Guo, G.; Zhou, J.; Hüser, N. Exosome-transmitted p120-catenin suppresses hepatocellular carcinoma progression via STAT3 pathways. Mol. Carcinog. 2019, 58, 1389–1399.

34. Yang, Z.; Zhao, N.; Cui, J.; Wu, H.; Xiong, J.; Peng, T. Exosomes derived from cancer stem cells of gemcitabine-resistant pancreatic cancer cells enhance drug resistance by delivering miR-210. Cell. Oncol. 2020, 43, 123–136.

35. Boelens, M.C.; Wu, T.J.; Nabet, B.Y.; Xu, B.; Qiu, Y.; Yoon, T.; Azzam, D.J.; Victor, C.T.-S.; Wiemann, B.Z.; Ishwaran, H.; et al. Exosome Transfer from Stromal to Breast Cancer Cells Regulates Therapy Resistance Pathways. Cell 2014,

159, 499–513.

36. Wolfson, B.; Eades, G.; Zhou, Q. Roles of microRNA-140 in stem cell-associated early stage breast cancer. World J. Stem Cells 2014, 6, 591–597.
37. Li, Q.; Eades, G.; Yao, Y.; Zhang, Y.; Zhou, Q. Characterization of a Stem-like Subpopulation in Basal-like Ductal Carcinoma in Situ (DCIS) Lesions. J. Biol. Chem. 2014, 289, 1303–1312.
38. McNamara, M.A.; Nair, S.K.; Holl, E.K. RNA-Based Vaccines in Cancer Immunotherapy. J. Immunol. Res. 2015, 2015, 1–9.
39. Feng, Z.; Meng, S.; Zhou, H.; Xu, Z.; Tang, Y.; Li, P.; Liu, C.; Huang, Y.; Wu, M. Functions and Potential Applications of Circular RNAs in Cancer Stem Cells. Front. Oncol. 2019, 9, 500.
40. Dai, J.; Su, Y.; Zhong, S.; Cong, L.; Liu, B.; Yang, J.; Tao, Y.; He, Z.; Chen, C.; Jiang, Y. Exosomes: Key players in cancer and potential therapeutic strategy. Signal Transduct. Target. Ther. 2020, 5, 145.
41. Xu, J.; Liao, K.; Zhou, W. Exosomes Regulate the Transformation of Cancer Cells in Cancer Stem Cell Homeostasis. Stem Cells Int. 2018, 2018, 1–16.
42. Valcz, G.; Buzás, E.I.; Szállási, Z.; Kalmár, A.; Krenács, T.; Tulassay, Z.; Igaz, P.; Molnár, B. Perspective: Bidirectional exosomal transport between cancer stem cells and their fibroblast-rich microenvironment during metastasis formation. NPJ Breast Cancer 2018, 4, 1–7.
43. Wang, L.; He, M.; Fu, L.; Jin, Y. Exosomal release of microRNA-454 by breast cancer cells sustains biological properties of cancer stem cells via the PRRT2/Wnt axis in ovarian cancer. Life Sci. 2020, 257, 118024.
44. Lin, X.-J.; Fang, J.-H.; Yang, X.-J.; Zhang, C.; Yuan, Y.; Zheng, L.; Zhuang, S. Hepatocellular carcinoma cell-secreted exosomal microRNA-210 promotes angiogenesis in vitro and in vivo. Mol. Ther. Nucleic Acids 2018, 11, 243–252.
45. Turdo, A.; Porcelli, G.; D'Accardo, C.; Di Franco, S.; Verona, F.; Forte, S.; Giuffrida, D.; Memeo, L.; Todaro, M.; Stassi, G. Metabolic Escape Routes of Cancer Stem Cells and Therapeutic Opportunities. Cancers 2020, 12, 1436.
46. Garcia-Mayea, Y.; Mir, C.; Masson, F.; Paciucci, R.; Lleonart, M. Insights into new mechanisms and models of cancer stem cell multidrug resistance. Semin. Cancer Biol. 2020, 60, 166–180.
47. Rossi, F.; Noren, H.; Jove, R.; Beljanski, V.; Grinnemo, K.-H. Differences and similarities between cancer and somatic stem cells: Therapeutic implications. Stem Cell Res. Ther. 2020, 11, 1–16.
48. Steinbichler, T.B.; Dudás, J.; Skvortsov, S.; Ganswindt, U.; Riechelmann, H.; Skvortsova, I.I. Therapy resistance mediated by exosomes. Mol. Cancer 2019, 18, 58.
49. Dandawate, P.R.; Subramaniam, D.; Jensen, R.A.; Anant, S. Targeting cancer stem cells and signaling pathways by phytochemicals: Novel approach for breast cancer therapy. Semin. Cancer Biol. 2016, 40–41, 192–208.
50. Huang, R.; Rofstad, E.K. Cancer stem cells (CSCs), cervical CSCs and targeted therapies. Oncotarget 2017, 8, 35351–35367.
51. Sun, Z.; Wang, L.; Zhou, Y.; Dong, L.; Ma, W.; Lv, L.; Zhang, J.; Wang, X. Glioblastoma Stem Cell-Derived Exosomes Enhance Stemness and Tumorigenicity of Glioma Cells by Transferring Notch1 Protein. Cell. Mol. Neurobiol. 2019, 40, 767–784.
52. Hwang, W.-L.; Lan, H.-Y.; Cheng, W.-C.; Huang, S.-C.; Yang, M.-H. Tumor stem-like cell-derived exosomal RNAs prime neutrophils for facilitating tumorigenesis of colon cancer. J. Hematol. Oncol. 2019, 12, 1–17.
53. Aramini, B.; Masciale, V.; Haider, K.H. Defining lung cancer stem cells exosomal payload of miRNAs in clinical perspective. World J. Stem Cells 2020, 12, 406–421.
54. Brocco, D.; Lanuti, P.; Simeone, P.; Bologna, G.; Pieragostino, D.; Cufaro, M.C.; Graziano, V.; Peri, M.; Marino, P.D.; Tursi, M.D.; et al. Circulating Cancer Stem Cell-Derived Extracellular Vesicles as a Novel Biomarker for Clinical Outcome Evaluation. J. Oncol. 2019, 2019, 5879616.