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Research Article

Role of Tumor Microenvironment in Cancer Stem Cell and Clinical Application

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Abstract

Cancer stem cells can differentiate and self-renew. Therefore, they are resistant to traditional therapies and cause cancer relapse. The most determinant factor for the CSCs resistance is the tumor microenvironment, which contains many aspects to prevent CSCs from being eradicated. In this review, we will introduce different aspects according to the tumor microenvironment (TME) like hypoxia, which allows CSCs to flourish in the TME; CAF, which contributes to the self-renewal quality of CSCs; immune cells, which could potentially incapacitate cancer cells and decrease the stemness of CSCs, and different major signaling pathways that help with the proliferation and survival of CSCs. We also conclude with the major clinical trials involved in each of the signaling pathways, which presents possibilities to assist with therapy.

Keywords: Cancer stem cell, Tumor Microenvironment, Hypoxia, Cancer-associated fibroblasts, Immune cells, Notch, WNT, Hedgehog.

Abbreviations: CSCs: Cancer stem cells; EMT: Epithelial Mesenchymal Transition; TME: Tumor microenvironment; HIF: Hypoxia-inducible factors; CAF: Cancer-associated Fibroblasts; MDSCs: myeloid-derived suppressor cells; TAMs: tumor-associated macrophages; TANs: tumor-associated neutrophils; BCC: Basal cell carcinoma; ECM: Extracellular matrix; ROS: reactive oxygen species; VEGF: Vascular endothelial growth factor; CCL2: C-C motif ligand 2; LOX: lysyl oxidase; nk cells: natural killer cells; mAbs: monoclonal antibodies; CML: chronic myeloid leukaemia; TKI: tyrosine kinase inhibitors; MM: Multiple myeloid; CLL: chronic lymphocytic leukemia.

Introduction

Cancer is an illness without a completely effective cure yet. Statistically, in 2020, the four major cancer types alone resulted in the deaths of approximately 606,520 people in the US [1]. Not to mention, a tremendous number of patients are undergoing therapeutic resistance and even for "recovered" patients, which are mostly caused by cancer stem cells. Cancer stem cells (CSCs) are characterized by self-renewal and differentiation abilities [2]. It is tricky to identify CSCs. However, surface markers, like CD111 and CD44, allow the identification of CSCs [3]. Additionally, functional assays include ALDH1 and Hoechst Exclusion Assay, which have also been used to detect CSCs; all the markers present the possibility to eradicate CSCs [4].

The first origin theory for CSCs derivation is from stem cells, and another possibility is the development from progenitor cells, which are more abundant while still containing the ability of self-renew [5]. CSCs could also be developed from differentiated cells by de-differentiation.2 CSCs have been known to be resistant to traditional therapies like chemotherapy and radiotherapy [6]. There are many contributing factors including Epithelial Mesenchymal Transition (EMT), Detox proteins and multidrug resistance, dormancy, resistance to DNA damage-induced cell death, tumor environment, epigenetics, and signaling pathways [7]. For example, CSCs have the ability to proliferate slower to avoid being targeted by chemotherapy, which targets faster proliferating cells [8].

Possible solutions include immunotherapy, which targets the use of tumor antigens to affect the balance between apoptosis and proliferation [9]. However, immunosuppression presents conflicts to the success of immunotherapy, and furthermore, there are inhibitor therapy and nanotherapy [10]. Preclinical and clinical trials are being held for the testing of additional therapies. Investigating how CSCs are therapeutic-resistant and its functions will aid in the success of a therapy.

Hypoxia

Hypoxic regions, along with acidic and necrotic regions are authentication marks of hostile solid tumors [11]. Specifically, interactions between the hypoxic niche and CSCs lead to therapeutic resistance, tumor heterogeneity, and stemness maintenance [12]. Hypoxic stress normally happens along with nutrient restriction and acidic stress, which stimulates the growth the subpopulations of cells that are adapted to survive in nutrient-restricted conditions [13]. In turn, the cells encourage shifts toward aerobic glycolysis and glutamine-mediated fatty acid production [14]. Because of this, CSCs can live and flourish in the nutrient-deprived regions, giving rise to stem cell characteristics.5

When exposed to hypoxic stress, CSCs are enriched which leads to the resistance to traditional therapies.6 Distinct resistance mechanisms have been proposed, like the induction of Hypoxia-inducible factors (HIF) signaling that ends with signaling pathways [15]. HIFs, such as HIF-1 and HIF-2, regulate the effects of hypoxia [16]. HIF-1 is globally expressed in multiple tissues when responding to acute hypoxia; narrowing in, HIF1a can activate Notch and WNT signaling directly, as well as regulating metabolic adaptations after nutrient deprivation [17]. In addition, HIF-2 is able to maintain stemness characteristics in neuro and glioblastoma cells, while remaining elevated under chronic hypoxia. Also, it upregulates key transcription factors controlling stem cell maintenance [18].

Since CSCs have a high capacity to thrive in nutrient-deprived regions, stemness programs are promoted along with phenotypes of dormancy and migration.11 CSCs express high levels of HIF-1 in hypoxic conditions, which in turn elevates angiogenesis and VEGF expression in the region [19]. CSCs which reside in hypoxia also demonstrate different immunologic features and interactions within the niche. VEGF has many functions, including assisting PD-L1 expression and subduing the dendritic cell function, showing that therapies displaying T cell and dendritic cells will not be as effective when targeting the hypoxic niche [20]. CSCs that are in contact with hypoxia can increase and keep other niches. Hypoxic CSCs can migrate using upregulation of epithelial-mesenchymal signaling, or EMT signaling [21]. Their migration changes in adhesion receptor expression. Because of this, hypoxia furthers therapeutic resistance. They are distinctly placed to avoid the therapeutic stressors contrasted with non-stem tumor cells in the hypoxic microenvironment because of the lower manufacturing of reactive oxygen species, or ROS [22].

CAF

CAFs, or cancer-associated fibroblasts, are a cellular subtype being studied to create new target therapies along with anticipating patients' results. CAFs reside in the CSC microenvironment with differentiated neoplastic cells and normal cells [23]. They play an important role in the TME (tumor microenvironment) by being in a complex system of tumor-stroma evolution and angiogenesis [24]. Reciprocal crosstalk between CSCs and the cells mentioned above contributes to self-renewal ability. It is also possible that CAFs stem from resident fibroblast activation, as well as adipocytes, endothelial, and pericytes conversion [25]. In addition, CSCs secrete various cytokines and ligands that change ordinary fibroblasts to CAFs to reinforce self-renewal and proliferation. CAFs supply molecules such as soluble factors and proteases to assist in ECM synthesis or remodeling. Meanwhile, it also provides cytokines, growth factors, and chemokines [26]. A tight crosstalk with the CSCs concerns the CAF secreted factors that direct their plasticity, chemoresistance, and self-renewal capacity. The factors in turn regulate the CSCs stemness characteristics to support and induce aggressiveness.25 Amid the different cytokines and growth factors that CAFs release, many studies emphasized the role of IL-6 and IL-8 in maintaining the stem-like characteristics of cancer cells and the induction of tumor growth, chemoresistance, and metastasis formation [27].

Additionally, research has shown that hyperactive NF-kB signaling drives the subset of CAFs while sustaining the cancer stemness by discharging IL6 and IL8 [28]. In line with this observation, Korkaya et al. have shown that in the subpopulation of resistant BC cells, the inflammatory loop IL-6/STAT-3/NF-kB can be activated by the trastuzumab treatment, which corresponds with the of CSCs [29]. Therapeutically, the management of anti-IL-6 receptor antibody returns the stemness phenotypes of tumor cells [30]. Aside from cytokines, CAFs also secrete growth factors, an example being hepatocyte growth factors, or HGF, which induces invasiveness of stem cells [31]. As an example, in hepatocellular carcinoma, activation of MET/FRA1/HEY1 cataract was used by HGF to sustain cancer cell stemness [32]. Consequently, HGF and CCL2, both examples of growth factors secreted by CAFs, upregulate the stem-like characteristics by the WNT and Notch, key stemness regulators.32 Finally, in addition to cytokines and growth factors, CAFs secret chemokine proteins, an example being SDF-1 [33]. It is highly exhibited on the surface of CSC, and it associates with CXCR4, its receptor, allowing the regulation of stem phenotype by the activation of PI3K/AKT and Wnt/b-catenin signaling pathways

[34]. It was found that CXCR4+ cells were more likely to achieve the stem properties and phenotypes compared to CXCR4- cells, while proliferation of CD44+ and CD24- BC cells is also boosted [35]. Another example of a chemokine, CCL2, assists CSC self-renewal that initiates NOTCH signaling pathway.12

The key role of CAFs in the maintenance of CSC and drug disorderliness allows the utilization of therapeutic strategies. Blocking CAF and crosstalk from CSCs can be used to increase patients' survival. A new subpopulation of CAFs, CD10+ and GPR77+, was recognized and corresponds highly with decreased patient survival in different cancers [36]. Additionally, some in vitro experiments emphasized that CAFs assure a CSC reservoir in distinct tumors that increase stem marker expressions such as CD44, Sox2, and Bmi-1, assist CSC pool expansion, and self-renewal abilities [37]. Medium conditioned by CAF encouraged the tumorigenic behavior and the belligerence shown by CSCs [38].

Immune Cells

A feature of cancer cells is the ability to lead infiltrating immune cells to protumorigenic and immunosuppressive conditions. Suppression of adaptive immunity can be caused by the polarization and activation of cells like myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMS), and T cells, which impacts cell fate along with survival. These different kinds of immune cells can stimulate the dedifferentiation process of CSCs. Zoomed in, the induction of stemness was related to reduced anti-cancer immune cells like CD8+ T cells, polarization of infiltrating macrophages, B cells, and natural killer cells. The phenotypic plasticity displayed in CSCs can increase cancer hallmarks because of their ability to transdifferentiate into fibroblasts, pericytes, and endothelial cells, meaning it assists in tumor angiogenesis, inflammation, and cell niche development. Barring of immune cells from the TME has been related with inaccurate diagnosis in the bulk of cancers. When accounting for 21 solid cancer types, the exclusion of immune cells was shown to connect with the presence of stemness. Increase of stemness correlates with higher intratumoral heterogeneity, with the possibility of shielding antigenic clones from the immune system [39].

CSCs are known for recruiting and dividing TAMs, which originate from bone-marrow-derived macrophages, or BMDMs and local tissue inhabitant macrophages, which source from progenitors and hematopoietic stem cells. The recruitment is propelled by many different chemokines that are produced by macrophages, cancer cells, or other stromal cells, like C-C motif ligand 2 (CCL2), lysyl oxidase (LOX), or CCL3 [40]. In addition to the TAM's characteristics, because of their substantial plasticity and diversity, their populations can be diverged between two groups, the M1 phenotype that's "classically activated" or the M2 phenotype, which is "alternatively activated". Microglia and macrophages are recruited to tumor sites where they acquire amoeboid morphology while adopting an M2 tumor-promoting phenotype, which in turn contributes to the immunosuppressive tumor environment [41]. When low levels of IFN- γ and high levels of IL-10 are secreted by M2 TAMs, microglia behave like a potent Treg cell and supports suppression of immunity in the glioma environment. TAMs is closely related with the STAT3 pathways [42]. For instance, in pancreatic cancer, TAMs were discovered to assist CSC function with STAT3. In addition, TAM adhesion and immunosuppressive role in gliomas is positively correlated with STAT3 mediated vascular cell adhesion protein-1 expression [43].

Myeloid derived suppressor cells are a heterogeneous population of undeveloped myeloid cells composed of myeloid progenitors and precursors of granulocytes, macrophages, and dendritic cells. Recent studies have shown that when myeloid populations are expanded, they can sensitize tumors to traditional therapies [44]. The position of these populations has received a lot of attention in terms of comprehending protumorigenic immune cell function. For example, STAT3 in cancer cells can be activated by MDSC-derived interleukin-23, and the inhibition of MDSC by depletion or antibody blockage (anti-IL-23) can sensitize androgen deprivation therapy in autochthonous models. Similar results are found in pancreatic cancer [45]. CSC-derived exosomes can increase the survival of suppressive neutrophils that encourage cancer growth, which correlates with the discovery of the lack of natural killer (nk) cells. When there are surface activating receptors present without any signs of inhibiting receptors, nk cells can directly lyse MHC-I-deficient tumor cells or other pathogens. In the usual condition, binding surface inhibitory receptors that have HLA class I antigens inhibits the activation of nk cells. The purpose of the antigens is to maintain homeostasis and to defend non pathological cells [46].

Immunotherapy has recently surfaced as a possible successful strategy for cancer treatment. Its effectiveness is because cancer cells usually upregulate immune-inhibitory cell surface signals like PD-L1, which is a programmed death ligand, to elude immune-mediated killing [47]. This suggests that checkpoint blockade could be a potent procedure for eliminating the subfraction. Immune checkpoint therapy anchors blocking antibodies in opposition to these inhibitory molecules, which in turn derepress the tumor's immune response. CSCs present in pancreatic cancer upregulate CD47 that allows the evasion of innate immune killing, which makes them a pertinent target for the CD47 blocking antibodies by increasing TAM1 population [48]. Targeting TANs and/or TAMs increase the sensitivity to chemotherapy both in in vivo and preclinical models [49]. In addition, CSCs urge resistance to

adoptive T cell transfer, referring to the engineer of patient-derived T cells to target a certain cancer antigen and create an immune response after re-transplant [50]. The findings of a population of CSCs in squamous cell carcinoma favorably eluded T cells by expressing CD80, which caused the fatigue and relapse of T cells suggesting that the potency of immunotherapy in targeting cancer cells with "stemness" differs by tissue and specific strategy. Because of immunotherapy's recent surfacing, the effect of heterogeneous cancer cell populations on the clinical strategies is not fully comprehended yet. This means that a critical area for future study is studying the aggressive CSC populations and how they may elude immunotherapy with resistance [51].

Signaling pathway

Notch Signaling

Notch signaling is a crucial factor of stem cell preservation. It has been observed that Notch signaling ligand Jag1 presented in the vascular niche in cancer cells activate Notch signaling [52]. More specifically, Jag1 takes part in stem cell proliferation as well as stem cell niche formation in intestinal cancers models, which are absent of APC; an interesting observation about Jag1 is that it supports hair follicle stem cells proliferation when expressed by Tregs in a non-tumoral context [53]. These properties of Notch signaling pathway could increase stemness features in neighbor cells in cancer where TME cells express Jag1 [54]. In addition, recent studies proved that Notch signaling in mammary gland macrophages can be activated by DII1, which is derived from mammary stem cells [55]. This in turn fortifies mammary gland stem cells self-renewal by macrophage derived Wnt ligands [54].

Cell lineage specification in developing lymphocytes as well as the marginal zone's regulation of B lymphocyte subsets involves Notch signaling [56]. In addition, Notch signaling is also involved in the differentiation of different cells, including helper, Treg, lymphoid, and dendritic cells. Notch signaling is important in many aspects [57]. For example, it regulates the main component of the anti-tumor immune function, the CD8+ cytotoxic T cell [58]. However, some functions of Notch signaling, such as instances in CD8+ T cells derived from colon cancer patients, need context and has the possibility of decreasing PD-1 expression to increase cytotoxic activity [59]. Furthermore, treatment that uses DII1, a multivalent protein to accelerate the reduction of tumor growth supports the role of Notch signaling to sustain antitumoral T lymphocyte activity by enhancing the antigen-specific cytotoxicity as well as evoking lymphocyte T differentiation [60]. In addition, Notch signaling is essential to regulate different elements of the immunosuppressive environment, with TAMs as an example [61]. Additional studies displayed that inducing the M1-macrophage phenotype involves Notch signaling. Macrophages lacking Notch signaling decrease the presentation activity of antigen [62]. When Notch is activated by force, expression of N1ICD suppresses tumor growth by revoking the function of TAM; in turn, TAM displays a transcriptomic signature connected to the Notch pathway [60].

Aberrant Notch signaling has been recognized in different types of cancer. The Notch pathway's pathogenic role potentially depends on the tumor type. In terms of clinical oncology, the inferences of the Notch signaling pathway complexity and diversity are a double-edged sword [63]. Initially, when the Notch pathway is targeted, it has the possibility to affect numerous cell types other than mature tumor cells and CSCs at the same, such as vascular endothelial cells and immune cells [64]. There are potential outcomes that turn out to be advantages, like the inhibition of angiogenesis, but there could also be drawbacks, including the toxicities or the repression of anticancer immunity [63]. To successfully develop therapeutic agents to target the Notch pathway, a complete comprehension of the mechanisms of the Notch signaling's roles in certain cancers in addition to the utilization and development of mechanism-based combination regimens is required [65]. Currently, researchers have developed various divisions of Notch pathway inhibitors that have different targets and mechanisms of action, along with several agents that are at different periods of clinical development [66]. The oldest and the biggest class of agents that target Notch signaling are γ-secretase, also known as GSIs, which block the Notch receptors' second proteolysis and releases the intracellular domain.66 For example, the merging of GSI MRK-003 and trastuzumab completely cures HER2-positive breast cancer in mouse models. An additional example is BMS-906024, which has been tested with non-small-cell lung cancer in preclinical models [67]. Another approach to hinder aberrant Notch signaling is to target Notch ligands that have monoclonal antibodies, or mAbs [68]. Treatment involving anti-DLL4 mAbs impedes the development of functional capillaries, which causes disordered angiogenesis along with the immediate effects of Notch signaling in tumor cells [69]. In amalgamation with numerous treatments, like immune-checkpoint inhibitors, assorted studies of demcizumab, a humanized anti-DLL4 IgG2 mAb, have been finished with currently unavailable results.69 However, this agent is not in clinical development anymore. Besides DLL4, researchers are pursuing DLL3 as a therapeutic target in small-cell-lung cancer [70]. In addition to mAbs targeting Notch ligands, there are also some that target Notch receptors. For instance, brontoctuzumab, an anti-Notch1 mAb with an average antitumor activity has been demonstrated in clinical studies throughout the years [71].

Wnt signaling

Wnt signaling makes up one of the dominant mechanisms that regulate tissue morphogenesis while repair and embryogenesis take place. In addition to that, Wnt signaling controls the downstream signaling cascade, whether canonical or non-canonical, consequently has effect on the cellular cytoskeleton, as well as transcriptional control of differentiation and proliferation, along with organelle dynamics [72]. The three dominant pathways the Wnt signaling cascade encompasses the canonical Wnt pathway, the non-canonical planar-cell polarity pathway, and the non-canonical Wnt-calcium pathway [73]. The first pathway involves activating a transcriptional transactivation complex that consists of T cell-specific transcription factor, β-catenin, and lymphoid enhancer-binding factor [74]. The latter pathway is independent of β-catenin, and assists in the regulation of the cytoskeleton of the cell. The final pathway mentioned is involved in the regulation of intracellular calcium levels.74 Irregular Wnt signaling has relations with various cancers, like breast, colorectal, oral, lung, hematopoietic, and cervical cancer [75]. The canonical Wnt pathway is generally involved in the development of numerous human cancers. The interchanges between receptor complexes and Wnt ligands interferes with the β-catenin destruction complex, which in turn leads β-catenin to build up in the cytoplasm [76]. Afterwards, the TCF—LEF transcription complex is activated by β-catenin transfer to the nucleus, which leads to the expression of diverse genes with functions; for instance, the enhancement of migration and proliferation [77]. The β-catenin-independent pathway uses different ways of downstream signaling that could obtain a transcriptional response instead of the utilization of β-catenin-LEF or β-catenin-TCF.73 Overall, these pathways are classified based on the type of Wnt receptor and co-receptor they utilize the paired downstream receptors. The regulation of cell polarity during morphogenesis involves the PCP pathway [78]. In addition, the Wnt or Ca+2 pathway is associated with inflammation, cancerogenesis, and neurodegenerative diseases [79].

The effects of the Wnt signaling pathway are expanded to tumorigenesis by modulating the tumor microenvironment using fine crosstalk between infiltrating immune cells like leukocytes and transformed cells [72]. Wnt signaling and the crosstalk with different immune cells affect tumor progression both positively and negatively [72]. Beneficially, it assists in the renewal and maintenance of leukocytes. However, it induces immune tolerance, which restricts antitumor response [80]. Stromal cells of TME secretes growth factors that take part in the activation of Wnt signaling in the nucleus. For instance, hepatocyte growth factor, or HGF stimulation in colorectal cancer cells increases its separation from Met and β-catenin phosphorylation in tyrosine residue [80]. This results in the upregulation of β-catenin expression in the PI3-K dependent pathway.81 Several studies have been conducted, which present the possibility that β-catenin and Met help cells enter the cell cycle and prevent apoptosis [82]. For instance, cervical cancer progression has been proved to be correlated with c-Met overexpression [83]. Consequently, crosstalk between Wnt or β-catenin in CRCs and TME-released HGF promotes tumor growth and invasion [84]. An additional growth factor involved in the activation of β-catenin signaling is the platelet-derived growth factor, or PDGF for short. A study on this growth factor by Yang et al. implies that release of β-catenin is caused by PDGF treatment [85]. Wnt signaling is also involved in EMT, and in turn promotes the maintenance of CSCs. β-catenin interacts with LEF or TCF in the nucleus and begins the EMT process [86]/ Moreover, TCG-β and EGF increases p68 phosphorylation at tyrosine and needs p68 for initiating EMT. Therefore, the p-68-β-catenin axis could correspond to a common product for different signaling pathways [87].

Conclusively, dysregulated Wnt signaling contributes to tumorigenesis in many different types of cancers. Targeting Wnt pathway is of great interest in oncology research [88]. Studies over this have given rise to different inhibitors related to Wnt pathway that are able to interfere in important carcinogenesis features, such as metastasis and tumor invasiveness [89]. Pharmacological antagonists of the Wnt pathway can be classified into four dominant groups. First, there are the agents that target transmembrane proteins or ligands that participate in Wnt signaling [90]. Second, Porcupine inhibitors that intrude on the processing and secretion of Wnt ligands [91] Third, the agents that start caspases or hinder tankyrase, which keep the multiprotein destruction complex intact, therefore advancing the degrading of β-catenin. The last category contains the downstream β-catenin-TCF-LEF-dependent transcription inhibitors [92] Every single one of these categories has been clinically tested 88.

In addition, experimental antagonists of Wnt pathway associated with transmembrane ligands or proteins comprise of mAbs, decoy receptors, ADCs, and inhibitors of small molecules with several targets [93]. However, not all of these have reached clinical development yet [94]. More specifically, an example of a neutralizing humanized mAb to DKK1, an extracellular protein, is DKN-01, which functions like an endogenous Wnt-signaling antagonist by promoting LRP5/6 co-receptors internalization [95]. Preliminary results of a phase I study which combines DKN-01 with paclitaxel (NCT02013154) demonstrated that the patients are well tolerated, with minor side effects [96]. Another recombinant Wnt ligand decoy receptor, Ipafricept, includes the extracellular human Fzd8 part combined with lgG1 Fc fragment. Studies demonstrated that Ipafricept works well in a FIH phase

I trial involving patients suffering from advanced-stage solid tumors [97]. This trial led to extended SD in 3 patients who had germ cell cancer or desmoid tumors. In addition, Foxy-5 is a Wnt5A-mimicking peptide that activates Fzd2 and 5, which leads to the activation of downstream Wnt5A signaling [98]. There is a possibility that Foxy-5 has antimetastatic activity by hindering migration and endothelial tumor cell invasion with the induction of Wnt5A signaling [99]. Some β-catenin inhibitors have been studied as single agents or part of combination regimens. For instance, peptidomimetic drug CWP232291 activates caspases, which leads to β-catenin degradation, therefore reducing β-catenin target genes survivin and cyclin D1 expression [100]. It is currently being tested as monotherapy for patients with recurrent and/or refractory myeloid malignancies (NCT01398462) and in combination with lenalidomide and dexamethasone in patients with Multiple Myeloma (NCT02426723).101

Hedgehog Pathway

The Hedgehog Pathway, otherwise known as the HH signaling pathway, contributes greatly to embryonic development. In addition, the aberrant activity of the HH pathway in adult tissues is connected to several solid neoplasms [102]. Different HH isoforms like Indian hedgehog, Sonic hedgehog, or Desert hedgehog have been processed and released by HH ligand-secreting cells [103]. The isoforms, mainly using paracrine signaling, bind to Patched 1, or PTCH1, and PTCH2, which are transmembrane receptors, which leads to the suppression of the inhibitory activity against a transmembrane protein, Smoothened (SMO) [102].

In addition, HH signaling participates in early haematopoietic development, and potentially in non-malignant haematopoiesis and the general preservation of haematopoietic stem cells [104]. Research also suggests that aberrant HH signaling has rudimentary roles in maintaining and inducing leukemia stem cells (LSCs) in several hematological malignancies [105]. For instance, unusual HH signaling has been recognized in myeloid LSCs, while increased expression of HH pathway is connected to chemotherapy resistance in acute myeloid leukemia (AML) cell lines [106]. Patients diagnosed with AML show that GLI1 upregulation is associated with disease relapse, low overall survival rate, and drug resistance [104]. Also, HH signaling is activated in chronic myeloid leukemia (CML) and assists BCR–ABL1-positive LSC expansion [107]. These cells are also resistant to BCR–ABL1 tyrosine kinase inhibitors (TKI). Consequently, it is involved with the progression of CML [108].

Likewise, the HH pathway is activated in Multiple Myeloma (MM) stem cell compartment, but the clonal expansion of MM can be rescinded by HH pathway's pharmacological inhibition in MM cell lines 107. However, in chronic lymphocytic leukemia (CLL), downstream HH pathway molecules such as GLI1, 2, BCL2, and SUFU expression are upregulated and connected to disease progression [109]. The activation of dysregulated HH pathway is also prominently involved in tumorigenesis of basal cell carcinoma, or shortly BCC, of the skin [110]. Almost all these tumors have constitutive ligand-independent HH pathway activation because mutations in PTCH1 leads to loss-of-function, while mutations in SMO leads to gain-of-function [111]. Paracrine or autocrine signaling that are dependent on ligands is another process of HH pathway activation. Aberrant HH signaling has been involved in a medulloblastoma tumor subtype, defined as SHH [112]. This mainly happens in young patients and causes about 30% of all medulloblastomas. Several studies have shown decrease in heterozygosity and somatic mutation of PTCH1, which is an HH pathway negative regulator in this subset of medulloblastomas [105].

The exploration of pharmacological agents that target the HH pathway in solid and hematological malignancies has regulatory approval [113]. However, it is still being investigated. HH pathway targets SMO, HH ligands, and GLI transcription factors, while GLI and SMO agents have been tested in clinical research [114]. Some direct cyclopamine-competitive SMO inhibitors include sonidegib and Vismodegib, which have been FDA approved for metastatic BCC treatment along with recurrent locally advanced BCC in patients who aren't going to participate in surgery or radiotherapy [109]. Therefore, sonidegib and vismodegib have supplied comparable overall response rate for patients with locally advanced BCC. In addition, another inhibitor, Taladegib, has shown effectiveness in patients suffering from advanced-stage BCC [115]. Mutations in SMO have been found in around half of SMO inhibitor resistant BCCs. These mutations comprise of factors that affect four ligand binding pocket residues that are rudimentary to SMO autoinhibition, which consequently results in activation of this receptor [116]. Targeting GLI transcription factors are a promising therapeutic option because the HH pathway downstream effectors can also increase the upregulation of genes assisting in proliferation and survival without depending on the canonical HH pathway [117]. Agents that target GLI mediated transcription like GANT58 and 61 are focused on overcoming tumor resistance to SMO inhibitors [114]. In addition to that, researchers have observed promising responses to HH pathway inhibitors in patients with SHH-subtype medulloblastoma [114]

Conclusion

Overall, after analyzing different components in the tumor microenvironment of CSCs and their clinical applications, there is a deeper understanding established on this topic. Since CSCs lead

to therapy-resistant factors for cancer, these different clinical trials present possible solutions to overcome this dilemma. Different factors in the tumor microenvironment have been addressed to eliminate CSCs, which provide new insights to improve prognosis of treatment in cancer patients.

References

1. Rebecca L Siegel, Kimberly D Miller, Hannah E Fuchs, Ahmedin Jemal (2021) Cancer statistics, 2021. CA Cancer J Clin 71(1): 7-33.
2. Zuoren Yu, Timothy G. Pestell, Michael P. Lisanti, Richard G. Pestell (2012) Cancer stem cells. Int J Biochem Cell Biol 44(12): 2144-2151.
3. Tyrel T Smith, Justin C Roth, Gregory K Friedman, G Yancey Gillespie (2014) Oncolytic viral therapy: targeting cancer stem cells. Oncolytic Virother (3): 21-33.
4. Xiaoli Zhang, Kimerly Powell, Lang Li (2020) Breast Cancer Stem Cells: Biomarkers, Identification and Isolation Methods, Regulating Mechanisms, Cellular Origin, and Beyond. Cancers (Basel) 12(12): 3765.
5. Pedro M Aponte, Andrés Caicedo (2017) Stemness in Cancer: Stem Cells, Cancer Stem Cells, and Their Microenvironment. Stem Cells Int: 5619472.
6. Lan Thi Hanh Phi, Ita Novita Sari, Ying-Gui Yang, Sang-Hyun Lee, Nayoung Jun, et al. (2018) Cancer Stem Cells (CSCs) in Drug Resistance and their Therapeutic Implications in Cancer Treatment. Stem Cells Int: 5416923.
7. Genevieve Housman, Shannon Byler, Sarah Heerboth, Karolina Lapinska, Mckenna Longacre, et al. (2014) Drug resistance in cancer: an overview. Cancers (Basel) 6(3): 1769-1792.
8. Jihe Zhao (2016) Cancer stem cells and chemoresistance: The smartest survives the raid. Pharmacol Ther 160: 145-158.
9. Hugo Gonzalez, Catharina Hagerling, Zena Werb (2018) Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev 32(19-20): 1267-1284.
10. Terry R. Medler, Tiziana Cotechini, Lisa M. Coussens (2015) Immune response to cancer therapy: mounting an effective antitumor response and mechanisms of resistance. Trends Cancer 1(1): 66-75.
11. Briana C Prager, Qi Xie, Shideng Bao, Jeremy N Rich (2019) Cancer Stem Cells: The Architects of the Tumor Ecosystem. Cell Stem Cell 24(1): 41-53.
12. Liqun Yang, Pengfei Shi, Gaichao Zhao, Jie Xu, Wen Peng, et al. (2020) Targeting cancer stem cell pathways for cancer therapy. Signal Transduct Target Ther 5(1): 8.
13. Wafaa Al Tameemi, Tina P Dale, Rakad M Kh Al-Jumaily, Nicholas R Forsyth (2019) Hypoxia-Modified Cancer Cell Metabolism. Front Cell Dev Biol 7: 4.
14. Jie Zheng (2012) Energy metabolism of cancer: Glycolysis versus oxidative phosphorylation (Review). Oncol Lett 4(6): 1151-1157.
15. Marta Prieto-Vila, Ryou-U Takahashi, Wataru Usuba, Isaku Kohama, Takahiro Ochiya (2017) Drug Resistance Driven by Cancer Stem Cells and Their Niche. Int J Mol Sci 18(12): 2574.
16. Amar J Majmundar, Waihay J Wong, M Celeste Simon (2010) Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 40(2): 294-309.
17. Kuppusamy Balamurugan (2016) HIF-1 at the crossroads of hypoxia, inflammation, and cancer. Int J Cancer 138(5): 1058-1066.
18. Brian Keith, Randall S Johnson, M Celeste Simon (2011) HIF1alpha and HIF2alpha: sibling rivalry in hypoxic tumour growth and progression. Nat Rev Cancer 12(1): 9-22.
19. Bryan L Krock, Nicolas Skuli, M Celeste Simon (2011) Hypoxia-induced angiogenesis: good and evil. Genes Cancer 2(12): 1117-1133.
20. Ju Yang, Jing Yan, Baorui Liu (2018) Targeting VEGF/VEGFR to Modulate Antitumor Immunity. Front Immunol 9: 978.
21. Chang Dong Yeo, Nahyeon Kang, Su Yeon Choi, Bit Na Kim, Chan Kwon Park, et al. (2017) The role of hypoxia on the acquisition of epithelial-mesenchymal transition and cancer stemness: a possible link to epigenetic regulation. Korean J Intern Med 32(4): 589-599.
22. Daohong Zhou, Lijian Shao, Douglas R. Spitz (2014) Reactive oxygen species in normal and tumor stem cells. Adv Cancer Res 122: 1-67.
23. Micol Eleonora Fiori, Simone Di Franco, Lidia Villanova, Paola Bianca, Giorgio Stassi, et al. (2019) Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance. Mol Cancer 18(1): 70.
24. Maonan Wang, Jingzhou Zhao, Lishen Zhang, Fang Wei, Yu Lian, et al. (2017) Role of tumor microenvironment in tumorigenesis. J Cancer 8(5): 761-773.
25. Pei-Yu Chen, Wen-Fei Wei, Hong-Zhen Wu, Liang-Sheng Fan, Wei Wang (2021) Cancer-Associated Fibroblast Heterogeneity: A Factor That Cannot Be Ignored in Immune Microenvironment Remodeling. Front Immunol 12: 671595.
26. Randolph S Watnick (2012) The role of the tumor microenvironment in regulating angiogenesis. Cold Spring Harb Perspect Med 2(12): a006676.
27. Leilei Tao, Guichun Huang, Haizhu Song, Yitian Chen, Longbang Chen (2017) Cancer associated fibroblasts: An essential role in the tumor microenvironment. Oncol Lett 14(3): 2611-2620.
28. Daniel E Johnson, Rachel A O'Keefe, Jennifer R Grandis (2018) Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol 15(4): 234-248.
29. Siti-Fauziah Hendrayani, Bothaina Al-Harbi, Mysoon M Al-Ansari, Gabriela Silva, Abdelilah Aboussekhra (2016) The inflammatory/cancer-related IL-6/STAT3/NF-kappaB positive feedback loop includes AUF1 and maintains the active state of breast myofibroblasts. Oncotarget 7(27): 41974-41985.
30. Sujin Kang, Toshio Tanaka, Tadamitsu Kishimoto (2015) Therapeutic uses of anti-interleukin-6 receptor antibody. Int Immunol 27(1): 21-29.
31. Fei Xing, Jamila Saidou, Kounosuke Watabe (2010) Cancer associated fibroblasts (CAFs) in tumor microenvironment. Front Biosci (Landmark Ed) 15(1): 166-179.
32. Eunice Yuen Ting Lau, Jessica Lo, Bowie Yik Ling Cheng, Mark Kin Fai Ma, Joyce Man Fong Lee, et al. (2016) Cancer-Associated Fibroblasts Regulate Tumor-Initiating Cell Plasticity in Hepatocellular Carcinoma through c-Met/FRA1/HEY1 Signaling. Cell Rep 15(6): 1175-1189.
33. Tongyan Liu, Chencheng Han, Siwei Wang, Panqi Fang, Zhifei Ma, et al. (2019) Cancer-associated fibroblasts: an emerging target of anti-cancer immunotherapy. J Hematol Oncol 12(1): 86.
34. Ke Chen, Ying-hui Huang, Ji-long Chen (2013) Understanding and targeting cancer stem cells: therapeutic implications and challenges. Acta Pharmacol Sin 34(6): 732-740.
35. Kaladhar B Reddy (2020) Stem Cells: Current Status and Therapeutic Implications. Genes (Basel) 11(11): 1372.
36. Tu-Xiong Huang, Xin-Yuan Guan, Li Fu (2019) Therapeutic targeting of the crosstalk between cancer-associated fibroblasts and cancer stem cells. Am J Cancer Res 9(9): 1889-1904.
37. Demeng Chen, Mansi Wu, Yang Li, Insoon Chang, Quan Yuan, et al. (2017) Targeting BMI1(+) Cancer Stem Cells Overcomes Chemoresistance and Inhibits Metastases in Squamous Cell Carcinoma. Cell Stem Cell 20(5): 621-634 e626.

38. Xian-Ling Qian, Yi-Hang Pan, Qi-Yuan Huang, Yu-Bo Shi, Qing-Yun Huang, et al. (2019) Caveolin-1: a multifaceted driver of breast cancer progression and its application in clinical treatment. Onco Targets Ther 12: 1539-1552.

39. Alex Miranda, Phineas T Hamilton, Allen W Zhang, Swetansu Pattnaik, Etienne Becht, et al. (2019) Cancer stemness, intratumoral heterogeneity, and immune response across cancers. Proc Natl Acad Sci U S A 116(18): 9020-9029.

40. Theerawut Chanmee, Pawared Ontong, Kenjiro Konno, Naoki Itano (2014) Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 6(3): 1670-1690.

41. Qianquan Ma, Wenyong Long, Changsheng Xing, Junjun Chu, Mei Luo, et al. (2018) Cancer Stem Cells and Immunosuppressive Microenvironment in Glioma. Front Immunol 9: 2924.

42. Ni Tong, Zhenqiang He, Yujie Ma, Zheng Wang, Ziming Huang, et al. (2021) Tumor Associated Macrophages, as the Dominant Immune Cells, Are an Indispensable Target for Immunologically Cold Tumor-Glioma Therapy? Front Cell Dev Biol 9: 706286.

43. Laura Lorenzo-Sanz, Purificación Muñoz (2019) Tumor-Infiltrating Immunosuppressive Cells in Cancer-Cell Plasticity, Tumor Progression and Therapy Response. Cancer Microenviron 12(2-3): 119-132.

44. Dmitry I Gabrilovich (2017) Myeloid-Derived Suppressor Cells. Cancer Immunol Res 5(1): 3-8.

45. L Paige Ferguson, Emily Diaz, Tannishtha Reya (2021) The Role of the Microenvironment and Immune System in Regulating Stem Cell Fate in Cancer. Trends Cancer 7(7): 624-634.

46. Ombretta Melaiu, Valeria Lucarini, Loredana Cifaldi, Doriana Fruci, (2020) Influence of the Tumor Microenvironment on NK Cell Function in Solid Tumors. Front Immunol 10: 3038.

47. Judith A Seidel, Atsushi Otsuka, Kenji Kabashima (2018) Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. Front Oncol 8: 86.

48. Michael Zhang, Gregor Hutter, Suzana A Kahn, Tej D Azad, Sharareh Gholamin, et al. (2016) Anti-CD47 Treatment Stimulates Phagocytosis of Glioblastoma by M1 and M2 Polarized Macrophages and Promotes M1 Polarized Macrophages In Vivo. PLoS One 11(4): e0153550.

49. Zhao H, Lei Wu, Guifang Yan, Yu Chen, Mingyue Zhou, et al. (2021) Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 6: 263.

50. Yelei Guo, Kaichao Feng, Yao Wang, Weidong Han (2018) Targeting cancer stem cells by using chimeric antigen receptor-modified T cells: a potential and curable approach for cancer treatment. Protein Cell 9(6): 516-526.

51. Xiaolei Li, Changshun Shao, Yufang Shi, Weidong Han (2018) Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol 11(1): 31.

52. Abdellah Akil, Ana K Gutiérrez-García, Rachael Guenter, J Bart Rose, Adam W Beck, et al. (2021) Notch Signaling in Vascular Endothelial Cells, Angiogenesis, and Tumor Progression: An Update and Prospective. Front Cell Dev Biol 9: 642352.

53. Demin Li, Massimo Masiero, Alison H Banham, Adrian L Harris (2014) The notch ligand JAGGED1 as a target for anti-tumor therapy. Front Oncol 4: 254.

54. Christian T Meisel, Cristina Porcheri, Thimios A Mitsiadis (2020) Cancer Stem Cells, Quo Vadis? The Notch Signaling Pathway in Tumor Initiation and Progression. Cells 9(8): 1879.

55. Rumela Chakrabarti, Toni Celià-Terrassa, Sushil Kumar, Xiang Hang, Yong Wei, et al. (2018) Notch ligand Dll1 mediates cross-talk between mammary stem cells and the macrophageal niche. Science 360(6396): eaan4153.

56. Ping Zhang, Ying Zhao, Xiao-Hong Sun (2013) Notch-regulated periphery B cell differentiation involves suppression of E protein function. J Immunol 191(2): 726-736.

57. Wei Xiao, Zhiyong Gao, Yixing Duan, Wuxiong Yuan, Yang Ke (2017) Notch signaling plays a crucial role in cancer stem-like cells maintaining stemness and mediating chemotaxis in renal cell carcinoma. J Exp Clin Cancer Res 36: 41.

58. Shin-Ichi Tsukumo, Koji Yasutomo (2018) Regulation of CD8(+) T Cells and Antitumor Immunity by Notch Signaling. Front Immunol 9: 101.

59. Yanyan Han, Dandan Liu, Lianhong Li (2020) PD-1/PD-L1 pathway: current research in cancer. Am J Cancer Res 10(3): 727-742.

60. Michelle A Kelliher, Justine E Roderick (2018) NOTCH Signaling in T-Cell-Mediated Anti-Tumor Immunity and T-Cell-Based Immunotherapies. Front Immunol 9: 1718.

61. Mahnaz Janghorban, Li Xin, Jeffrey M Rosen, Xiang H-F Zhang (2018) Notch Signaling as a Regulator of the Tumor Immune Response: To Target or Not To Target? Front Immunol 9: 1649.

62. Esra'a Keewan, Saleh A Naser (2020) The Role of Notch Signaling in Macrophages during Inflammation and Infection: Implication in Rheumatoid Arthritis? Cells 9(1): 111.

63. Emmanuel N Kontomanolis, Sofia Kalagasidou, Stamatia Pouliliou, Xanthoula Anthoulaki, Nikolaos Georgiou, et al. (2018) The Notch Pathway in Breast Cancer Progression. ScientificWorldJournal 2018: 2415489.

64. Julia O Misiorek, Alicja Przybyszewska-Podstawka, Joanna Kałafut, Beata Paziewska, Katarzyna Rolle, et al. (2021) Context Matters: NOTCH Signatures and Pathway in Cancer Progression and Metastasis. Cells 10(1): 94.

65. Vandana Venkatesh, Raghu Nataraj, Gopenath S Thangaraj, Murugesan Karthikeyan, Ashok Gnanasekaran, et al. (2018) Targeting Notch signalling pathway of cancer stem cells. Stem Cell Investig 5: 5.

66. Naoko Takebe, Dat Nguyen, Sherry X Yang (2014) Targeting notch signaling pathway in cancer: clinical development advances and challenges. Pharmacol Ther 141(2): 140-149.

67. Pohlmann P R, Mayer I A, Mernaugh R (2009) Resistance to Trastuzumab in Breast Cancer. Clin Cancer Res 15(24): 7479-7491.

68. Lehal R, Jelena Zaric, Michele Vigolo, Charlotte Urech, Viktoras Frismantas, et al. (2020) Pharmacological disruption of the Notch transcription factor complex. Proc Natl Acad Sci U S A 117(28): 16292-16301.

69. Austin Gurney, Timothy Hoey (2011) Anti-DLL4, a cancer therapeutic with multiple mechanisms of action. Vasc Cell 3:18.

70. Dwight H Owen, Michael J Giffin, Julie M Bailis, Marie-Anne Damiette Smit, David P Carbone, et al. (2019) DLL3: an emerging target in small cell lung cancer. J Hematol Oncol 12(1): 61.

71. Meng-Xi Xiu, Yuan-Meng Liu, Bo-Hai Kuang (2020) The Role of DLLs in Cancer: A Novel Therapeutic Target. Onco Targets Ther 13: 3881-3901.

72. Patel S, Alam A, Pant R, Chattopadhyay S (2019) Wnt Signaling and Its Significance Within the Tumor Microenvironment: Novel Therapeutic Insights. Front Immunol 10: 2872.

73. MacDonald B T, Tamai K, He Xi (2009) Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell 17(1): 9-26.

74. Ishitani T, Ninomiya-Tsuji J, Matsumoto K (2003) Regulation of lymphoid enhancer factor 1/T-cell factor by mitogen-activated protein kinase-related Nemo-like kinase-dependent phosphorylation in Wnt/beta-catenin signaling. Mol Cell Biol 23(4): 1379-1389.

75. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I,Ayala-San Nicolas M,(2019) WNT Signaling in Tumors: The Way to Evade Drugs and Immunity. Front Immunol 10: 2854.

76. Shuang Shang, Fang Hua, Zhuo-Wei Hu, (2017) The regulation of beta-catenin activity and function in cancer: therapeutic opportunities. Oncotarget 8(20): 33972-33989.

77. Cadigan K M, Waterman M L (2012) TCF/LEFs and Wnt signaling in the nucleus. Cold Spring Harb Perspect Biol 4(11): a007906.

78. Komiya Y, Habas R (2008) Wnt signal transduction pathways. Organogenesis 4(2): 68-75.

79. Bian J, Dannappel M, Wan C, Firestein R (2020) Transcriptional Regulation of Wnt/beta-Catenin Pathway in Colorectal Cancer. Cells 9(9): 2125.

80. Grivennikov S I, Greten F R, Karin M (2010) Immunity, inflammation, and cancer. Cell 140(6): 883-899.

81. Persad A, Geetha Venkateswaran, Li Hao, Maria E Garcia, Jenny Yoon, Jaskiran Sidhu,et al. (2016) Active beta-catenin is regulated by the PTEN/PI3 kinase pathway: a role for protein phosphatase PP2A. Genes Cancer 7(11-12): 368-382.

82. Michael Kahn (2014) Can we safely target the WNT pathway? Nat Rev Drug Discov 13(7): 513-532.

83. Tamer Refaat, Eric D Donnelly, Sean Sachdev, Vamsi Parimi, Samar El Achy, et al. (2017) c-Met Overexpression in Cervical Cancer, a Prognostic Factor and a Potential Molecular Therapeutic Target. Am J Clin Oncol 40(6): 590-597.

84. Bin Ma, Michael O Hottiger (2016) Crosstalk between Wnt/beta-Catenin and NF-kappaB Signaling Pathway during Inflammation. Front Immunol 7: 378.

85. Chao J, Yang L, Yao H, Buch S (2014) Platelet-derived growth factor-BB restores HIV Tat -mediated impairment of neurogenesis: role of GSK-3beta/beta-catenin. J Neuroimmune Pharmacol 9(2): 259-268.

86. Kaplan Z, Zielske S P, Ibrahim K G, Cackowski F C (2021) Wnt and beta-Catenin Signaling in the Bone Metastasis of Prostate Cancer. Life (Basel) 11(10): 1099.

87. Damian Medici, Elizabeth D Hay, Daniel A Goodenough (2006) Cooperation between snail and LEF-1 transcription factors is essential for TGF-beta1-induced epithelial-mesenchymal transition. Mol Biol Cell 17(4): 1871-1879.

88. Krishnamurthy N, Kurzrock R (2018) Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors. Cancer Treat Rev 62: 50-60.

89. Zhan T, Rindtorff N, Boutros M (2017) Wnt signaling in cancer. Oncogene 36(11): 1461-1473.

90. Jung Y S, Park J I, Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond beta-catenin and the destruction complex. Exp Mol Med 52: 183-191.

91. Jun Liu, Shifeng Pan, Mindy H Hsieh, Nicholas Ng, Fangxian Sun, et al. (2013) Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. Proc Natl Acad Sci U S A 110(50): 20224-20229.

92. Sushil C Regmi, Su Young Park, Seung Joo Kim, Suhrid Banskota, Sajita Shah, et al. (2015) The Anti-Tumor Activity of Succinyl Macrolactin A Is Mediated through the beta-Catenin Destruction Complex via the Suppression of Tankyrase and PI3K/Akt. PLoS One 10(11): e0141753.

93. Tran F H, Zheng J J (2017) Modulating the wnt signaling pathway with small molecules. Protein Sci 26(4): 650-661.

94. Monica Sharma, Kevin Pruitt (2020) Wnt Pathway: An Integral Hub for Developmental and Oncogenic Signaling Networks. Int J Mol Sci 21(21): 8018.

95. Giralt I, Gabriel Gallo-Oller, Natalia Navarro, Patricia Zarzosa, Guillem Pons, et al. (2021) Dickkopf Proteins and Their Role in Cancer: A Family of Wnt Antagonists with a Dual Role. Pharmaceuticals (Basel) 14(8): 810.

96. Shaib W L, Nammour J P, Gill H, Mody M, Saba N F (2016) The Future Prospects of Immune Therapy in Gastric and Esophageal Adenocarcinoma. J Clin Med 5(11): 100.

97. Antonio Jimeno, Michael Gordon, Rashmi Chugh, Wells Messersmith, David Mendelson, et al. (2017) A First-in-Human Phase I Study of the Anticancer Stem Cell Agent Ipafricept (OMP-54F28), a Decoy Receptor for Wnt Ligands, in Patients with Advanced Solid Tumors. Clin Cancer Res 23(24): 7490-7497.

98. Giacomo Canesin, Susan Evans-Axelsson, Rebecka Hellsten, Agnieszka Krzyzanowska, Chandra P Prasad, et al. (2017) Treatment with the WNT5A-mimicking peptide Foxy-5 effectively reduces the metastatic spread of WNT5A-low prostate cancer cells in an orthotopic mouse model. PLoS One 12(9): e0184418.

99. Veronika Jenei, Victoria Sherwood, Jillian Howlin, Rickard Linnskog, Annette Säfholm, et al. (2009) A t-butyloxycarbonyl-modified Wnt5a-derived hexapeptide functions as a potent antagonist of Wnt5a-dependent melanoma cell invasion. Proc Natl Acad Sci U S A 106(46): 19473-19478.

100. Esther Martinez-Font, Marina Pérez-Capó, Oliver Vögler, Javier Martín-Broto, Regina Alemany, et al. (2021) WNT/beta-Catenin Pathway in Soft Tissue Sarcomas: New Therapeutic Opportunities? Cancers (Basel) 13(21): 5521.

101. Dima D, Dower J, Comenzo R L, Varga C (2020) Evaluating Daratumumab in the Treatment of Multiple Myeloma: Safety, Efficacy and Place in Therapy. Cancer Manag Res 12: 7891-7903.

102. Ana Marija Skoda, Dora Simovic, Valentina Karin, Vedran Kardum, Semir Vranic, et al. (2018) The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosn J Basic Med Sci 18(1): 8-20.

103. Pettigrew C A, Asp E, Emerson C P (2014) A new role for Hedgehogs in juxtacrine signaling. Mech Dev 131: 137-149.

104. Hofmann I, Elizabeth H Stover, Dana E Cullen, Junhao Mao, Kelly J Morgan, et al. (2009) Hedgehog signaling is dispensable for adult murine hematopoietic stem cell function and hematopoiesis. Cell Stem Cell 4(6): 559-567.

105. Ita Novita Sari, Lan Thi Hanh Phi, Nayoung Jun, Yoseph Toni Wijaya, Sanghyun Lee, et al. (2018) Hedgehog Signaling in Cancer: A Prospective Therapeutic Target for Eradicating Cancer Stem Cells. Cells 7(11): 208.

106. Abraham A, Matsui W (2021) Hedgehog Signaling in Myeloid Malignancies. Cancers (Basel) 13(19): 4888.

107. Moradi F, Sadegh Babashah, Majid Sadeghizadeh, Arsalan Jalili, Abbas Hajifathali, et al. (2019) Signaling pathways involved in chronic myeloid leukemia pathogenesis: The importance of targeting Musashi2-Numb signaling to eradicate leukemia stem cells. Iran J Basic Med Sci 22(6): 581-589.

108. Alves R, Ana Cristina Gonçalves, Sergio Rutella, António M Almeida, Javier De Las Rivas, et al. (2021) Resistance to Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia-From Molecular Mechanisms to Clinical Relevance. Cancers (Basel) 13(19): 4820.

109. Gupta S, Takebe N, Lorusso P (2010) Targeting the Hedgehog pathway in cancer. Ther Adv Med Oncol 2(4): 237-250.

110. Jean Y. Tang, Po-Lin So, Ervin H. Epstein (2007) Novel Hedgehog pathway targets against basal cell carcinoma. Toxicol Appl Pharmacol 224(3): 257-264.

111. Petrov K, de Almeida Magalhaes T, Salic A (2021) Mechanism and ultrasensitivity in Hedgehog signaling revealed by Patched1 disease mutations. Proc Natl Acad Sci U S A 118(6): e2006800118.

112. Chi Young Ok, Rajesh Ramachandra Singh, Francisco Vega (2012) Aberrant activation of the hedgehog signaling pathway in malignant hematological neoplasms. Am J Pathol 180(1): 2-11.

113. Rimkus T K, Carpenter R L, Qasem S, Chan M, Lo H W (2016) Targeting the Sonic Hedgehog Signaling Pathway: Review of Smoothened and GLI Inhibitors. Cancers (Basel) 8(2): 22.

114. Pietrobono S, Gagliardi S, Stecca B (2019) Non-canonical Hedgehog Signaling Pathway in Cancer: Activation of GLI Transcription Factors Beyond Smoothened. Front Genet 10: 556.

115. Dummer R, P A Ascierto, N Basset-Seguin, B Dréno, C Garbe, et al. (2020) Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion. J Eur Acad Dermatol Venereol 34(9): 1944-1956.

116. Scott X Atwood, Kavita Y Sarin, Ramon J Whitson, Jiang R Li, Geurim Kim, et al. (2015) Smoothened variants explain most of the drug resistance in basal cell carcinoma. Cancer Cell 27(3): 342-353.

117. Avery J T, Zhang R, Boohaker R J (2021) GLI1: A Therapeutic Target for Cancer. Front Oncol 11: 673154.