Iraqi Journal of Cancer and Medical Genetics

Cancer Stem Cell Markers in Iraqi Patients with Solid Tumor: Review Article

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Abstract:

Cancer stem cells (CSCs) or in another term, tumor intimation cells (TICs), represent a small distinct subpopulations cells within cancer cells which have capability for potential self-regeneration and cell proliferation. During division, TICs or CSCs produced two deferent cell types; one cell is progenitor cell and anther is tumor cell that drive tumor initiation and tumor progression. Previous studies on cancer stem cell markers in solid tumor types that including breast cancer, colon cancer and thyroid cancer have using specific markers to detect cancer stem cells, but it is remain not fully clear as the stem cell stairway these markers collapse. In this study we compounded moreover by the existence of multiple cancer stem cell subtypes within solid tumors, making realization depending on the use of different markers. This mini review paper concentrate on the recent information in cancer stem cell markers including aldehyde dehydrogenase (ALDH1A1), CD44 , ATP binding protein G2(ABCG2) or breast cancer resistance protein (BCRP) and OCT3/4 highlight their used and validity in Iraqi patients with solid tumors.

Key words: *Breast cancer, CD44, ALDH1A1, OCT3/4, ABCG2*

Introduction:

Cancer is a class of heterogeneous group of diseases characterized by out-controls growth of the cells. This proliferation if allow to carry on and diffusion could be lethal. Rather than the primary tumor, death related cancer result from tumor spread and metastasis (1). Cancer is multi step, multi gene disease originating from single abnormal cell (2). Uncontrolled proliferation of cancer cells usually resulted from protein coding gene mutations that controlled cells division. Accumulation of these mutations led to abnormal cells grows and form tumor. Some of these cells undergo successive round of mutation and selective expansion led to form tumor mass. Since malignant growth can occur in virtually all sites of the body, there are over 100 different types of cancer, and each is classified by the type of cell that is initially affected (3). Cancer cells have ability to self-sufficiency in growth signals, escape from apoptosis, insensitive to anti-growth signals, unlimited replicative possibility, sustained angiogenesis and tissue invasion and metastasis (4).

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Cancer Stem Cells (CSCs)

Cancer stem cells (CSCs) or tumor initiation cell (TIC) are cancer cells that found within tumors that have characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. CSCs have ability to self-renewal and differentiation; therefore these cells are tumorigenic (tumor forming) in contrast to other non-tumorigenic cancer cells. CSCs may generate tumors through disturbances of the renewal process of stem cells (5). These cells are hold out to preserve in tumors as a distinct population cause tumor relapse and metastasis by giving rise to form new tumors. Cancer stem cells are also capable of regenerated after morphological and biochemical apoptosis by recall blebbishield emergency program (6).

The concept that cancer might developed from small population of cells or CSCs comes from hematopoietic field and it becomes the leader in the identification of stem and progenitor cells and their resulting lineages (7). The leukemic stem cells (LSCs) were first described as CSCs in human acute myeloid leukemia (AML). Bonnet and Dick demonstrated that a small percentage of CD34+ CD38−AML cells have LSCs with the ability of self-renewal, differentiation,

proliferation and, were able to reconstitute a heterogeneous cell population when transplanted in NOD/SCID (non-obese diabetic/severe combined immunodeficiency) mice (8). The same concept was realistic in solid tumor that valid relatively recently. Identification of cancer stem cells in solid tumor come from the study of Al-Hajj and colleagues by using cells isolated from primary tumor of breast cancer patients (9). Less than hundred cells with CD44 highCD24low/−Lin− phenotype have ability to form new tumor when transplanted into mammary fat pad of NOD/SCID mice, while a tens of thousands of the other tumor cells were non-tumorigenic. In the study of Ginestier and collegues demonstrated that less than twenty cells that have CD44 highCD24low phenotype which were aldehyde dehydrogenase (ALDH+) able to form a new tumor in NOD/SCID mice (10). These cells recreated heterogeneity of initial cancer, manifestation tumorigenic and non-tumorigenic cells.

This recapitulation can be repeated during several passaging in NOD/SCID, illustrate the capacity of these cells in both self-renewal potential and differentiation (11). Because the functional of stem cells like properties of this type of cells, the term (cancer stem cells) is suitable descriptor. This term descript that these cells are not, in fact stem cells re-wired although they may be. According to that, the term CSCs referred to the cells within tumor that have ability to self-renewal and lead to heterogeneous lineage of cancer cells that constitute the tumor (12). The CSCs may results either from a normal tissue SC that gain acquired mutation that converted those normal cells to tumorigenic cells or from extra differentiation of progenitor or mature cells that has de-differentiated and acquired the capacity to self-renewal in addition to tumorigenic mutation.

Cancer stem cells and normal stem cells are share many similarities in terms of self-renewal, production of differentiated progeny, expression of specific cell membrane markers and oncogenes, utilization of same signaling pathways, and the importance of the stem cell microenvironment (13). CSCs are not synonymous with normal stem cells. Cancer stem cells differ significantly from normal stem cells in their tumorigenic activity. According to that, we can define cancer stem cells out of four important properties: (A): self-renewal—the cancer stem cells are small population of cells those can be serially transplanted out of multiple generations, indicating the self-renewing activity. (B): Differentiation—pluripotent cancer stem cells have ability to form either tumorigenic daughter cancer stem cells through symmetrical cell division and create a bulk population of non-tumorigenic cells by asymmetrical cell division. (c): Tumorgenesity—cancer stem cells have tumorigenic activity when transplanted into animals. (d): Specific cell surface markers, by which cancer stem cells can be identify and separated from the non-stem cells (14). Thus, according to that the most important feature of cancer stem cells is self-renewal and lineage capacity.

Markers Used to Identify CSCs

In order to clarify the activity and function of cancer stem cells in solid tumor, Potential biomarkers expression of cancer stem cells was studied extensively to understand the behavior of these cells in cancer progression, metastasis and resistance to conventional therapy (15, 16). Selectable marker that either organized on the cell membrane or that predominantly expressed in the cytoplasm or in the nucleuses of normal stem cells that expanded to CSCs. As mentioned above, definition of cancer seam cells CD44+, ALDH+ in the following in addition to other putative marker such as OCT3/4 and ABCG2 will be discussed.

CD44

CD44 is transmembrane glycoprotein that plays important roles in several cellular properties including Cell proliferation, cell differentiation, cell growth, cell migration, cell motility and survival. CD44 encoded by the CD44 gene on Chromosome 11 and it has been referred to as HCAM (homing cell adhesion molecule), Pgp-1 (phagocytic glycoprotein-1), Hermes antigen, lymphocyte homing receptor, ECM-III, and Hutch-1. CD44 plays a key role in metastasis of cancer cells by acting as intermediate link between cell-cell and cell- environment interaction through its ability to bind with hyaluronic acid (HA), a transmembrane glycosaminoglycan (17) as well as to other ligands include collagen, fibrinogen, fibronectine, serglycin, mucosal vascular addressin, chondroitin sulfate, laminin, osteopotnin, L and E-selectin and class II histocompatability complex invariant chain (18).

CD44 is excessively expressed over the body, and binding to its ligands depend on an external signaling. There are 20 exons are involved in the CD44 genomic organization molecule. The first five and the end five are constant. While the middle ten exons (v2-v10) between these constant exons are variable that according on variant expression which may be removed. The other three exons (16-18) are constant, and the end two exon (19-20) are variable. The exon between 1-17encode in the extracellular domain of the protein, while exon 18 is transmembrane domain, while the exon 19 and 20 are end in cytoplasmic tail (19) Alternative splicing and glycosylation protein increase generation of CD44 isoforms that range in size (85-230 KDa), functionally and tissue localization (20).The gene and protein structure illustrated in figure (1).

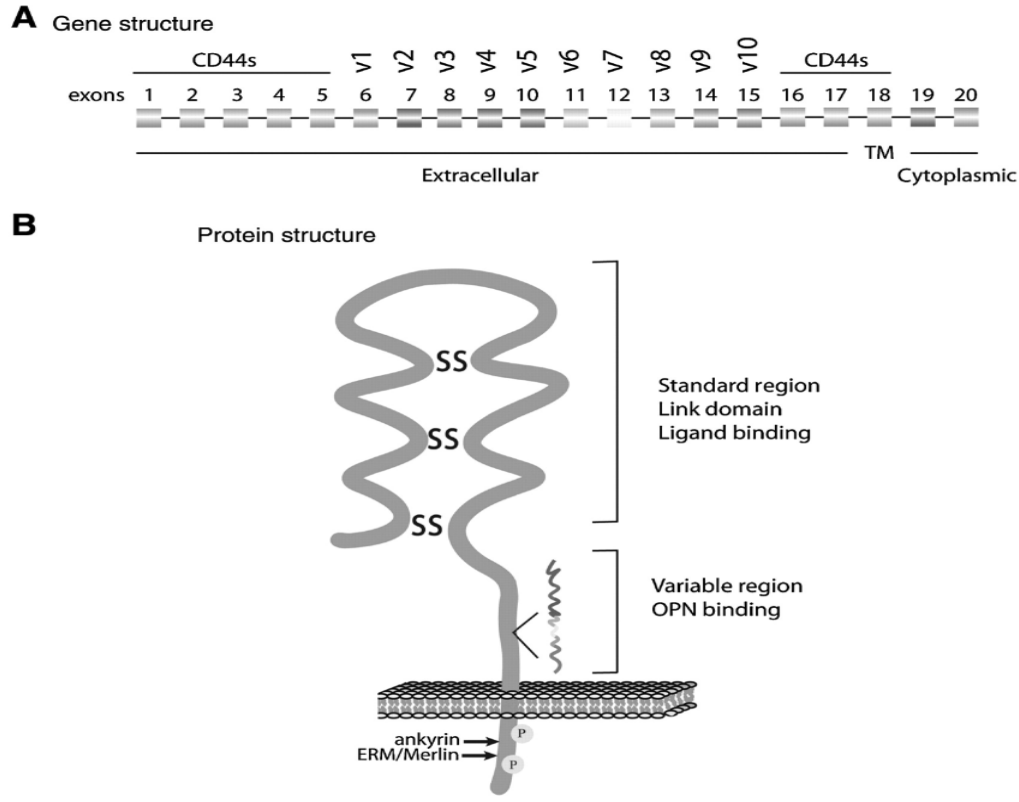

Figure (1):*CD44 gene and protein structure. A, the CD44 gene is encoded by 20 exons, the first 5 of which are constant for all CD44 isoforms. Exons 6–15 are encoded by alternative splicing, 16–18 are constant, and 19–20 are inserted by alternative splicing. The first 17 exons comprise the extracellular region, exon 18 encodes the transmembrane domain, and exons 19 and 20 encode the cytoplasmic tail. B, the CD44 protein consists of a globular extracellular domain that is stabilized by disulphide bonding of 6 cysteine residues and contains binding sites for hyaluronan (a region known as the link domain) and other CD44 ligands. Insertion of variant exons lengthens the stalk structure and exposes binding sites for additional glycosaminoglycan.*

CD44 was found in three states in normal tissues: the active, inducible and inactive forms. The active form is result by least glycosylation of the protein. Inducible CD44 referred to moderate glycosylated required activation by cytokines, monoclonal antibody, phorbol ester or growth factor. Inactive form is the most glycosylated protein and this type is unable to bind with HA (18).The types of CD44 glycosylation not effect only on molecular weight but also in differentially charged environment that cause effect on CD44 activity (21).

CD44 take part in cell-cell and cell-extracellular interaction through binding with specific ligands, facilitate cells adhesion and migration. Interaction between CD44 and HA cause formation of CD44-HA complex and this complex was degraded by lysosomes (22). In cell-cell interact CD44 permit aggregation of cells by binding of endogenous and exogenous hyaluronan. CD44 implicated in lymph node homing and activation of lymphocytes by binding with mucosal adhesion. CD44 also embroil in mylopoiesis and lympopoiesis, angiogenesis, chemokine, growth factors and apoptosis signaling (22).

In cancer, CD44 play important role in tumorigenesis by allowing for more colony formation by increased adhesion to its plurality ligands in the surrounding environment, induction of cellular growth factors, facilitate degradation of the surrounding extracellular matrix allowing cellular migration and tumor expanded (23). Moreover, Cd44 has been shown to interact with matrix metalloproteinases (MMPS) by binding with these enzymes on the cell surface of tumor cells leads to increase tumor cells invasion through depredated collagen IV the main component of basement membrane (24). In cancer stem cells, CD44 play important role in metastasis behavior of these cells and protection against program cell death (apoptosis), which an important characterization for tumor initiation and metastasis initiation cells (25, 26). In addition, cell-cell and cell-extra cellular matrix interaction adherence could give an advantage for cancer stem cells as they could transport through blood stream and reach the second site (27). Previous studies demonstrated the role of CD44-HA interaction in CSCs migration and metastasis in different solid tumors. In head and nuck cancer, formation of

this complex cause promotes growth through EGFR-MAP/ERK- dependent mechanism (28) and through HER2-β-catenin-depending manner in ovarian cancer (29). In breast cancer, formation of CD44-HA complex leads to activation of transcriptional factors such as Nango and OCT3/4 (an embryonic stem cell transcriptional factors) which leads to proceed activation of SOX2, REX1 and multi drug resistance protein1 (MDRP1) (30).While, expression of these marker lead to increase aggressiveness and metastasis in Iraqi women with stage II and III breast cancer (31). On the other hand, the expression level of this marker may be used as a diagnostic marker in papillary thyroid carcinoma (32).

The expression of CD44 all these activity results as response to this complex formation may provide CSCs properties especially with regard to radio and chemotherapy resistance.

Previous studies showed increased CD44 expression in Iraqi patients with solid tumors. Nawal et al (33) showed in the study the expression levels of CD44, CD133 and ALDH in colorectal cancer revealed convey wide range of different expression of markers related to colorectal carcinoma and IHC study may help in early diagnosis and detection of cancer with more attention to increased rate at younger age groups. On the other hand, in the study of benign colorectal tumor, Nawal et al showed that cancer like stem cell markers include CD44, CD166 and ALDH are co localized more in benign tumor glands as compared to that in normal tissues which backing the concept that increase the number of stem like cells hyper proliferation may predispose colonic mucosa to subsequent transformation (34). Meanwhile, our previous studies in Iraqi patients with solid tumors revealed significantly increased in CD44 expression level in breast cancer (31) and papillary thyroid carcinoma (32). These results showed high correlated between CD44 expression level with patient's clinical features including tumor stage, grade, age and gender.

ALDH-1A1

Aldehyde dehydrogenase-1 (ALDH-1) is a detoxifying enzyme belongs to family of 19 NADP depending enzymes that play key roles in oxidization of intracellular and extracellular aldehydes to their corresponding carboxylic acids (35). Different subfamily are responsible for many activity in the body facilitation of retinoic acid biosynthesis, cyclophosphamides metabolism and its derivatives and removed toxic substance by converted reactive oxygen species to nonreactive molecules (36). ALDH1 play important for protection of cellular homeostasis by scavenging of reactive aldehydes resulting from lipid peroxidation. High ALDH-1 expression level is associated with chemo-therapy resistance by interfering with cytotoxic drugs used in the treatment of cancer (14). Previous studies have revealed that ALDH-1 participate in normal and cancer stem cell differentiation, invasion and metastasis in breast cancer are mediated by a cellular subcomponent with stem cell characteristics expressing ALDH1(37) (Figure 2).

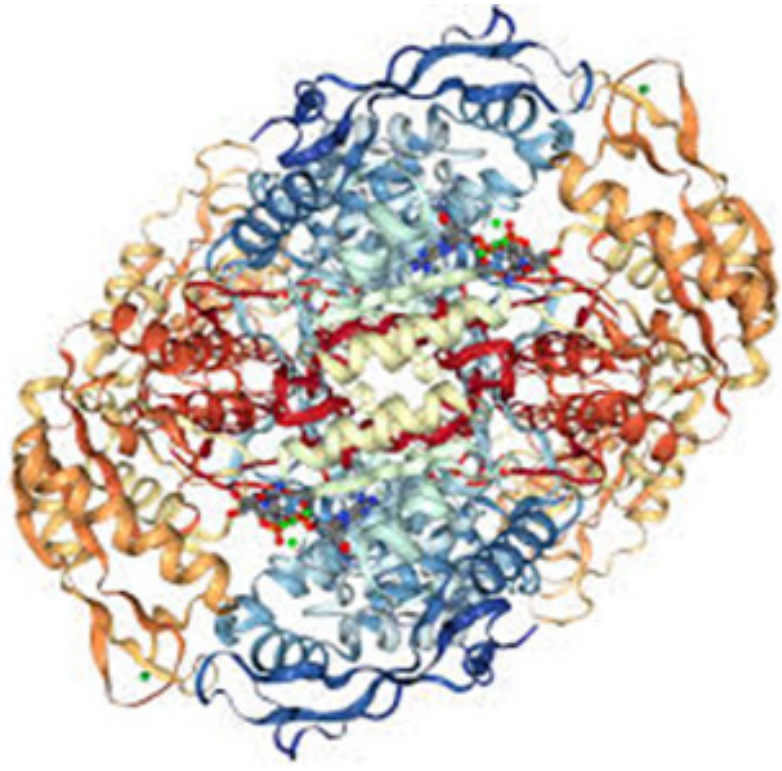

Figure (2): *The whole ALDH1A1 function, structure and protein interaction*

These results mark that the breast cancer cells with ALDH1 phenotype take part in the acquisition of progenitor lineaments (38). Moreover, previous study described assembly of ALDH-1 over expression with early metastasis and reduced overall survival in inflammatory breast cancer has further explain the critical roles of ALDH-1 positive malignant cells in mediate the clinical aggressive behavior of breast cancer (39). In addition, elevated ALDH-1 expression has been used to identify and isolated a variety of normal SC, most distinct the human hematopoietic stem cells (HSCs) (40) and murine neural stem cells (41). Moreover, ALDH-1 was used to identify CSCs in leukemic cancer stem cells (42), colon cancer stem cells (43), head and neck squamous carcinoma (44) and breast epithelial stem cells (45).

Thus, ALDH-1 is act as important marker of both normal and cancerous stem cell population. Immunostaining and gene expression of both normal and malignant breast tissues shown that ALDH-1 is potential isoform responsible for the observed ALDH-1 activity in these stem cell populations (46). Moreover, to the conferred resistance to cyclophosphamides and its derivatives, the drug that used in the treatment of breast cancer, ALDH-1 is responsible for metabolism of retinal to retinoic acid (47), which represent important step in cellular differentiation during development and stem cell self- protection from endogenous aldehydes for the duration of organism life (48). Formation of retinoic acid (RA) interacts with nuclear retinoic acid receptor (RAR) and retinoid X receptor (RXR).This complex cause down expression of histone deacetylase, which control the epigenetic regulation of gene expression (49). It's thought that this ALDH-1 dependent gene regulation and drug resistance play important role in creating CSC phenotype. In different solid tumor in Iraqi patients, we found that ALDH1A1 was significantly increase in breast cancer, colon cancer and papillary thyroid cancer and this highly expression was associated with increase tumor aggression, invasive and cancer metastasis. (32, 33, 50).

In the study of Nawal et al (34) in colorectal cancer, they found that ALDH was elevated in normal adjacent to mucinous adenocarcinoma (NAMC) as compared to non-adjacent to normal mucinous adenocarcima (NANMC) in all groups and in different ages. While, in the study of Basim et al (51) in seventy cases including benign polyps (juvenile & hamartomous polyps) & benign looking colonic tissue showed that ALDH1A1 are co-localized more in benign tumor glands than healthy looking normal which support the idea that increase the number of stem like cells hyper proliferation may predispose colonic mucosa to subsequent transformation.

In our previous study in esophageal cancer cell line we found that ALDH expression level was significantly elevated in cancer cells after cells starved to different period of time (50). On the other hand, we found in the study of cancer stem cell markers in thyroid cancer that the ALDH expression level was elevated in Iraqi patients with thyroid cancer calls as compared with non-cancerous cells (32).

OCT3/4

OCT3/4 or POU5f1 is a transcriptional factor belongs to homobox Pit-Oct-Unc superfamily that plays a critical roles in self-regeneration and pluripotent of stem cells in embryonic phase. The highly expressed of this protein was found in the interior part of unfertilized oocytes cells, germ cells and fundamentally in the embryonic stem cells (52). Increased Oct3/4 expression supports the undifferentiated situation of pluripotent stem cell. On the other hand, down regulation of Oct3/4 expression activate stem cells to continuous differentiation lead to formation of very specialized daughter cells. This is a proof by the lost of pluripotentcy in the internal cell mass cells of POU5f1 in mouse embryos. This expression where loss in the differentiation of embryonic stem cells into a trophoblastic cells (53) (Figure 3).

Several studies has shown that highly expression of Oct4 leads to conversion of embryonic stem cells a cross primitive endoderm and mesoderm state (54). On the other hand, reduction in Oct3/4 expression can prompt differentiation of ESC into trophectoderm cells (55). This expression of Oct3/4 in ESCs is important to maintain a specific lineage of ESC differentiation in addition to different fates growth. Moreover, the exact mechanism that regulated Oct3/4 expression protein in embryonic stem cells is still unclear. Previous study suggest that there is a sensitive sensor mechanism exists able to detect and regulate the expression levels of OCT3/4 within embryonic stem cells (56). This transcriptional family regulate different genes that consist of an octamer motif (ATGCAAAT) in their promoter or enhancer regions (57). The human Oct3/4 gene is located on chromosome 6 and consists of five exons.Oct3/4 encodes for three main variants created by substantial splicing referred as Oct3/4A, Oct3/4B and Oc3/4B1 (58). Both Oct4A and Oct4B are differ in exon 1 which is missing in the amputate Oct4B and it specifically consists of exon 2a. These two variants are identical in exons 2-5 exon (59). OctB1 is identical to Oct4B except it has an additional exon 2c (60). The protein that products from OctB1 gene have not been distinguished yet (Figure 3).

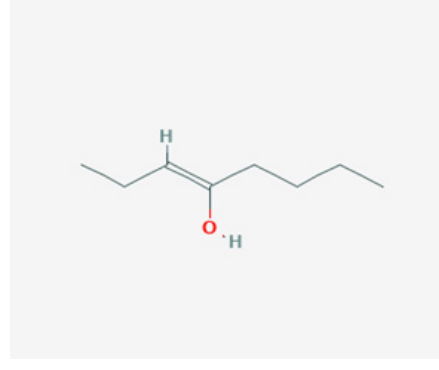

Figure 3: *Structure and function of OCT3/4. (OCT 3-en 4-ol (C8H16O)*

Stop codon TGA is located in the additional exon 2c of Oct4B1 which is spliced out in Oct4B mRNA (61). Hence, Oct4B1 cannot encode the full length Oct4B. Oct4A is expressed specifically in the nucleus of embryonic stem cells, human somatic stem cells, and somatic tumor cells and at a basal level in some adult stem cells (61). The functional protein for Oct4A has not been dependably identified in the non-pluripotent cells, and it is remain not clear if the basal expression of Oct4A in non-pluripotent cells gives any biological function. However, a high expression level of Oct4A protein is found in pluripotent cells (62). In human somatic stem cells, tumor cells, adult tissues as well in pluripotent cells, Oct4B is expressed at low levels. Oct4B expression generally in the cytoplasm (62), and there is no evidence to suggest that the Oct4B isoform may be involved in the generation of induced stem cells (iPSC). Oct4B has play a key role in the stress response (63).

Role of OCT3/4 in tumor progression

Oct3/4 is expressed in different malignant tumors and the expression level of OCT3/4 has been correlated with tumor grade and disease progression (64). Compared with low Oct4 expression tumors, high expression levels of Oct3/4 have been correlated with tumor spread, metastases and shorter patients overall survival rates (64).

A previous study on breast cancer has shown that expression of Oct3/4 in normal epithelial breast cells lead to the production of cells with tumor initiation behavior and colonization capacity (65). These cells showed high grade, poorly differentiated breast cancer in NOD mice and illustrated a genomic profile enriched in an embryonic transcription factor network, suggesting that targeting of Oct3/4 in the cells may represent a novel oncogenic therapy (65). Moreover, recent study showed that epithelial to mesenchymal transition (EMT) play important role in both morphogenesis through embryonic development (66) and in the transformation of primary tumor to invasive neoplasm (67). Recently, several studies have illustrated that epithelial to mesenchymal transition also plays a vital role in tumor recurrence which is confirm to be strongly associate with the cancer stem cells phenotype (67).

Role of Oct3/4 in drug resistance

As mention above, OCT3/4 regulated the pluripotentcy and self-renewal of cancer stem cells (CSCs), Oct4 plays important role in the survival of a population of CSCs with drug resistance phenotype (68). Different studies demonstrated that the cells with high expression level of OCT3/4 showed highly resistance to cytotoxic therapy both in vitro and in vivo. In the study of Wang et al on hepatocarcinoma cells, they found that the cells who expressed high OCT3/4 level tend to be more resistance to cisplatin and doxorubicin that used in the treatment of liver cancer as compared with normal cells both in vivo and in vitro (68). Moreover, Tsai et al found that the cells which expressed elevated level of OCT3/4 along with nango (transcriptional factor) showed significantly resistance to cisplatin in oral squamous cell carcinoma patients (69). Treatment with cisplatin in oral cancer cells results generation of subpopulation cells with significantly to cytotoxic drug enriched with stem/progenitor cells with high invasive and metastatic properties (69). This proposed that cancer cell that expressed high Oct3/4 and survive when treated with cisplatin could generate a heterogeneous population of differentiation cells with capability to become metastatic.

In support of this concept, cells that exhibit drug resistance in prostate cancer cell line have been shown to have high OCT3/4 expression level and this enhanced invasive potential in vitro assay and tumorigenic propriety in vivo assay. Targeting of OCT3/4 gene by specific molecules reduced drug resistance of these cells to cytotoxic agents and this suggest that OCT3/4 play important role in both tumorigenesis and maintain drug resistance phenotype.

In Iraqi patients with thyroid cancer, the obtained data extends the research in this field in order to confirm the suggestion of using the detected cancer stem cell markers in the diagnosis (confirming malignancy) in suspicious or undetermined FNAB beside other molecular tests that have already been confirmed to be associated with thyroid cancer (32). On the other hand, OCT3/4 was significantly increase in breast cancer nuclease cells and this gene expression lead to increase tumor invasive and metastasis (33). Moreover, the result of OCT3/4 expression in colon cancer was found to be associated with tumor aggression and metastasis.

In the study of Mohammed et al on 60 samples of bladder carcinoma showed that the OCT3/4 expression level was significantly increased in high-grade TCC; OCT4 can be considered as a key regulator of tumor progression, aggressive behavior, and metastasis. Furthermore, it is a reliable marker for the early diagnosis and the designed chemotherapy of bladder cancer (70). On the other hand, anther founding of the role of OCT3/4 expression level in tumor development and progression was achieved by Khalida et al (71) in benign prostate hyperplasia and in prostate cancer of 50 Iraqi patients with prostate and benign prostate cancer. They found that OCT3/4 participate in prostate cancer related with patients age. Meanwhile, our previous studies in breast cancer and thyroid (30, 31) reveled increased OCT3/4 expression levels in different solid tumor in Iraqi patients. These results and other study improved the role of OCT3/4 in solid tumors developments, progression and metastasis.

ATP-binding cassette (ABC) G2

Multi-resistance or multidrug resistance (MDR) which refers to the ability of the cells and whole organisms to present resistance to enormous range of drugs that are functionally and structurally unrelated diversification, has turn in to a clinical hurdle in a plurality of tumors since to the introduction to chemo-radio therapy. Different previous studies with cancer cell lines showed that there is a highly express of superfamily transporter members including, ATP binding protein G2, ATP binding protein G1 and ATP binding protein C1. The highly expressed of these different ABC transporters in plasma membranes leads to increased outflow and reduced intracellular cumulation of several unrelated anti-cancer drugs, caused to multidrug resistance (72). The family of

ATP binding cassette are a huge family of glycoproteins that located on the membrane of the cells. This superfamilly contain over 48 members with ability to mediate the transport a broad of different substance throw cellular membranes (73). Hydrolysis of different substance by using the energy of ATP is predominantly participate in the efflux of intracellular materials including metabolic products, sterols, lipids, vitamins, lipids, toxins as well as exogenous drugs that defused from extracellular components into or intracellular compartments such as peroxisomes and endoplasmic reticulum. Therefore, these transporters play important roles in a majority of pathological, physiological and pharmacological processes (74).

The first discovered of ABCG2 in the resistance of breast cancer cell line to doxorubicin as a chemotherapeutic agents. This chemotherapeutic resistance protein is a main member of the ATP-binding cassette transporting family. This protein existing on chromosome 4 at q22 region and encoding 72-kDa membrane protein (75, 76). It is mainly expressed in different tissues such as the embryonic and adults stem cells, placental syncytiotrophoblasts, in addition to various organs such as liver, gastrointestinal tract, pancreas, soft muscles in addition to hematopoietic tissues (77- 79) (Figure 4).

Structure of ABCG2 protein*

All human ABC transporters have a distinctive modular architecture, consisting of at least one hydrophilic nucleotide binding domain (NBD) located in cytoplasm and one hydrophobic membrane-spanning domain (MSD). Based on the structure and arrangement of NBD and MSD, they can be grouped into 'full transporters', 'half transporters' and non-transporter type ABC proteins (80). Full transporters, such as ABCB1, comprise two homologous halves and are characterized by two MSDs and two NBDs with an arrangement of MSD1-NBD1- MSD2-NBD2. Other types of full transporters, such as ABCC1, have an extra MSD (MSD0) at the amino terminus with a domain structure of MSD0-MSD1-NBD1-MSD2-NBD2. Half transporters contain only one MSD and one NBD, which are about half the size of a full transporter. These half transporters include members of the ABCD subfamily and some of the ABCB subfamily with a domain structure of MSD-NBD, and members of the ABCG subfamily with a reversed NBD-MSD configuration. The non-transporter ABC proteins include members of the ABCE and ABCF subfamilies that do not have MSDs (81) (Figure 4).

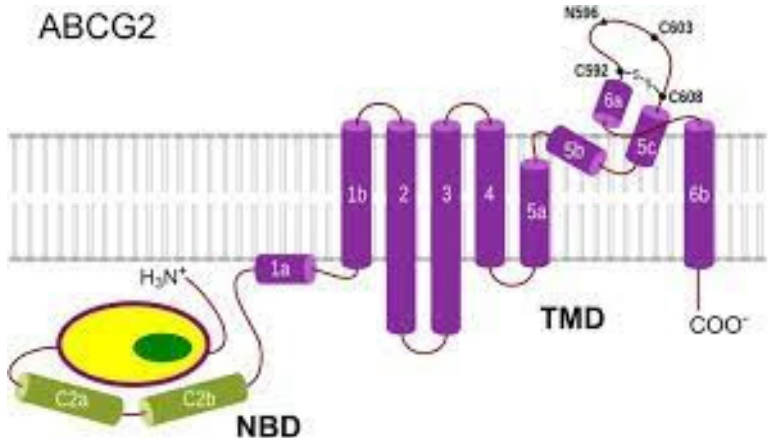

Figure 4: structure-function relationship in ABCG2: insights from molecular dynamics simulations and molecular docking

Role of ABCG2 in Solid Tumors

Correlations between the expression level of ABCG2 and prognosis of solid tumors have also been studied. Similar to the studies of hematopoietic malignancies, some studies of solid tumors showed positive correlation between ABCG2 expression level and prognosis while others did not. In breast cancer patients, it was found that ABCG2 expression correlates with response to anthracycline-based chemotherapy (82). While, in another study of breast cancers, no such correlation was identified (83). Thus, whether ABCG2 overexpression contributes to MDR in solid tumors is currently inconclusive. More studies are clearly neededto investigate the role of ABCG2 in drug resistance and chemotherapy response of solid tumors. The information about the participation of ABCG2 in breast cancer progression, metastasis and resistance to chemotherapy in Iraqi women with breast cancer are rare. On the other hand, the results of ABCG2 expression in thyroid cancer showed significantly increase in papillary thyroid carcinoma and this expression related with useful of this gene in papillary thyroid carcinoma diagnosis (32).

Conclusion

Cancer stem cell or cancer initiation cells play a critical role in the progression, invasion and metastasis of a tumor cells by providing self-renewal and differentiation capacity.

Cancer stem cells may consider a key role in the recurrence, invasion, and metastasis and chemo-radio resistance in solid tumor. According to this respect, the rate of survival in patients with solid tumor may be related to cancer stem cells expression level. Recently, there is no single biomarker available for accurate isolation and characterization of CSCs in solid tumor. Identification of reliable markers is required to characterize CSCs in OSCC as this could ensure the clinical effectiveness of future targeted treatments, possibly resulting in a more effective outcome.

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