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REVIEW ARTICLE

CD133 AS A BIOMARKER OF THYROID CANCER STEM CELLS

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ABSTRACT

A rare malignant cells population exists in the tumor cells, with exclusive self-renewal ability and capable of differentiate into various cell lineages, determined as cancer stem cells (CSCs). They can produce cancer cells in tumors and perform a crucial function in the initiation and maintenance of a tumor. Beyond the scope of this review manuscript, related articles about the detection history, structure and functions of CD133 as a surface marker for CSCs, its role in thyroid neoplasia especially anaplastic thyroid carcinoma (ATC), were found by search in PubMed, Scopus, Springer, and Science direct. It was concluded that the positive CD133 cells as undifferentiated cells have a crucial role in the flunk of radio-iodine cure. The CD133interacts with various signaling pathways such as: PI3K/AKT, Wnt/β-catenin, Notch, NF-κB and causes expression of stemness markers, cancer cell differentiation suppressor, apoptosis inhibitor, and generate a cancer cell with self-renewal ability, tumorigenic potential, and multi drug resistant. Hence, targeting the positive CD133 cellsis a good choice to eradicate the advanced tumors as well as ATC. The target therapyapproach couldruin them by several strategies likeusing certain antibodies, lentivirus vector application, RNA interference applying, activating the γδ T cells, and aptamers.

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INTRODUCTION

A rare malignant cells population, which exists in the tumor cells, with exclusive self-renewal ability and capable of differentiate into various cell lineages, is known as cancer stem cells (CSCs). They can produce cancer cells in tumors and performa crucial function in the initiation and maintenance of a tumor. Hence, they have a huge proliferative potential power with prolonged lifespan and able to impel metastasis, invasion and heterogeneity in cancers (Jaggupilli *et al.,* 2012). Scilicet, these cells can be caused wretched prognosis in the patients, raise of repetition grades and opposition against chemo-radio-therapy in them(Clevers, 2011). Any gene mutation that happens in normal stem/progenitor cells, enables them to recover the property of self-renewal and arise CSCs (Murar and Vaidya, 2015; Li, 2013).

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In the recent two decades, focus on detection and recognition of CSCs aiming ateradicating cancer, the topicthat has attracted considerable interest. Several studies suggested that a CSC niche plays a main role in various cancer relapses. Until the present time, they have been recognized in different cancers such as: colorectal cancer (Merlos-Suárez *et al.,* 2011; de Sousa *et al.,* 2011), colon cancer (Vermeulen *et al.,* 2008), head and neck squamous cell carcinoma (Joshua *et al.,* 2012), ovarian cancer(Ponnusamy *et al.,* 2011), breast cancer (Gökmen-Polar *et al.,* 2011; Mukherjee *et al.,* 2014), colon cancer (Oshima *et al.,* 2014; Garza-Treviño *et al.,* 2015), hepatocellular carcinoma (Nikolaou *et al.,* 2015), non-small cell lung cancer (Zakaria *et al.,* 2015), and thyroid cancers (Xing *et al.,* 2014; Pillai *et al.,* 2011; Todaro *et al.,* 2010; Ahn *et al.,* 2014; Shimamura *et al.,* 2014; De Falco *et al.,* 2012). The gold standard of CSCs' identification or discrimination is evaluating them by specifying their surface markers and then surveying the tumor generation after transplanting these cells into immune-defective animal design (Clarke *et al.,* 2006; Cheng *et al.,* 2010). In these times, various markers for human CSCs such as: $CD133^{+}$, $CD44^{+}$ $CD24^{-/low}$, $CD326^{+}$, integrin

$\alpha2\beta1^{hi}$, BCL-2, nuclear beta-catenin, BMI-1, BrdU, Ki67, CD49f (integrin a6), CK5/14,CK8/18, GST-p, ABCG2/ Hoechst 33342, OCT3/4, P63, P27, SCA-1, SMO (Smoothened), CDCP1, CXCR4,CD26, CD166, CD29, CD24, Lgr5, EpCam, ALDH1, CDCP1, CC188, etc. were discovered in different malignancies (Klonisch *et al.,* 2008; Wang, 2009; Ren *et al.,* 2013).

Detection History &Structure of CD133

PROM1 gene is located on chromosome 4 (4p15.33) and chromosome 5 in human and mice, respectively. CD133, also named prominin-1, is the product of this gene. For the first time in 1997, CD133 was described as anantigen for hematopoietic stem cell as distinct from other embryonic epithelial cells. A product of the human CD133 gene is a five-extend across plasma membrane glycoprotein with 865 amino acids and 120 kDa molecular weight (Figure 1). Its N-terminal is extracellular domain and cytoplasmic tail as a C-terminal containing 59 amino acids. Cytoplasmic loops contain two small cysteine rich, while two very large loops, each having four potential sites for N-linked glycosylation, are considered as extracellular domains (Miraglia *et al.,* 1997; Yin *et al.,* 1997).

Biochemical analysis showed that this glycoprotein inside a separate cholesterol-based membrane and by micro-domainsjoined to the plasma membraneand cholesterol, reciprocally (Marzesco, 2013). This localization playsa significant role in supportinga proper lipid constitution within the plasma membrane. During embryonic maturation, six alternative promoters (P1-P6) with numerous splice variants are responsible for CD133 regulation (Irollo and Pirozzi, 2013; Sompallae *et al.,* 2013). Actually, alternative splicing and any promoter activity could induce disparate expression of CD133 (Grosse-Gehling *et al.,* 2013). Also, going after varied glycosylation area, it can be wrapped differently while camouflagingspecialepitopes (Kemper *et al.,* 2010).

This glycoprotein has two isoforms: CD133-1 and CD133-2.CD133-1 isoform is principally expressed in human fetal liver, blood and bone marrow whereas multiple stem cell niches are CD133-2 site expression (Yu *et al.,* 2002).Furthermore, another protein named prominin-2 is a member of the same family as CD133/prominin-1, but is unable to perform a similar function (Yao *et al.,* 2009). At the present time, researchers have detected CD133 as a surface marker of CSCs not only in the hematopoietic stem cells but also in the foreskin samples (Bhaskara Balaji *et al.,* 2013), normal skin and in epithelial cutaneous tumors (Nam-Cha *et al.,* 2013), renal cells (Grange *et al.,* 2014), pancreatic cancer (Bao *et al.,* 2014), colon cancer (Coco *et al.,* 2012), colorectal cancer (Jeon *et al.,* 2010), brain tumor (Brescia *et al.,* 2013), normal glia (Holmberg Olausson *et al.,* 2014), liver malignancy (Ma, 2013), malignant rhoboid tumor of the kidney (Yanagisawa *et al.,* 2009), non-small cell lung neoplasia (Salnikov *et al.,* 2010), endometrial tumors (Rutella *et al.,* 2009), ovarian cancer (Long *et al.,* 2012), bone tumor (Tirino *et al.,* 2008), gastric carcinoma (Ishigami *et al.,* 2010), melanoma (Rappa *et al.,* 2008), myelofibrosis (Triviai *et al.,* 2015), and anaplastic thyroid carcinoma (ATC) (Jung *et al.,* 2015). Asignificant number of data showed that the glycosylation positions of this protein are intensified by hypoxia and mitochondrial malfunction (Lehnus *et al.,* 2013). Later, it was shown that several factors such as: expression of hypoxia inducible factor 1α (HIF-1α) which subsequently inhibits the mammalian target of rapamycin (mTOR) C1 activity, demethylation of promoter-1 of CD133 following inhibition of DNA methyl transferases 1 (DNMT1) &DNMT3β by transforming growth factor β1 (TGFβ1), beginning the NF-κB signaling with Toll-like receptors 7 &8 (TLR), microRNA (miRNA) profiling (miR-130b) and epigenetic factors caused a reversible plethora expression of CD133 (Li, 2013).While other various elements, such as increased miR-451 expression without cytokine cocktails, can bring about the positive CD133 erythroid cell differentiation and decrease theCD133 marker expression (Madka and Rao, 2011; Feng *et al.,* 2010).

CD133 function

Usually, CD133 marker can be expressed in diverse cell typeslike somatic stem/progenitor cells, developing epithelial and some differentiated cells. As presented in Figure 2, with different signals, it is involved in stemness markers expression, cancer cell differentiation suppressor, apoptosis inhibitor, and generate a cancer cell with self-renewal ability, tumorigenic potential, and multi-drug resistant. However, full functions of CD133 are greatly unknown. This glycoprotein, through connecting to Notch-signaling pathway, plays a vital role in binary cell destiny, differentiation of intestinal epithelium and lymphopoiesis (Ulasov *et al.,* 2011). Furthermore, PI3K/Akt pathway can be induced by Src and CD133 phosphorylation. This pathway mediates the tumorigenic genes generation, self-renewal ability, apoptosis inhibition, and NF-κB production (Wei *et al.,* 2013). The CD133 cells enhanced c-FLIP (FLICE [FADD-like IL-1β-Converting Enzyme]-Inhibitory Protein) expression through NF-κB, capable of opposition to TRAIL (TNF-Related Apoptosis-Inducing Ligand), thus they did not respond to apoptosis signaling (Zobalova *et al.,* 2008). Also, they gained multi-drug resistance ability through DNA-PK (Protein Kinase)-PI3K/AKT- NF-κB pathway (Xi *et al.,* 2016).Epithelial-mesenchymal transition (EMT) and augment invasiveness can be persuaded via the NF-κB and self-renewal signaling pathway activation (Nomura *et al.,* 2015) or up regulating N-cadherin expression (Ding *et al.,* 2014). The lipid droplets, which are cyclooxygenase 2 (COX-2) reservoirs, in positive CD133 cells are possibly controlled by activated Akt while expanding the expression level of the lipid-storage protein LSD2/perilipin. Also, lipid droplets are appropriate regions for prostaglandin E2 (PGE2) production. The high PGE2 creation would join the heterotrimeric G proteins (member of Gs family) and modulate the PI3K/Akt and Wnt/β-catenin signaling pathways. Scilicet, after GDP/GTP replace, α subunit of Gscanadhere cooperatively to the Axin andruins the β-catenin composite (Axin, CK1, APC, and GSK-3β).Then, GSK-3β (Glycogen Synthase Kinase-3β) is set free and inactive after phosphorylated by Akt. Also, free βγ subunits can stimulate the PI3K/Akt signaling pathway (Rappa *et al.,* 2015). The CD133 contributestohistone deacetylase (HDAC6) and acts as negative regulation factor of degradation. On the other hand, CD133 and HDAC6 through deacetylation, adhereto some molecules and activate them. For exampleβ-catenin, which is a main molecule of the Wnt signaling pathway, can be activated via this manner and increase proliferation (Mak *et al.,* 2012). However, through starting the Wnt signaling and paracrine arousal of angiogenesis, their progenitor cells can promote the cureof diabetic ischemic ulcers (Barcelos *et al.,* 2009) and is able to get involved through angiogenesis and form the capillary tubes(Akita *et al.,* 2013).

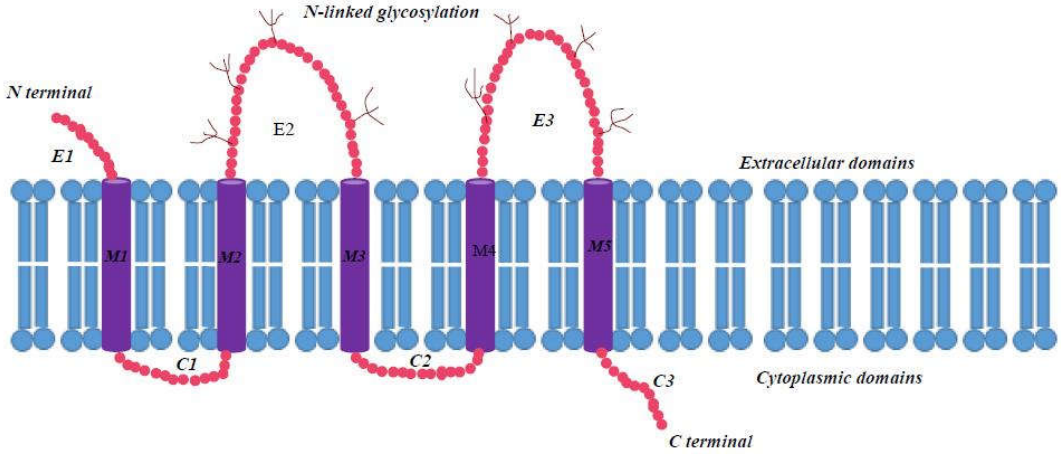

Figure 1. A schematic representation of CD133 localization in plasma membrane of cancer stem cell

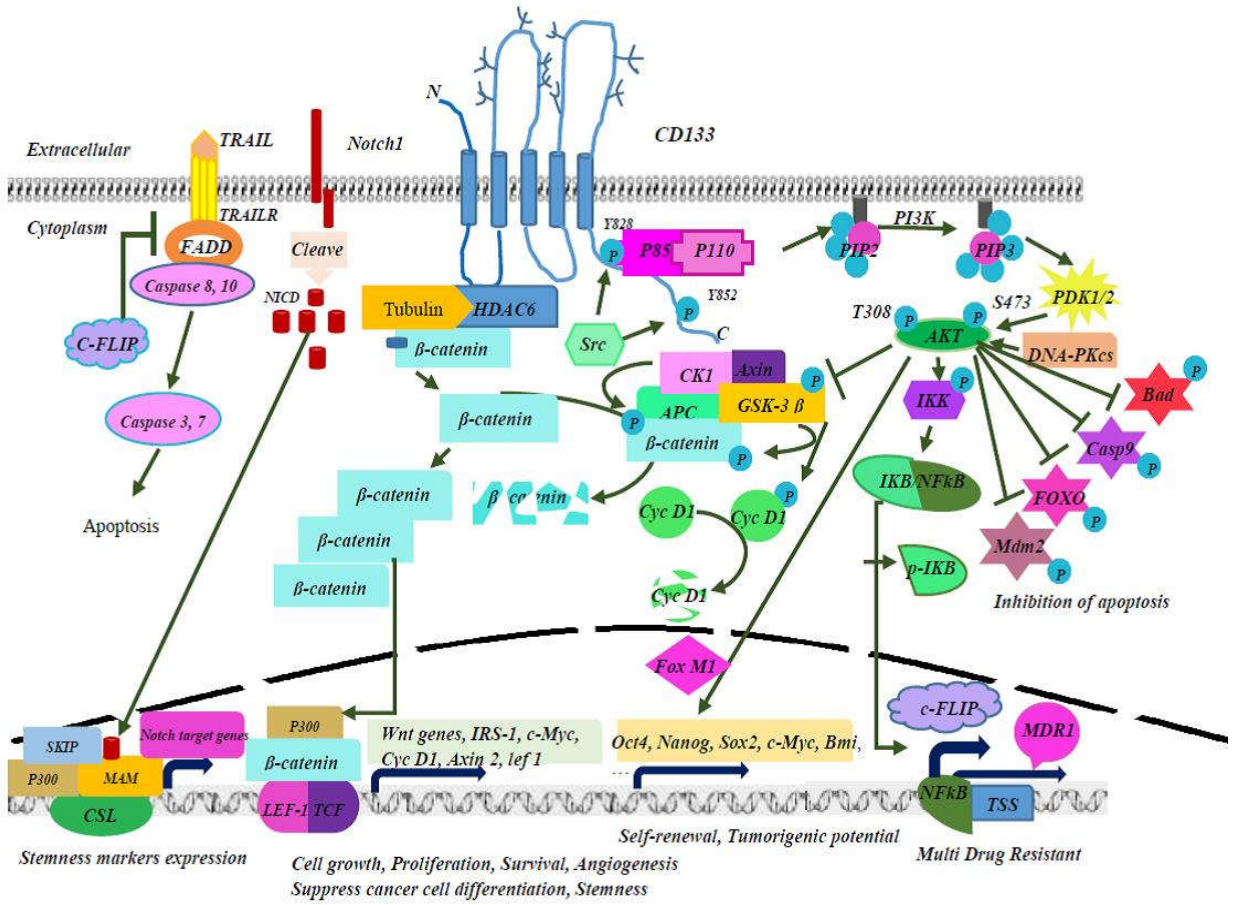

Figure 2. A schematic view for some CD133 cell functions. With different signals, it can inhibit apoptosis, express stemness markers, suppress cancer cell differentiation, and generate a cancer cell with self-renewal ability, tumorigenic potential, and multi drug resistant. *Abbreviations:* TRAIL (TNF-Related Apoptosis-Inducing Ligand); TRAILR (TNF-Related Apoptosis-Inducing Ligand Receptor); FADD (Fas-Associated Death Domain); C-FLIP (FLICE [FADD-like IL-1β-Converting Enzyme]-Inhibitory Protein); NICD (Notch Intracellular Domain); CSL (CBF1–SU(H)–LAG1); MAM (Mastermind); HDAC6 (Histone Deacetylase 6); LEF (Lymphoid Enhancing Factor); TCF (T-Cell Factor); Src (Src [Sarcoma] homology domains); APC (Adenomatosis Polyposis Coli); CK1 (Casein Kinase 1α); GSK-3β (Glycogen Synthase Kinase-3β); Cyc D1 (Cyclin D1); Fox M1 (Fork head box M1); IRS-1 (Insulin Receptor Substrat-1); c- Myc (Myelocytomatosis viral oncogene homolog); Oct4 (Organic cation/carnitine transporter4); Sox2 (SRY [Sex determining Region Y)-box 2); PIP2 (Phosphatidyl Inositol 4,5-bisphosphate); PIP3(Phosphatidyl Inositol 3,4,5-trisphosphate); PI3K (Phosphatidyl Inositol 3-Kinase); PDK (Pyruvate Dehydrogenase Kinase); IKB (I-kappa B kinase beta); NF-$_k$ B (Nuclear Factor Kappa B subunit 1); MDR (Multi Drug Resistant); FOXO (Forkhead box, sub-group O); Bad (BCL2 Associated agonist of cell Death); P(Phosphorylation).

A novel study suggested that *PROM1* dysfunction occurs together with *Apc* gene heterozygosity and significantly causes high tumor-genesis. Furthermore, *PROM1* is a target for the Wnt signaling regenerative pathways and acts as a defensive factor against early phase, inflammation and tumor-genesis (Karim *et al.,* 2014).Deterioration of the proliferative function of $CD133^{+}VEGFR2^{+}$ and $CD34^{+}VEGFR2^{+}$ in thalassemia patients is accompanied by vascular dysfunction (Cheung *et al.,* 2012).Usually, PI3K/AKT- Fox M1 (Fork head box M1) pathway is active in positive CD133 cell. Consequently, it becomes proficient in the tumorigenic genes expression like c-Myc (Myelocytomatosis viral oncogene homolog); Oct4 (Organic cation/carnitine transporter4), and Sox2 (SRY [Sex determining Region Y]-box 2) (Quan *et al.,* 2013). Clinico-pathological and immuno-histochemicalstudies suggested that CSCs with high expression level of CD133 protein were nearly associated with angiogenesis, poor stage, and metastasis of tumors. Also, they can partake to awful prognosis and therapies resistance (Pitule *et al.,* 2014; Vincent *et al.,* 2014; Ha¨ggblad Sahlberg *et al.,* 2014) specifically resist against radio-therapy (Han *et al.,* 2015). However, the meta-analysis data revealed that CD133 was afreeagent connected to reducing the survival rate (Wang *et al.,* 2012).

It appears that by using the RNA-interference tactic prominin-1/CD133 has amajor role in the uptake of transferrin and can be involved in iron metabolism via transferrin-CD133-iron network (Bourseau-Guilmain *et al.,* 2011). It has been approved that disk dysmorpho-genesis and photoreceptor deterioration could happen due to failure inthe cholesterol-binding of CD133 protein (Zacchigna *et al.,* 2009).Another function of prominin-1 is entangling the formation of the epididymal stereocilia and the tail of spermatozoa; hence, it playsa crucial role in the biogenesis of spermatozoa (Fargeas *et al.,* 2004).Compared to CD133-negative cells, the CD133-positive cells are more interactive to their stromal microenvironment; therefore, they are more tumorigenic than CD133- negative cells (Chao*et al.,* 2012). Mutual signaling is significant between the positive CD133CSCs, their niches for preserving the existing CSCs and persuading stem cell phenotype in the differentiated tumor populations (Mak *et al.,* 2014). Taken together, sometimes CD133 phenotypic marker is useful. For example, it could be advantageous for inducing vascular-creation in the ischemic heart cells through transplantation (Zhang *et al.,* 2010).

Thyroid cancer stem cell

Thyroid malignancy is the most frequent endocrine cancer. Based on histologic appearance and natural history, it is classified into four subtypes. Papillary (PTC), follicular (FTC) and medullary thyroid cancers (MTC) are categorized in well-differentiated thyroid cancers. Both papillary and follicular subtypes are the most common types of thyroid cancers. Tumor cells in the papillary subtype form the finger-like or papillary structures whereas in the follicular subtype, tumor cells have the follicles that are similar to normal thyroid follicles. Also, MTC is a well-differentiated thyroid cancer subtype. In this malignancy, tumor cells arise from the para-follicular C cells of the thyroid gland and are capable of manufacture calcitonin peptide and secrete it into the bloodstream. The tumor cells of medullary subtype are unable to concentrate radio-iodine, secrete thyroglobulin and respond to serum thyroid-stimulating hormone level (Hedayati *et al.,* 2015; Vitale, 2013).

The fourth subtype is anaplastic thyroid cancer (ATC). It has undifferentiated tumor cells that arenot similar to the normal thyroid cells and cannot form the follicles. It is highly aggressive and does not respond toradioactive iodine, serum thyroid-stimulating hormone level and all presently valid treatment modalities (Bozorg-Ghalati and Hedayati, 2015; 2016).Several CSC markers such as: side population phenotype, positive CD133, ALDH activity, CD44, CD326 (Nakashima *et al.,* 2015), POU5F1, insulin and insulin-like factor, are originally informed as thyroid CSCs biomarkers (Bhatia *et al.,* 2014). The hypothesis that CSCs can reconstitute and preserve tumor growth in ATC has been supported by several studies (Zheng *et al.,* 2010; Yun *et al.,* 2014). In addition, this subject that radio-resistance and undifferentiated status of the tumor cells in ATC might be due to the CD133-expressing in thyroid cancer cells has been investigated (Ke *et al.,* 2013). Cancer stem-like cells are improved partially in thyroid cancer cell lines, and are not exactly like the side population (SP) cells (Mitsutake *et al.,* 2007).A retrospective study indicated that hematopoietic stem-cells transplantation (HSCT), specifically during childhood and adolescence, is arisk factor for converting to secondary thyroid carcinoma (Cohen *et al.,* 2007). Data from the researches of ATC cell lines revealed that CSCs are regulated by thyrotropin, and able to launch tumors in immuno-deficient mice and have elevated resistance to chemotherapy (Zito *et al.,* 2008; Friedman *et al.,* 2009).

Radio-iodine therapy following tumor surgical excision is the common treatment of patients with ATC diagnosis. However, most of them are resistant to these cures (Gervasi *et al.,* 2012). Investigations have revealed that sodium-iodide symporter (*NIS*) gene expression and its correct protein functions play a crucial role in thyroid hormone biosynthesis network. In addition, it has the vital functions in radio-iodine uptake and successful radio-iodine therapy (Damle *et al.,* 2011).Thyroid CSCs, as undifferentiated cells, have no *NIS* gene/protein expression ability; therefore, they are unable to capture radioactive iodine comparable to differentiated thyroid follicles. Scilicet, positive CD133 cells have aninfluential role in the flunk of radio-iodine therapy (Sell, 2006). An immunohistochemistry and molecular studies suggested that CSC markers such as CD133 and nestin were more highly expressed in ATC than PTC (Jung*et al.,* 2015). Anotherstudy showed that epithelial-mesenchymal transitions (EMT), area production source of stemsin thyroid cancers. As the result, they canproduce therapeutic resistant cells and cause tumor recurrence (Ma *et al.,* 2014). Furthermore, the genetic evaluation of bone marrow-derived mesenchymal stem cells provides more knowledge (Murgia *et al.,* 2016). A survey of the multiple pluripotent stem cell markers in human ATC suggested that the stem cell factor SOX2 has a substantial role in the distinction of stem cells in ATC (Carina *et al.,* 2013). Further bioinformatics analysis on the ATC cell line (SW1736) indicated that deregulated particular genes involved in the miRNAs biogenesis (DICER1, RNASEN, and EIF2C2), control of the cell cycle (TP53, CCND1) and the mitochondrial activity (COX8A) might lead to ATC transformation with the undifferentiated nature of cells and CSC enrichment (Arancio *et al.,* 2015).A spheroid-forming assay showed that some cells from ATC cell lines formed thyrospheres which can express the stem cell markers (Nanog and Oct4) that are able to self-renew. Also, they are capable of inducing metastatic tumors and the clinical features of human ATC after injection into the thyroid gland of NOD/SCID mice (Li *et al.,*2013).

Target therapy

Review of the current knowledge about CD133 showed that it is a suitable option for target therapy. Toinhibitthe cell motility, tumor cell growth, spheroid-forming capacity and tumorigenic ability, we can reduceits expression by flavonoid, or reveal its protein to certain antibodies, especially those labeled with ^{125}I (Damle *et al.,* 2004; Wang *et al.,* 2015; Jin *et al.,* 2012).In other target therapy strategy, lentivirus vector application is useful which includesa single chain antibody against CD133 (Bayin *et al.,* 2014).With RNA interference implementing can inhibit the CD133 gene expression (Yu *et al.,* 2014). Novel CD133 aptamers will assist future involvement of CSCs targeted therapeutics (Shigdar *et al.,* 2013). Human beta-defensin 2 (hBD-2) in concentrations more than 100 nM is usefulfor suppression of thyroid cancer cell growth and migration. Also, it canaffect *E-cadherin* and *Vimentin* expression and histologic type of thyroid cancer cells (Zhuravel *et al.,* 2014). In immunotherapy, activating the γδ T cells (for example Vγ9Vδ2 T cells) by any agents which cause their agglomeration within cells can intensify antitumor activities and targeting CSCs (Todaro*et al.,* 2009).Inducing differentiation in the transformed cells, especially in ATC cells is possible with some inhibitors such as histone deacetylase inhibitor (Haghpanah *et al.,* 2014). As the result of Notch pathway inhibition, CD133-positive CSCs can exhaust and restrain the development of the tumor (Fan *et al.,* 2010).

Conclusion

So far, despite several studies and investigations, scientists have not found aneffective treatment for advanced thyroid cancers, especially ATC which is radio-chemo resistant. Based on several data, various factors and elements might be involved in this problem. It seems that thyroid CSCs, especially those who have CD133 surface marker, play an important role in resistance therapy. They are regulated by thyrotropin and can initiate malignant cells' production. These undifferentiated cells have a crucial role in the flunk of radio-iodine therapy. Also, theyinteract with various signaling pathways such as: PI3K/AKT, Wnt/β-catenin, Notch, NF-κB and linked to angiogenesis, poor score and metastasis of tumors. Understanding of thyroid CSCs' biology and their molecular and cellular mechanisms is needed to find out a drastic treatment in target therapy manner and overcome resistance to chemo-radio therapy. Certain antibodies, lentivirus vector application, RNA interference applying, activating the γδ T cells, are different ways to destroy them. We hope that someday successful treatment for will be detected for patients who suffer from thyroid cancer, especially ATC, and cannot respond to present treatment.

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