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Review

Mechanisms of cancer stem cells drug resistance and the pivotal role of HMGA2

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ABSTRACT

Nowadays, the focus of researchers is on perceiving the heterogeneity observed in a tumor. The researchers studied the role of a specific subset of cancer cells with high resistance to traditional treatments, recurrence, and unregulated metastasis. This small population of tumor cells that have stem-cell-like specifications was named Cancer Stem Cells (CSCs). The unique features that distinguish this type of cancer cell are self-renewing, generating clones of the tumor, plasticity, recurrence, and resistance to therapies. There are various mechanisms that contribute to the drug resistance of CSCs, such as CSCs markers, Epithelial mesenchymal transition, hypoxia, other cells, inflammation, and signaling pathways. Recent investigations have revealed the primary role of HMGA2 in the development and invasion of cancer cells. Importantly, HMGA2 also plays a key role in resistance to treatment through their function in the drug resistance mechanisms of CSCs and challenge it. Therefore, a deep understanding of this issue can provide a clearer perspective for researchers in the face of this problem.

1. Introduction

As a result of growth in our understanding of cancer's cellular and molecular biology, improved and novel technologies have been developed for early diagnosis, imaging, and treatment strategies (e.g., resonance imaging, nanotechnology, photo-therapies, health care information technology, targeted drug delivery systems, etc.). However, these strategies have limited efficacy for most types of cancer, principally for recurrent and advanced metastatic cancers [1–4]. Moreover, the majority of the traditional therapies lack adequate effectiveness because of the heterogeneity of cancer cells due to the fact that there are no identical characteristics for all the cells of a tumor. Thus, there is no homogeneous response for the therapies that result in future potential recurrence [5]. Nowadays, the focus of researchers is on perceiving the heterogeneity observed in a tumor. The researchers studied the role of a specific subset of cancer cells with high resistance to traditional treatments, recurrence, and unregulated metastasis. This small population of cancer cells that possess stem-cell-like features were called Cancer Stem Cells (CSC) [6]. CSCs are tumor cells with the ability to self-renewal and differentiation. It happens mostly when reactivation of the involved pathways in early development at the wrong time in the wrong place. Cancer cells acquiring these stemness properties activate the pathways

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and take the capability of migration; they present resistance to treatment and can induce growths of primary and secondary tumors [7–9]. What is more, CSCs are associated with chemoresistance through diverse mechanisms such as surface markers, EMT, hypoxia, tumor microenvironment components, and signaling pathways. One of the proteins with a possible role in CSCs signaling pathways is the "high-mobility group AT-hook 2" (HMGA2)[10]. HMGA2 protein is a non-histone architectural transcription factor with the ability to modulate the transcription of several genes. It is realized through binding to AT-rich sequences in the minor groove of B-form DNA and changing the chromatin configuration. Consequently, various biological processes are affected by HMGA2, such as DNA damage repair processes, the cell cycle process, epithelial-mesenchymal transition, apoptosis, senescence, angiogenesis, metastasis, telomere restoration, and drug resistance [11–13]. In the following review study, we discussed the mechanisms associated with CSCs drug resistance and the role of HMGA2 in this process.

2. Cancer stem cells and characteristics

Liquid and solid tumors are made of many bulk cancer cells with a few numbers of CSCs [14]. CSCs are quiescent self-renewing cell types pre-existing in primary cancers that are localized in the tumor niches and bear enhanced functional capacity for inducing growth of cancer, reconstructing their heterogeneity, and making variations in the regenerative capacity of cancer [15–17]. By injecting these cells into immunodeficient laboratory animals, types of cancers can be induced and studied [18]. Originally, CSCs were described as a subpopulation of cancer cells with the potential of expanding the pool of CSCs and differentiating into progenitor cancer cells through asymmetric and symmetric divisions [19]. Because CSCs were firstly identified in human acute myeloid leukemia (AML), they have been harvested from most of the solid tumors and malignancies with the hematopoietic origin [20], and it has been attested that they have tumorigenic activity in various cancers, such as liver, brain, colon, lung, ovarian, breast, pancreas, melanoma, neck and head, bladder, and prostate [21]. There are two different theories for describing the function of CSCs: [1] according to the hierarchical theory, the location of CSCs is at the hierarchy top level with the ability to generate clones of the tumor bulk. Therefore, they are made as to the origin of the heterogeneous developing tumor. [2] According to the stochastic theory, the origin of tumors is associated with random mutations that occur in normal cells. Then, a stemness phenotype can be acquired by additive mutations. Therefore, every single cell in the tumor can become a CSC [22–24]. Nevertheless, these theories are not mutually exclusive according to recent models, and it seems that the plasticity of cancer cells is vital for the interconversion between stem phenotypes and non-stem phenotypes. It has been found that there is a relationship between the epithelial-to-mesenchymal transition (EMT) process and the reverse transition (mesenchymal to epithelial), with the progression of cancer, as a pattern of cell plasticity [25,26]. Previous concepts have considered the EMT/MET as a binary process, while according to the developing concepts, some phenotypic manifestations of a hybrid epithelial-mesenchymal (E/M) state are noted in various tumors between the MET state and the EMT, and it has been associated with stemness properties [27–29].

2.1. Plasticity of CSCs

CSCs are protected against chemo-radio-therapeutic insults through the reversible conversion capacity [30,31]. Such inter-conversion is dependent on the response to endogenous and exogenous stimuli and there are many factors that regulate it such as tumor microenvironment, genetic evolution, metabolic adaptation, epigenetic mechanisms, and phenotypic plasticity of CSCs [32–35]. It has been indicated that CSCs are stimulated for gaining plasticity as differentiated cancer cells and it is possible to reprogram them in reaction to certain environmental signals. Therefore, proliferation capacity and CSC-like properties are initiated [36,37]. Consequently, when cancer cells receive certain signals from their tumor microenvironment, they will exit the static phase, and the plasticity process is enhanced [38]. Hence, the malignant behavior of the tumor cells is corroborated by the interactions with the tumor microenvironment, driving the phenotypic plasticity mode in cancer cells. As an example, there is an interconnection between non-CSCs and CSCs neoplastic cells in the stroma of breast, colon, and pancreatic cancer, where signaling factors are secreted by stromal cells received by epithelial cells. It results in a signaling cascade to coordinate an epithelial to mesenchymal transition [39,40]. Cellular plasticity can be induced by some cytokines of the tumor microenvironment. For example, the differentiation state of CSCs can be altered by pro-inflammatory mediators, like IL-6 and TNF, which is accomplished through upregulation of mesenchymal genes, and EMT-type switch is promoted [41,42]. Additionally, when the necessary factors for the revitalization of the self-renewal process are absent, IL-6 is secreted by CSCs for attracting mesenchymal stem cells (MSC), leading to the promotion of cancer cells stemness by NF-κB upregulation [43,44]. Some therapeutic approaches to inhibit CSCs and overcome drug resistance include the use of neutralizing antibodies or decoy receptors to suppress the initiation of signaling pathways in non-CSCs (IL17Ab, IL8Ab). Another method is to disrupt receptors' function on the CSCs or non-CSCs, such as TGFβR (through SB431542, and LY2157299 as TGFβR inhibitor). In addition, suppression of the signaling pathways that can promote by cytokines of the tumor microenvironment and activation of GFR is an appropriate therapeutic target on the CSCs and non-CSCs (BBI608: STAT3 inhibitor; IGFR-1 inhibitor; Dasatinib: Src kinase inhibitor) [45].

2.2. Drug resistance and CSCs

CSCs have the capability of inducing cell cycle arrest, which supports their ability for resistance to radiotherapy and chemotherapy [46,47]. In other words, radioresistance is related to CSCs' DNA repair machine and their slight concentrations of ROS (Reactive oxygen species), following from their overexpression of ROS scavengers. The low ROS value is accompanied by a disorder in cell cycle adjustment. Thus, it can be supposed that either CSCs can dormant themselves or quiescent [48]. Common chemotherapeutic agents choose the proliferating cells as the target for leading their apoptosis. Despite deleting the majority of proliferating tumor cells through successful cancer therapy, some CSCs could survive; and resulting in the promotion of cancer relapse because of their capacity of establishing higher chemo-resistance and invasiveness. Hence, it is essential to understand the related drug resistance mechanisms of CSCs so that effective therapeutic methods can be reached in cancer treatment [49,50].

2.2.1. CSCs markers associated with drug resistance

As studies indicate, there is an association between high expression of CD133 and resistance to the drugs. When CD133-positive CSCs are present in lung cancer, the ATP-binding cassette transporter (ABC) transporter ABCG2 expression is increased and leads to resistance of lung cancer to primary drugs, including paclitaxel and platinum. According to previous studies, therapy with a low dose of platinum can result in damage to DNA instead of the death of cells, with the possibility of inducing upregulation of ABCG2 and increasing the number of cells that are CD133 positive. Tumor resistance to platinum can be reduced with certain ABC transporter suppressor Verapamil or ABCG2 inhibitor Pantoprazole. Moreover, it has been reported that there is a correlation between CD133 expression and resistance to cisplatin. Although, it can be overcome by inhibiting the CD133 [51,52].

CD44 is described as a cell surface adhesion molecule with overexpression on CSCs. The interaction between CD44 and hyaluronan is the factor for the development of tumor, metastasis, and chemo-resistant phenotype expression. With CD44 overexpression, the cytotoxic impact of chemotherapy medications is impeded in different types of cancers.

Thus, there is an association between the high expression of CD44 and a poor prognosis in patients. As a result of the increased expression of CD44 in different cancers, an opportunity is provided for treating patients showing chemo-resistant malignancy [53].

According to investigations, ALDH1 has involvement in resistance to treatment. ALDH1 is a component from the aldehyde dehydrogenase enzymes superfamily that includes 19 human isozymes. It is a controlling factor for the aldehydes' oxidation to correspondent acids, and it has been proposed that detoxification of aldehyde through ALDH has an intermediator role generated in tumor cells treated with specific therapeutic factors confer therapy resistance to ALDH1 + tumor cells [54].

CD166 is involved as a CSCs marker in various types of cancers, like stomach, and colon. Besides, it is termed as an "activated leukocyte cell adhesion molecule" (ALCAM), which is a glycoprotein member of adhesion molecules [55–57]. Satar NA et al. recently have indicated that CD166/CD44/EpCAM triple-positive clones had a mediatory role in resistance to treatment and putative CSC features in human non-small cells in lung cancer cells [58]. CD9 and CD49f are other CSCs markers that contribute to drug resistance. Previous studies have reported the association between CD49f positive population and resistance to radiotherapy and taxane (an anti-microtubule and mitotic inhibitor agent). CD9 shows involvement in cell fusion, motility, adhesion, metastasis, signaling, and proliferation. In addition, CD9 has a significant role in human B-ALL (Acute lymphocytic leukemia) and shows the characteristics of the CSCs [59–61].

2.2.2. Epithelial-mesenchymal transition (EMT)

Research demonstrated there is co-expression of EMT markers and stem cell markers on circulating tumor cells from cases with induction of EMT and metastasis or activation of EMT transcription factors confers stem-like features in tumor cells [62,63]. Particularly, neoplastic and normal breast stem cells represent analogous markers with cells undergoing EMT. The production of unlimited numbers of CSCs is caused by more differentiated neoplastic cells. Activation of EMT is associated with drug resistance [64,65]. ZEB1 is an EMT regulator, importantly playing role in vital properties of CSCs, including the stemness regulation and chemo-resistance induction via transcriptional regulation of O-6-Methylguanine DNA Methyltransferase (MGMT) through cMYB and miR-200c in malignant glioma. Besides, it is possible to use improved invasive potential, expression of EMT markers, and tumorigenicity for predicting the anti-EGFR antibody cetuximab resistance in the cells [66,67].

2.2.3. Hypoxia

It has been shown that HIF and Hypoxia signaling pathways have a contribution to the sustenance and regulation of CSCs and EMT phenotypes, like cell migration, angiogenesis, and invasion [68–70], through increasing expression of IL-6, VEGF, and CSC signature genes, like Oct4, EZH2 (Enhancer of zeste homolog 2), and Nanog, in pancreatic cancer [71]. Hence, hypoxia-inducible factor (HIF) and the hypoxia signaling pathway could affect CSC therapy resistance. The survival and persistence of CML cells in hypoxic microenvironments are facilitated by the HIF1-α signaling pathway and HIF1-α upregulation that is independent of BCR-ABL1 kinase activity. In a similar way, gefitinib-resistant lung CSCs are increased by hypoxia in EGFR mutation-positive non-small cell lung cancer (NSCLC) via upregulation of IGF1 (insulin–like growth factor 1) expression via HIF1α and activation of IGF1 receptor. Similar to the other hypoxic tumor, upregulation of autophagy in pancreatic tumors occurs in the micro-environmental condition with a lack of essential components and low oxygen. The clonogenic survival and pancreatic CSC migration are then promoted [72–74]. Alternative mechanisms of drug resistance related to hypoxia are illustrated in Fig. 1 [75].

2.2.4. Cells involved in inducing drug resistance of CSCs

Previous studies have shown that tumor-associated macrophages

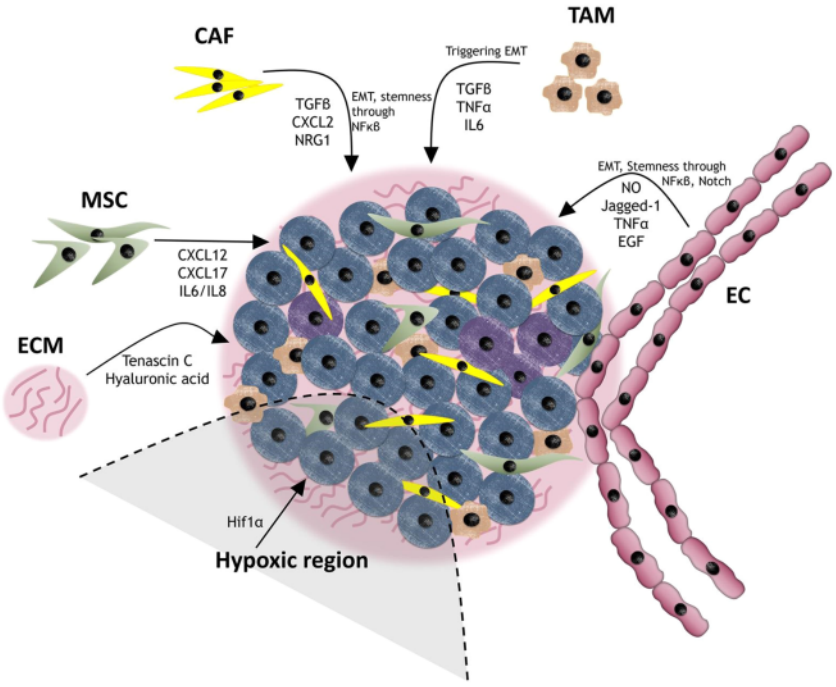

Fig. 1. CSCs are surrounded by tumor associated cells like CAFs, TAMs, MSCs, ECM (Extracellular matrix), and ECs (Endothelial cell). The CSCs in a hypoxic environment receive stimulatory factors from neighboring cells that boost drug resistance [75].

(TAMs) can promote chemoresistance in primary myeloma cells and myeloma cell lines by direct interaction with cancer cells in the TME (tumor microenvironment) and activation of caspase-dependent apoptotic signaling [76]. Additionally, as indicated by Jian Ma et al., TAM has the capacity of mediating drug resistance development by CCL5 secretion. CCL5 generated by TAMs is a facilitator of the EMT process through STAT3 signals, which leads to cancer metastasis and cell migration. STAT3 signaling activation can result in upregulation of the downstream transcription factor Nanog and drug resistance [77]. Huanrong et al. have observed that the colorectal cancer microenvironment has a high density of infiltrated macrophages in cases with oxaliplatin resistance than the oxaliplatin-sensitive individuals. Furthermore, an increase was observed in the expression of critical methyltransferase METTL3 (methyltransferase-like 3) and total N6-methyladenosine (m6A) RNA content in the colorectal cancer tissues in oxaliplatin-resistant cases. Besides, their finding showed that the oxaliplatin resistance was enabled by the M2-polarized TAMs through increased METTL3-mediated m6A modification in cells [78].

Cancer-associated fibroblasts (CAFs) have a significant contribution to non-neoplastic stromal compartments in different human tumors. According to previous works, they have the capability to modulate tumor cells through the formation of the communication network with cancer cells or with other elements. Therefore, they are vulnerable to cancer drug resistance [79,80]. A novel mechanism was described by Guangyue et al. for drug resistance related to CAFs. As reported by these authors, CAFs-derived exosomes can boost chemotherapy resistance in different human tumors through the delivery of bioactive molecules. Therefore, the exosomes of CAFs caused bladder cancer cell resistance to cisplatin and upregulated the expression of ABCB1 in cancer cells by transferring LINC00355 [81].

The results of various studies indicate that tumor-associated neutrophils (TANs) can support tumor development by promoting angiogenesis, tumor cell motility, invasion, and migration. Analysis of TANs isolated from colorectal cancer patients revealed that these cells represent CD11b, CD33, CD66b, CD45, Lin^-, and $HLA\text{-}DR^-$. They have a typical neutrophil morphology, but produce much more ROS and arginase 1 than autologous neutrophils. Moreover, TANs are capable to suppress the proliferation of activated autologous T lymphocytes. Sumagin et al. revealed that TANs are able to contribute to drug resistance, which includes angiogenesis, immunosuppression, immune checkpoint blockades, tyrosine kinase inhibitors, and enhanced cellular survival [82,83].

2.2.5. Inflammation and drug resistance

The frontline of carcinogenesis, therapy resistance, and tumor progression is inflammation. The Janus kinase (JAK)/ STAT signaling axis is an important pathway with a mediating role in the cellular response to inflammation and contribution to carcinogenesis. Through the JAK/STAT pathway, intercellular communication is coordinated between tumor cells and their immune microenvironment. With activating JAK/STAT, various proteins are expressed that contribute to cell proliferation and survival, self-renewal, stemness, the overall progression of the tumor, and evasion of immune surveillance mechanisms. Moreover, activation of JAK/STAT signaling has a mediating role in resistance to radiation therapy or cytotoxic agents, which regulates responses of a tumor cell to molecularly targeted and immune-modulating drugs [84]. The STAT3 and STAT 1 function is boosted by IFN-γ as IDO1 inducer. In A549/dx cells the IFN-γ has a great impact on IDO1 induction. This phenomenon may be related to the strong activity of JAK/STAT pathway in A549/dx cells. Interestingly, an autocrine release of IFN-γ has been detected in A549/dx cells; however, this concentration of IFN-γ is lower than one released by other immune cells, and it seems to be enough to activate the transcription of IDO1 in chemoresistance cells. Thus, an autocrine JAK/STAT/IFN-γ composition results in the induction of IDO1 in target cells. Despite IFN-γ function in IDO1 production, the role of other cytokines such as IL-4, IL-6, IL-1β, TNF-α, IL-13, and CD40L has been documented in this process. All the mentioned cytokines are activators of STAT3 genes; furthermore, IL-4, IL-13, and IL-6 activate the JAK1/STAT3 signaling. Eventually, all of these give rise to increase IDO1 expression and drug resistance [85]. Furthermore, CSCs were specifically enriched by long-term therapy of breast malignant cells with trastuzumab which indicates EMT phenotypes with the greater secretion of cytokines IL-6 in comparison to parental cells. Consequently, trastuzumab resistance is developed by these cells mediated by activating an inflammatory feedback loop associated with IL-6 for expanding the population of CSCs. Besides, in breast cancer, tumor cells can become resistant to trastuzumab through other mechanisms, such as a mutation in HER2 protein, alternative elevations of insulin-like growth factor receptor (IGFR), and intracellular changes in HER2 downstream signaling (phosphatase and tensin homolog (PTEN), PI3K/Akt) [86]. In a similar way, in triple-negative breast cancer, enhancement of IL-8 expression and autocrine TGF-β signaling can be observed following chemotherapeutic drug paclitaxel treatment, which results in the enrichment of the CSC population and recurrence of the tumor. Besides, a crucial role has been found for stroma-secreted chemokine SDF-1a and its receptor CXCR4 in the hematopoietic cell migration to the bone marrow. Hence, CXCR4/SDF-1α interaction intervenes in the leukemia cells' resistance to apoptosis caused by chemotherapy [87–90].

2.2.6. Signaling pathways and therapy resistance

2.2.6.1. Sonic Hedgehog pathway. The initial identification of the Sonic Hedgehog pathway (Shh) occurred in the fruit flies, with a key function in embryogenesis. The Hedgehog ligand binds to its receptor Patched (PTCH), enabling Smoothened (SMO)-mediated translocation of glioma-associated protein 1/2(Gli1/2) to the cell nucleus to induce the transcription of Shh target genes. The proliferation, migration, and differentiation of target cells are regulated spatially and temporally by Shh in a concentration-dependent way [91,92]. There is a relationship between Shh and chemo-resistance. The ABCG2 efflux pump is regulated by Shh signaling with ALDH activities and the resistance of EGFR-TKI is reversed. Additionally, malignant transformation phenotypes and CSC phenotypes are maintained by Shh signaling in CD44+ gastric cancer cells, and reserving Shh can cause a reversal of chemo-resistance in CD44 + cells. The Shh signaling pathway is activated by LncRNA-cCSC1, and the CD133 and CD44 expression is regulated. On the contrary, Shh-mediated-erlotinib resistance in CSCs is significantly reduced by let-7c and miR-200b [93–96]. From the TMV perspective, CAFs and TAMs have contributions to Shh-mediated therapy resistance: MFG-E8 is produced by TAMs, and MFG-E8 principally causes activation of Shh and amplification of its anti-cancer medication resistance. Besides, Shh shows participation in intracellular signaling, which modulates CSCs and CAFs synergistically for mediating therapy resistance [97,98].

2.2.6.2. Notch pathway. Signaling can be induced by DLL3, DLL4, and DLL1, and Jagged ligands (JAG2 and JAG1) expressed on the neighboring cells' surface that express their cognate receptors Notch1–4. Notch receptors cleavage and γ secretase (S3 cleavage) is promoted by ligand binding through ADAM/TACE enzymes (S2 cleavage), which leads to releasing the Notch intracellular domain that has interactions with transcriptional regulators of the nucleus for inducing a Notch gene-expression. In turn, Notch target genes cause regulation of key cell-fate choices, such as cell cycle progress, survival, and differentiation [99, 100]. The Notch pathway is activated by the CSCs for the promotion of chemotherapy resistance. Nanog leads to regulation of Notch signaling with ALDH activities and resistance to radiotherapy in breast cancer. Furthermore, it has been demonstrated that crosstalk between NF-κB and Notch has a contribution to resistance to treatment in triple-negative breast cancer. 5-FU resistance can be partially reserved through inhibition of ADAM-17, which is an important element of Notch

signaling, by Nectin-4. Following the binding of Fused Toes Homolog (FTS) with Notch1, Notch signaling is activated and expression of Sox2, Nanog, and Oct4 is upregulated that incrementing resistance to radiotherapy [101–105].

2.2.6.3. Hippo pathway. The Hippo pathway as a very conserved signaling pathway can regulate cell fate, proliferation, apoptosis, and maintenance of stem cells in different species. Researchers have established components of the Hippo pathway, such as scaffold proteins and an important kinase cascade, in mammals and drosophila. The Hippo pathway in mammals includes a key kinase cascade where Mst1/2 builds a complex with Sav1, an adaptor protein, which phosphorylates kinases Lats1/2. The transcriptional coactivators, TAZ and YAP1, are then phosphorylated and inhibited by Lats1/2, through the promotion of degradation, cytoplasmic retention, and ubiquitination. As suggested by recent data, CSCs properties are regulated by YAP1, and it confers resistance to therapy [106–109]. There is an association between YAP1 overexpression and its activation (nuclear localization) and weak prognosis in different types of tumors, e.g., gastric adenocarcinoma (GAC). As indicated by Wei et al., overexpression of YAP1 is observed in gastric cancer, and it intermediates CSC characteristics via its target SOX9. According to investigations, YAP1 has a strong mediatory role in radiation and chemo resistance via upregulating CDK6 and EGFR in esophageal cancer [110–112]. Based on research reports, TAZ is another hippo downstream effector that improves the tumor-seeding and self-renewal potentials of CSCs, conferring CSC-like characteristics on differentiated non-CSC cells in various cancer settings. As suggested by recent evidence, there is also an association between TAZ and resistance to therapy. Zhan z et al. showed an association between TAZ and drug resistance of pancreatic cancer [113,114].

2.2.6.4. Wnt/β-catenin signaling. Wnt/β-catenin signaling is a pathway required for the primary activation, cloning capacity, and self-renewal of CSCs. As reported by Fevr et al., Wnt/β-catenin signaling is blocked by inducible and tissue-specific β-catenin gene ablation, and the proliferation capacity of CSCs is reduced. The Expression of CSC surface markers is modulated by Wnt/β-catenin signaling [115–118]. On the other hand, Leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5) is regarded as a marker of CSCs and it is a target gene for the Wnt pathway. The level of surface marker LGR5 in CSCs is increased by activating Wnt/β-catenin signaling. LGR5-positive CSCs show resistance to chemotherapy. As a result of quick CSCs proliferation, LGR5-negative cells are transformed into LGR5-positive cells, resulting in the entrance of the cells into a static mode for escaping the drugs' toxicity [119–121]. Moreover, according to studies, there is a close relationship between Wnt/β-catenin signaling and the CSCs' ABC transporter. If Wnt/β-catenin signaling is inhibited, the mRNA expression related to the ABC transporter is downregulated that increasing the sensitivity of cancer cells to irinotecan and paclitaxel [122]. Furthermore, based on investigations, the CSC expansion and Wnt/β-catenin pathway in vitro and in vivo are activated by factors that are generated by fibroblasts, including hepatocyte growth factor (HGF). It seems that CSCs with high Wnt signaling activities in colon cancer are associated with stromal myofibroblasts secrete various factors for maintaining the active Wnt/β-catenin pathway. Therefore, the stemness properties of its adjacent cells are ensured. It has been found that in malignant pleural mesothelioma, Wnt/GSK3β/β-catenin pathway is upregulated, and Wnt-driven autocrine production of IL-1β and IL-8 can contribute to upregulation of ABCB5 that predicts poor response to chemotherapy [37,123].

2.2.6.5. NF-κB pathway. The NF-κB pathway has a mediatory role in chronic and acute inflammation in tumors. It has a vital role in the biology of the tumors and adjusts major processes in the progression and initiation of different carcinomas. The p50-p65 dimer is the key physiological element of NF-κB. Post-translational modification activates the active p50-p65 dimer further, and it is transferred into the nucleus. Thereby, the target gene expression is induced combined with other transcription factors. Recent studies have found preferential activation of NF-κB signaling in CSCs [124–127]. Salinomycin is an NF-κB inhibitor with the ability to induce apoptosis in ovarian cancer resistant to cisplatin [128]. Besides, NF-κB contributes to EMT progression. Shortly, activation of NF-κB is enhanced by Twist2, and expression of Twist2 is upregulated by NF-κB. Hence, a positive feedback loop is formed that causes activation of EMT and enhancement of CSC-like characteristics. Additionally, NF-κB activates hypoxia-associated stemness signaling [129–131], reverting ROS-induced apoptotic cell death in CSCs. Moreover, the following evidence supported a model of HER2-induced sequential activation of the IL-6 and IL-1α signaling pathways: (i) expression of IL-1α is upregulated by HER2 through MAPK-mediated activation of the PU.1 transcription factor; (ii) With binding secreted IL-1α to its receptor, NF-κB is activated that then binds to the IL1A and IL6 promoters and is activated through a feedback mechanism; (iii) with binding IL-6 to its receptor, the downstream STAT3 transcription factor is activated [132]. The HER2/NF-κB model showed the capacity of promoting chemotherapy resistance and tumorigenesis. Thakur reported another autocrine loop: cisplatin had a mediatory role in the activation of NF-κB only in CSCs that caused activation of the bimodal feedback loop of NF-κB-PIK3CA and NF-κB-TNFα. Moreover, an autocrine loop is promoted by this mechanism by activation of TNFα-NF-κB in CSCs. It also causes increasing PI3K/AKT and PIK3CA signaling. Hence, it leads to the stabilization of NF-κB. Activated PI3K/AKT confers resistance against cisplatin via modulating pro-apoptotic (decreasing in PUMA and Bax) and anti-apoptotic (increasing in cellular FLIP) genes. An anti-apoptotic, quiescent CSC state is maintained by the continuous supply of NF-κB through the TNFα-NF-κB autocrine loop and improved NF-κB stabilization by activated AKT, conferring survival against chemotherapeutics in resistant cells [133].

2.2.6.6. JAK/STAT pathway. Activation of JAK/STAT pathway is initially stimulated by ligands, especially growth factors and cytokines. With binding cytokines to their correspondent transmembrane receptor subunits, multimerization occurs with further subunits and close interactions of receptor-associated JAKs. The JAK family of tyrosine kinases include JAK3, JAK2, JAK1, and TYK2. After the placement of the receptor-associated JAKs in close proximity, trans-phosphorylation activates them. Activated JAKs phosphorylate tyrosine deposits on the cytokine receptor's cytoplasmic region so that docking sites are provided for the SH2 (Src Homology 2) domain of STAT proteins. When a component from the STAT family (STAT6, STAT5b, STAT5a, STAT4, STAT3, STAT2, and STAT1) binds to the phosphorylated receptor intracellular domain, JAK-mediated tyrosine is phosphorylated and the STAT is activated. When there are receptors with intrinsic tyrosine kinase activities (for example, EGFR), as a result of ligand binding, receptor autophosphorylation of tyrosine residues happens, serving as the docking regions for STATs, and receptor tyrosine kinase directly phosphorylates/activates the bound STATs. Activated STATs are translocated and dimerized into the nucleus and work as transcription factors there, which induces the expression of genes that control cellular survival, proliferation, and invasion, and shows a contribution to drug resistance [84,134].

3. A brief overview of the HMGA2

HMGA2 is commonly expressed during early development and embryogenesis in undifferentiated cells. However, with the progress of fetal development, it is expressed at a more restricted level. HMGA2 is expressed at the liver, uterus, and kidney in adulthood and late development, while it is less expressed in the lung and kidney [135,136].

Re-expression of HMGA2 is observed in various malignant and benign tumors, such as lung, breast, colorectal, pancreatic, and ovarian cancers [137–140]. As shown by full genome analysis, HMGA2 shows a preferential expression in stem cells, and with growing age, a progressive decay is observed in expression, partially because of increased expression of let-7b microRNA. Besides, HMGA2 expression is confined to the mesenchyme in normal development. In vivo tests in an HMGA2 null mice model have confirmed that HMGA2 has a role in spermatogenesis, stem cell development, and adipogenesis [141–143]. It has been implied in DNA translocations in mesenchymal tumors and lipomas. They produce chimeric transcripts where exons 4 and 5 can be replaced by other coding sequences, including Twist, Snail1, and Snail2, leading to HMGA2 binding to various genes with three AT-hooks. Gene expression can be inhibited and activated by these HMGA2 fusion proteins through modification of chromatin arrangement, and it has been indicated that some HMGA2 fusion proteins induce tumorigenicity [144,145]. Fig. 2 illustrates the schematic structure of HMGA2.

4. HMGA2 and CSCs

The involvement of HMGA2 in cancer stemness has been proved in various cancer types [146,147]. Behzad et al. found a positive relationship between CD133 and HMGA2 in breast tumors. According to their report, HMGA2 knockdown reduces the number of cancer colonies and decreases the size of mammospheres. Besides, according to their results, suppression of HMGA2 decreases the population of CD44+ and CD133+ cells [148]. Expression of the CSC markers (SOX2, Nanog, and ALDH) is reduced by HMGA2. Moreover, the expression of HMGA2 causes a more than 9-fold augment in CD133 positive cells of glioblastoma multiforme (GBM) neurosphere cells in comparison with CD133 negative cells. On the contrary, the stemness of GBM is reduced by HMGA2 knockdown. HMGA2 is a modulator of self-renewal potentials of embryonic stem cells and neural [149,150]. With the binding of HMGA2 directly to the SOX2 promotor, it regulates this gene's expression that encodes a crucial CSCs marker. Besides, the findings of another work showed the positive regulatory function of HMGA2 in the SOX2 role in anaplastic astrocytoma side population cells [146,151]. In addition, the expression of CSCs markers, including Oct4, Twist1, and CD44 is increased by HMGA2. HMGA2 is positively correlated to CD44 in gastric tumors. As a result of HMGA2 overexpression, the stomach cancer spherocytes and expression of the markers like ALDH1, CD44, Oct4, and SOX2, are increased [152]. Liang et al. also found interesting results about the induction of CSCs via HMGA2. According to their finding, M1 macrophages (pro-inflammatory phenotype) caused a subpopulation of CD24−/or low/ CD44 high or ALDH1+ cells with cancer stem cell-like phenotypes from different types of breast cancer cells (BCCs) in a paracrine way. Pro-inflammatory cytokines activate Stat3/NF-κB pathways in BCCs, which resulted in the ignition of Lin-28B-let-7-HMGA2 axis for inducing CSC via EMT. Besides, it has been stated that EMT is initiated by Stat3-coordinated Lin-28-B-let-7-HMGA2 axis in BCCs. As demonstrated by Liang, EMT/CSCs program is suppressed by the hindrance of Stat3/NF-κB pathways or Lin-28B-let-7-HMGA2 axis. Remarkably, M1-induced CSC formation and Nanog and Klf-4 expressions are directly repressed by the knockdown of HMGA2 [153].

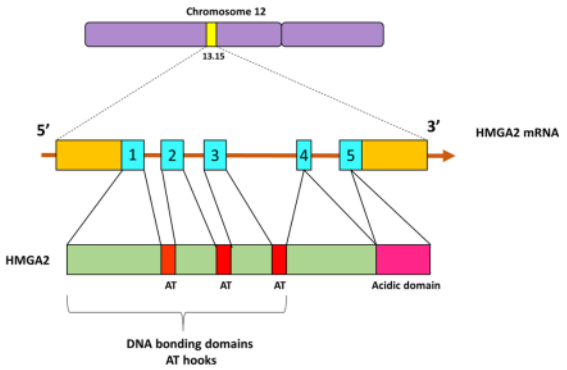

Fig. 2. The HMGA2 gene is located on chromosome 12 and (140 kb) consists of 5 exons. The product of the HMGA2 mRNA is a protein composed of 108 amino acids. This protein is made up of three AT-hook regions that bind to the DNA. In addition, there is an acidic domain whose function is unknown.

5. HMGA2 and drug resistance

The possible role of activated EMT in the induction of drug resistance has already indicated. TGF-β signaling pathway mediated in upregulation of HMGA2, resulting in EMT and tumor metastasis in vivo and in vitro as observed in breast and colorectal cancer mice models. According to the findings of the research, there is a co-association between HMGA2 and SMAD in binding to Snail promoter, which upregulates expression Snail, leading to induction of the EMT [154]. There is also an association between EMT process and the downregulation of epithelial markers, including zonula occludens 1 (ZO-1) and E-cadherin, and abnormal upregulation of mesenchymal markers, like N-cadherin and vimentin, as representative of EMT molecular hallmark [155,156]. Fig. 3 demonstrates these processes briefly. As revealed by previous works, various regulatory networks govern EMT, including TGF-β, active ERK1/2 (extracellular signal-regulated kinase), PDGF, and EGF signaling. Besides these signaling pathways, it has been proved that transcription factors, e.g., Snail, ZEB1, Slug, Twist, and ZEB2, critically play roles in the promotion of EMT [157]. Yang Li et al. indicated the possibility of activation of the EMT program by overexpression of HMGA2, which resulted in increased invasion and chemo-resistance of colon cancer cells. Additionally, EMT is induced by the expression of ectopic HMGA2 through HMGA2/Slug axis downstream of active TGF-β and ERK1/2 signaling [158,159].

In the previous section, it was mentioned that hypoxia is one of the mechanisms causing the induction of drug resistance. miRNAs, such as mir-196–5p, can mediate hypoxia-related therapy resistance. The miR-196 is encoded in the HOX gene cluster, and dysregulation has been reported in many types of cancer. It has been reported that these miRNAs can induce growth, metastasis, and therapeutic resistance [160–162]. As proved by Zheng et al., HIF-1α plays a mediatory role in reducing the expression of miR-196–5p under hypoxic conditions. It has been shown that as a result of miR-196–5p overexpression, the impaired proliferation and metastasis of cancer cells occur, while an opposite effect was observed with knocking down this miRNA. Besides, their findings showed direct regulation of HMGA2 by miR-196–5p (negative correlation) in hepatocellular carcinoma cells (HCC). Also, they showed it was sufficient to alter the HMGA2 expression to reverse the miR-196–5p inhibition/overexpression effects on HCC cell proliferation and metastasis. Hence, it was suggested that the miR-196–5p/HMGA2 axis is a critical pathway that regulates the progress of HCC or drug resistance [163]. The role of a number of HMGA2-related miRNAs in various cancers is summarized in Table 1.

Based on some evidence in previous studies, the expression of HMGA2 is modulated by CCAT1 through competitively binding to let-7. The research findings demonstrated the significant role of TAMs in upregulation of HMGA2 and CCAT1 expression and subduing the let-7b expression in cancer cells in comparison to M0-macrophages. According to these results, progression of cancer cells or drug resistance was supported by TAMs through activation of the CCAT1/let-7b/HMGA2 signaling pathway [164]. CAFs are other components of TME that have a vital role in treatment resistance. As previously demonstrated by Zhang et al., exosomes derived from CAFs are promotors of bladder cancer cell invasion and proliferation by transferring LINC00355. According to their findings, HMGA2 is a direct target of miR-15a-5p, and

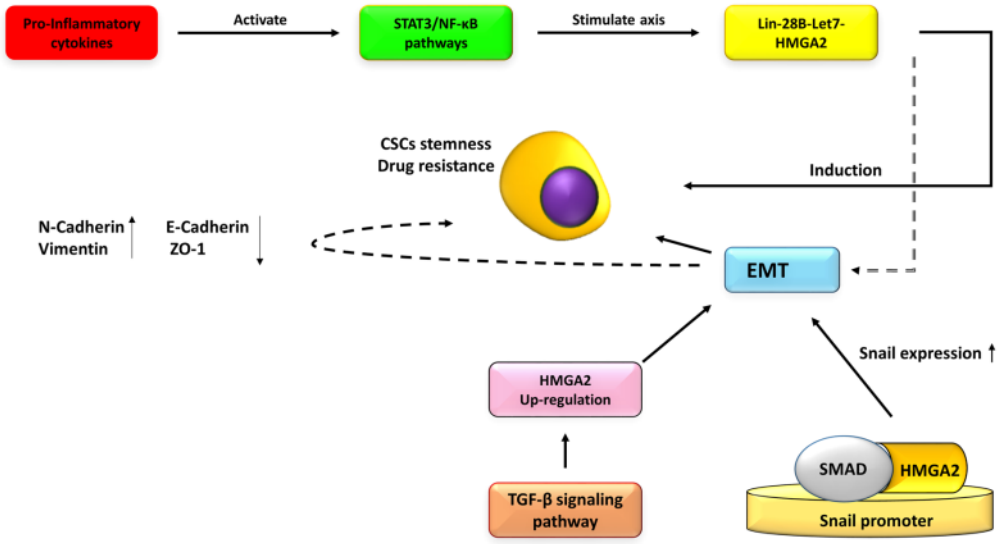

Fig. 3. Schematic of the mediating role of HMGA2 in inducing EMT, CSCs stemness, and drug resistance.

Table 1
The role of microRNAs associated with HMGA2 in diverse cancers.

Cancer Types	microRNA	Target	Function	Reference
Gastric cancer	microRNA-107	mTOR/HMGA2/P-gp pathway	• Reduced drug resistance	[181]
	microRNA-33b-5p	HMGA2	• Cell growth inhibition	[182]
		Bcl-xL	• Decreases chemoresistance	
		Bax		
Colorectal cancer	microRNA-194	N-cadherin	• Inhibition of cell growth	[183]
		HBEGF	• Reduced drug resistance	
		IGF1R	• Reduced EMT	
		MAP4K4	• Negative correlation with HMGA2	
		AKT2		
Esophageal squamous cell carcinoma	miR-125b-5p	HMGA2	• Inhibited the proliferation, invasion and metastasis	[184]
		CCNA2		
		MMP2, MMP7, MMP13		
		CCND1CCNE1		
Glioma	miR-34a-5p	HMGA2	• Increases sensitivity to the Temozolomide	[185]
			• Suppresses proliferation and migration	
Breast cancer	miR-216b	HMGA2	• Increases sensitivity to the 5-FU	[170]
			• Reverse correlation with circFBXL5	
			• Inhibits cell migration and invasion	
Non-small cell lung cancer	miR-363-3p	HMGA2	• Decreases proliferation and invasion	[186]
Ovarian cancer	miR-493–3p	HMGA2E2F5ETS1STK38LAKT2	• Induces apoptosis	[187]
			• Decreases chemoresistance	

HBEGF: heparin-binding epidermal growth factor-like growth factor; IGF1R: type 1 insulin-like growth factor receptor; MAP4K4: mitogen-activated protein kinase kinase kinase kinase 4; AKT2: AKT serine/threonine kinase 2; circFBXL5: circRNA F-box and leucine-rich repeat protein 5; STK38L: Serine/Threonine Kinase 38 Like.

the function of LINC00355 is like a sponge of miR-15a-5p for upregulation of HMGA2 expression. Inhibiting the expression of LINC00355 in BC cells could hinder the promoting effects of CAF-Exo on HMGA2 expression, cell invasion, and cell proliferation [165]. Furthermore, as shown by Luo et al., exosomal LINC00355 derived from cancer-related fibroblasts promote chemotherapy resistance in bladder cancer cells. Therefore, HMGA2 has an inevitable role in chemoresistance caused by CAFs [81].

According to experimental and clinical data, drug resistance and pharmacokinetics are changed in inflammatory states. Despite the induction of drug resistance by inflammatory response through JAK/STAT pathway and pro-inflammatory cytokines, the other mechanism is alterations in expression and activation of MDR following inflammation [166]. Chen et al. showed that JAK/STAT activation resulted in overexpression of HMGA2 [167]. Dutta et al. also demonstrated that STAT3-mediated up-regulation of Lin-28 results in a decrease in the let7 family of miRNAs, the HMGA2 upregulation, which is a let-7 target, and the EMT in breast cancer cells. It can induce drug resistance [168–170]. Furthermore, it has been ascribed that HMGA2 can induce the expression of SLUG. Moreover, Lourdes et al. detected that HMGA2 is positively correlated with SLUG. Their findings indicated that not only SLUG overexpression but also HMGA2 contribute to the progression of cancer. Thus, high expression of HMGA2 can promote the progression of the disease through the SLUG upregulation, and there could be a relationship between upregulation of HMGA2-MDR3 and chemotherapy resistance [171].

The signaling pathway is the other factor that can disrupt cancer therapy or drug resistance. The relationship between the HMGA2 gene and the Shh signaling pathway is not well-understood, and it requires further investigation. Notwithstanding, as mentioned by Bo et al.,

overexpression or depletion of HMGA2 does not have a significant impact on Shh-Glil signals [172]. Concerning Notch pathway, Cansu et al. indicated that direct HMGA2 regulation for mediating pro-metastatic functions of Notch signaling is not likely. Rather, the expression of HMGA2 could be changed for compensating for the impact of Notch signaling modulation on transcription for the sake of cell homeostasis [173]. On the contrary, it was demonstrated by Hou et al. that the HMGA2 downregulation can hinder Jagged-1/Notch signaling [174]. As findings of Jianxin Xu et al. indicated, HMGA2 can promote breast cancer invasion through modulation of Hippo-YAP signaling pathway. Also, they reported that as a result of HMGA2 downregulation, suppression of TNBC migration and tumor metastasis occurred through inhibiting EMT and Hippo-YAP pathway. Moreover, HMGA2 is regarded as a regulatory factor for Hippo-YAP signaling [140]. Zha et al. have already shown that in gastric cancer, HMGA2 was conducive to EMT through activating Wnt/β-catenin signaling. In a similar way, it was suggested by Wend et al. that there is a close association between the Wnt10B/β-catenin signaling and HMGA2, promoting metastatic triple-negative breast cancer cell proliferation [175,176]. Thanos et al. reported the first collaboration between the NFκB and HMGA families. It was indicated HMGA1, in combination with NFκB, caused induction of expression of IFN-β in virus infection immunity. As indicated by Noro et al., HMGA2 has a physical interaction with the p65/p50 subunits of NF-κB. HMGA2 has the ability to enhance the NFκB binding to the positive regulatory domain II (PRDII) transcription factor. HMGA2-dependent expression of IMP2 has been confirmed to have a vital role in tumorigenesis and during embryonic development [177–179]. Moreover, it was found by Behzad et al. that NF-kB signaling is inhibited by silencing HMGA2, resulting in reduced expression of the downstream molecules IL-8 and IL-6 and decreased activation of STAT3 pathway. According to their findings, cancer hallmarks are supported by HMGA2, and HMGA2 might be a promising target to overcome drug resistance and remedy [180].

6. Discussion

One of the main challenges in the field of cancer is achieving effective and successful treatment. However, often the prescribed treatments fail due to induced drug resistance and recurrence of cancer. CSCs can play a pivotal role in this process due to their characteristics (self-renewing, plasticity, generating clones of the tumor, recurrence, and chemoresistance) and have been given special attention. CSCs also play a direct role in the drug resistance process through various factors such as specific markers, EMT, hypoxia, cells of the tumor microenvironment, and signaling pathways. On the other hand, many studies have shown that CSCs can maintain tumor stemness and are also directly or indirectly involved in CSC-induced drug resistance. HMGA2 can increase the expression of specific markers of CSCs that lead to chemoresistance and play a role in several primary drug resistance signaling pathways simultaneously. Therefore, HMGA2 can be one of the keys to solving this puzzle, and by targeting it through different pathways, drug resistance can be overcome and improve treatment efficiency.

Ethical approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable

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PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11