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Impact of OCT4 and Its Related Signaling Pathways on Gastrointestinal Cancers: Focusing on Targeted Therapy

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ABSTRACT

There are many pieces of evidence support the effect of cancer stem cells on the initiation and progression of cancer. However, related mechanisms involved in these phenomena are far more complicated to understand. The function of different stemness factorsin cancer stem cells (CSCs) and their complex associations at different levels of cancer have been reported. Therefore, it seems that focusing on one master factor would be more helpful to complete the puzzle of singling pathways in these cells. Octamer-binding transcription factor 4 (OCT4) also known as POU domain, class 5, transcription factor 1(POU5F1), one of these key pluripotency factors, has important roles in both embryogenesis and tumorigenesis.

In this review, we gathered information about the association of different markers with OCT4 expression in three types of gastrointestinal cancers including esophageal, gastric and colorectal cancers.

OCT4 through different signaling pathways has an impact on different processes of gastrointestinal cancers such as proliferation, invasion, and metastasis.

Based on the literature, OCT4 has great effects on cancer progression at different stages, therefore we suggested it has potential implications in therapeutic options.

Keywords: Colorectal cancer; Esophageal neoplasms; Stomach neoplasms

INTRODUCTION

Stem cells possess self-renewal ability and capability of differentiation into multiple cell types.[1] One of the main features of stem cells is the expression of specific genes related to embryonic with determined molecular pathways.[2] For the first time, Yamanaka and his coworkers successfully generated induced pluripotent stem cells (iPSCs) from differentiated mouse fibroblasts, by induction of four key transcription factors including OCT4, SRY (sex-determining region Y)-box 2 (SOX2), Kruppel-like factor 4 (KLF4), and cellular myelocytomatosis (c-MYC).[3] They elucidated that expression of these four key transcription factors (OSKM) is important for differentiation potency and stem cell fate. Similarly, Nanog Homeobox (NANOG), another important transcription factor in stemness properties, has high-level expression in embryonic stem cells while it has very low expression in normal adult tissues.[4-6] Other

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reports have shown that OCT4 is the main regulator of pluripotency and differentiation, and it also has a role as the primary factor determining the fate of embryonic stem cells (ESCs) by regulation of several cell properties, particularly self-renewal and differentiation.[7]

Tumors include heterogeneous cell populations with diverse functions, phenotypes, and gene expression profiles.[8] Cancer stem cells (CSCs), as a subpopulation of tumor cells, share some properties with embryonic stem cells such as multi-lineage differentiation capability, infinite self-renewal, and preservation of the pluripotency level.[4] Furthermore, the impact of elevated expression of stemness factors in various cancers including gastric, colorectal, lung, prostate, bladder, esophageal, breast cancer and diseases with cancer's features have been noted and it is worth focusing on their CSCs impacts.[4-7,9-17] Based on CSC theory, similar signaling pathways control cancer and stem-like features, but mutations and dysregulation of genes have led to the deregulation of these pathways in CSCs.[18] It was clarified that CSCs increase the complexity of malignancies; for instance, the reason for failing of usual existing therapies in preventing the recurrence and metastasis is the presence of small side-population (SP) of CSCs which give rise to overexpression of drug transporters in these cells that are not sensitive to common therapies.[19] A variety of studies demonstrated that OCT4 is a key factor in tumor formation and its development. Santagata et al showed that OCT4 is overexpressed in embryonic and germ cells.[20] Cheng and his coworkers indicated the response to treatment of germ cell and their metastatic features could be evaluated by OCT4.[21] Saigusa et al also introduced OCT4/SOX2 as surgical prognosis and recurrence factor in rectal cancer patients.[22] Besides gastrointestinal cancers, it was shown that high expression of OCT4 exacerbates the tumorigenicity of breast cancer in a mouse model in comparison with a low level of OCT4 expression.[23]

This study aims to review the role of OCT4 and its effects on different pathways in gastrointestinal tract malignancies including esophageal, gastric, and colorectal cancers.

MATERIALS AND METHODS

We searched PubMed, Elsevier, google scholar, Clinicaltrials.gov, UniProtKB, Human Protein Atlas knowledge base for articles that were published from 1990 to 2019 as well as bibliographies of articles to include additional relevant studies; using the following combinations of MeSH terms with a manual search: OCT4, gastrointestinal cancers, esophageal cancer, colorectal cancer, gastric cancer, signaling pathways and gene therapy. Citations from all databases were imported into the Endnote library (version X7, Thomson Reuters, USA) and duplicate articles were removed. Full texts of articles were carefully read, and data were extracted for data extraction in Microsoft Word, and figure was drawn based on the information of articles.

OCT4

OCT4 (also known as OCT3, OCT3/4) is a member of the Pit-Oct-Unc (POU) transcription factor family.[24] This family stimulates the expression of downstream genes through binding to an octameric consensus sequence motif, AGTCAAAT.POU domain consists of 2 sub domains POUh and POUs which have 60 amino-acids in carboxyl-terminal homeodomain,and75 amino-acids in an amino-terminal POU specific region.[25] It is noted that its C-terminal domain is rich in serine, threonine, and proline, while the N-terminal domain is rich in proline and acidic residues that have a key role in transactivation.[25,26] Contrary to the OCT4 N-terminal domain, the C-terminal region is regulated through phosphorylation and has cell-specific functions.[27]

Generally, it has been demonstrated that OCT4 is exclusively expressed in embryonic stem cells.[27] This transcription factor is expressed initially in all blastomeres during embryonic development. After that, its expression is downregulated and limited to the inner cell mass (ICM), and finally restricted to the primitive endoderm and the trophectoderm. At puberty, its expression is completely dedicated and limited to the developing germ cells.[28-30] Various studies have demonstrated that OCT4 can be considered as one of the primary factors that determine the destiny of ESCs between maintaining stemness properties and a tendency towards differentiation.[27] Additionally, OCT4 seems to act in a dual manner, a repressor or an activator, in various cells and specific pathways.[31,32] Intriguingly, the only normal expression level of OCT4 can hold stem cells in a pluripotent form. Various studies confirmed that OCT4 is not expressed in normal somatic tissues but it has high-level expression in several solid cancers including breast, pancreatic and

colorectal cancers.[29,33-35] In this review, we focus on the impact of this marker on stemness features, tumor progression, relapse, and poor clinical outcomes in gastrointestinal cancers.

The human *OCT4* gene has multiple isoforms with at least three transcripts, *OCT4A*, *OCT4B,* and *OCT4B1*. It also has four protein isoforms including OCT4A, OCT4B-190, OCT4B-265 and OCT4B-164[36-38] (Figure 1) which the expression of these isoforms is variable in different cellular compartments.[39] OCT4A, as a sustainable factor for pluripotency and self-renewal of the cells, is mainly localized within the nucleus of the embryonic stem cells. On the other hand, OCT4B which is not involved in self-renewal, principally placed within the cytoplasm of somatic cancer cells.[38,40-42]

Pseudogenes (pg) are effective elements in the complex regulatory network involved in gene expression, specifically in the abnormal expression of parental genes.[43,44] There are seven pseudogenes of OCT4, known as OCT4-pg1–pg7, with high similarity to the parental gene sequence expressed in ESCs[45-47] (Figure 2). It is worth noting that OCT4-pg1, pg3, pg4, and pg5 are translated to proteins with highly homologous to OCT4A, while OCT4-pg2 and pg6 are not able to translate and there is no report about the possible products of the OCT4-pg7 so far.[48-50]

Investigation on several cancers from primary leukemia to solid cancers have shown the expression of OCT4 pseudogenes in these cancers.[51] Moreover, some of the OCT4 pseudogenes such as OCT4-pg4 have high expression levels in various human cancers. OCT4-pg4 upregulates OCT4 expression by binding to miR-145 through miRNA competing, which results in the induction of carcinogenicity.[52]

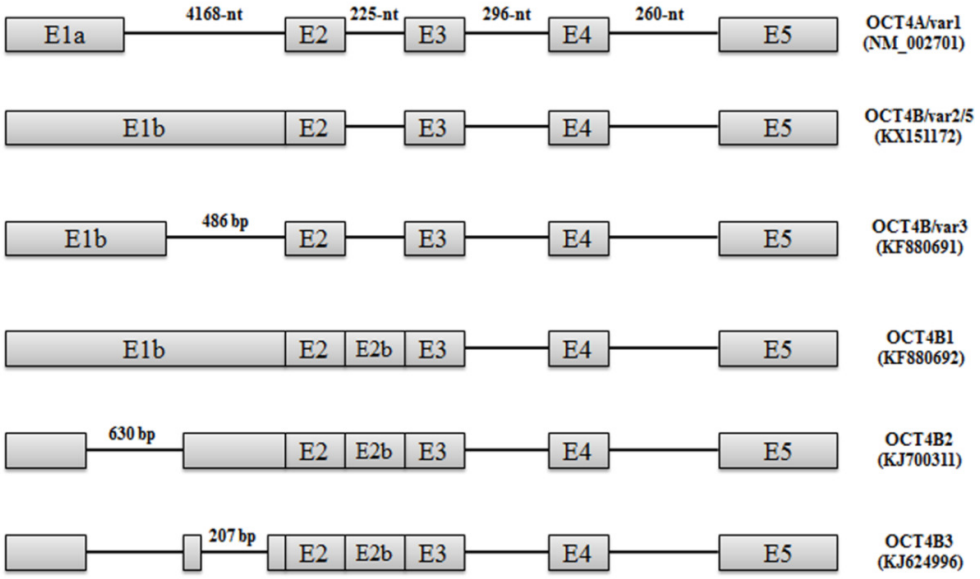

Figure 1. Different isoforms of OCT4 in human. Abbreviation: E: exon, nt: nucleotide, bp: base-pair, var: variant

Esophageal Cancer

Esophageal cancer (EC) is one of the highly lethal malignancies for death and poor prognosis. It is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide. There are two histological subtypes of EC, adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) which are clinically and epidemiologically different. ESCC is the most common subtype of EC in the world with a higher incidence in developing countries and is so high in countries such as China and Iran, along the path of the ancient Silk Road from East Asia to the Mediterranean, while the incidence of EAC is higher in developed countries.[53,54]

For the first time, the expression of OCT4 was revealed in human ESCC with the antibody AF1759 from research and development (R&D) System by immunocytochemistry.[55] It was shown that this main

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stemness marker was expressed in over 93% of ESCCs.[56] Growing literature revealed that higher expression level of OCT4 in patients associated with histopathological parameters including poor differentiation, higher histological grade, poorer overall survival, and poorer prognosis.[56-58] It has been indicated that OCT4 positively induces the expression of survivin and leads to cancer cell proliferation, cancer progression and even a poor survival and prognosis of ESCC.[59] The control of survivin expression, which is a key anti-apoptosis protein involved in cell survival is achieved through activation of various important signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), Signal transducer and activator of transcription 3 (STAT3),and Myc by OCT4[59] (Figure 3). Moreover, Li et al revealed that decreased expression of OCT4, using OCT4-shRNA, gives rise to inhibition of cell cycle at G2-phase and then leads to an increase in cell apoptosis.[59] On the other hand, OCT4 as the upstream factor of Cyclin D1 directly binds to the cyclin D1 (CCND1) promoter and induces esophageal cancer progression and invasion.[60] OCT4 expression in tumorospheres reflects the existence of a side-population of esophageal cancer stem cells (ECSCs) and its expression in xenograft tumors indicates that this marker has metastasis features.[56]

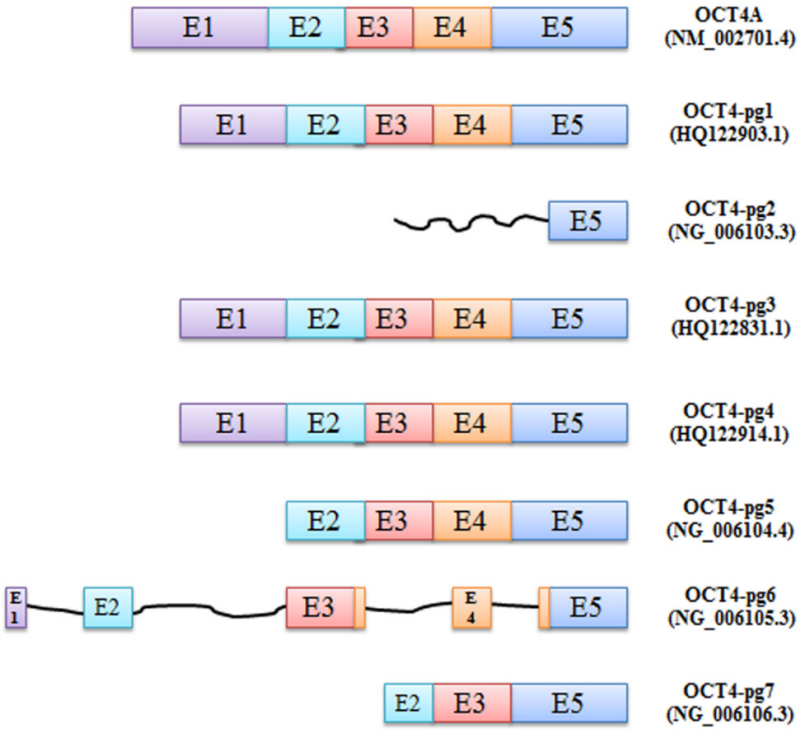

Figure 2. All pseudogenes of OCT4 in human. Abbreviation: E: exon, pg: pseudogenes

Li et al also reported that OCT4 leads to enhanced tumor progression, invasion, metastasis, and induction of epithelial-mesenchymal transition (EMT) in EC cells through vascular endothelial growth factor C/Receptor-3 (VEGF-C/VEGFR-3) signaling pathway. OCT4 induces VEGF-C expression and stimulates the VEGFR-3 phosphokinase activity and the downstream signaling pathways.[61] To study the effect of other transcription factors on OCT4, it was shown that the overexpressed Twist-related protein 1 (TWIST1) plays an important regulatory role in OCT4 expression and can be related to upregulation of this protein in ESCC cells.[62]

Interestingly, Vaiphei et al reported that in EC patients, OCT4 positive CSCs can play a vital role in response to therapy. They showed that because of

various clinical materials of chemoradiotherapy and adjoining non-carcinomatous esophageal mucosa, the expression of OCT4 in different histological subtypes of ESCC was associated with poorly differentiated tissues and low grade dysplastic and hyperplastic mucosa of the neighboring mucosa.[63]

These findings could contribute to potential gene target-based screening for targeted therapy of esophageal cancer and considerably would help to clarify the regulatory mechanism involved in the cell cycle progression of EC cells.[60]

Gastric Cancer

Gastric cancer (GC) is the fourth common malignancy and the second common cause of cancer-related deaths in the world. The rate of this cancer is variable in different geographical positions. It is noted that more than half of the affected people are in developing countries. To validate this issue, different studies have shown that the high-risk areas for GC are Eastern Europe, East Asia, as well as South and Central America. On the other hand, the low-risk areas for this malignancy are North America, North and East Africa, Southern Asia, Australia, and New Zealand.[64,65]

To identify and isolate the CSCs in gastric cancer, several markers including CD133, CD44, SOX2, OCT4, glioma-associated oncogene family zinc finger 1 (GLI1), protein AKT serine/threonine kinase (p-AKT), B lymphoma Mo-MLV insertion region 1 homolog (BMI1), and protein extracellular signal-regulated kinases (p-ERK) have been introduced.[66-73] Different mechanisms cause and maintain the CSCs in gastric cancer. Hong et al revealed that expression of some important stemness genes such as SOX2, NANOG, OCT4, and CD133 is controlled by Notch1 through regulating the expression of these genes at both mRNA and protein levels.[74]Further studies approved that up-regulation of Wnt1 increased spheroid formation of adenocarcinoma gastric cells (AGSCs) and could enrich the expression of OCT4 andCD44.[75,76] Furthermore, it has been shown that overexpression of a long noncoding RNA (lncRNA) ROR in gastric cancer stem cells (GCSCs) effects on CD133-mediated proliferation and invasion, as well as regulation of the expression of OCT4, NANOG, and SOX2 as CSC-related transcription factors.[77] Despite over-expression of most gastric cancer stem cell markers in several key processes such as the promotion of cellular proliferation and metastasis, previous reports proposed that only OCT4, compared with NANOG and SOX2, is a beneficial prognostic marker for distant metastasis or relapse after surgical operation.[40,70,78-82]

OCT4 has key roles in the initiation, development, and differentiation of human GC and its expression can be used as a biomarker for GC.[40] The growing body of the literature concentrated on the importance of this marker in clinical prognosis and prediction of unfavorable clinical outcome of GC patients. Generally, OCT4B1 is rapidly down-regulated upon induction of differentiation and also this isoform is overexpressed in embryonic stem cells.[41] Furthermore, Asadi et al suggested that OCT4B1 has a possible character in tumorigenesis of gastric cancer and is a probable new candidate biomarker with potential value in diagnosis and treatment of this cancer.[83] They revealed that interfering with the expression of OCT4B1 with specific siRNA in the AGS cell line caused significant changes in the cell cycle and morphology of these cells. Besides, the down-regulation of this marker pointedly elevated the effective activity of caspase-3/caspase-7 and the frequency of apoptosis in the cells.[83] Hayashi et al showed that the amplification of OCT4-pg1; an OCT4 pseudogene, is associated with poor prognosis in GC patients. However, POU5F1B might be predictable to retain stemness potential because of its high-level homology with OCT4A.[84] In a recent study, it was indicated that the main features of cancer including proliferation, drug resistance, migration, and invasion abilities were exacerbated after ectopic overexpression of OCT4/SOX2.[85]

Kong et al revealed that co-expression of two transcription factors High Mobility Group AT-Hook 2 (HMGA2) and OCT4 in GC patients are associated with metastasis, tumor invasion, high chance of recurrence and poor prognosis.[86] Guo et al reported that hypoxic conditions through EMT induction leads to the reduction of E-cadherin and increases the expression level of OCT4, SOX2, BMI1, N-cadherin, Snail, and vimentin both at the mRNA and protein levels.[87] On the other hand, these EMT based-variations via enhancing the stemness state of GC cells, increase their invasion and metastasis abilities.[87] Furthermore, it is noted that low expression of OCT4 epithelial cell adhesion molecule (EpCAM) was a favorable prognostic factor in patients with GC.[88] Wang et al established that down-regulation of Mel-18, a polycomb group protein, was associated with poor prognosis and negatively

correlated with up-regulation of OCT4, SOX2 and Gli1, as stem cell markers, in GC tissues.[89] In this

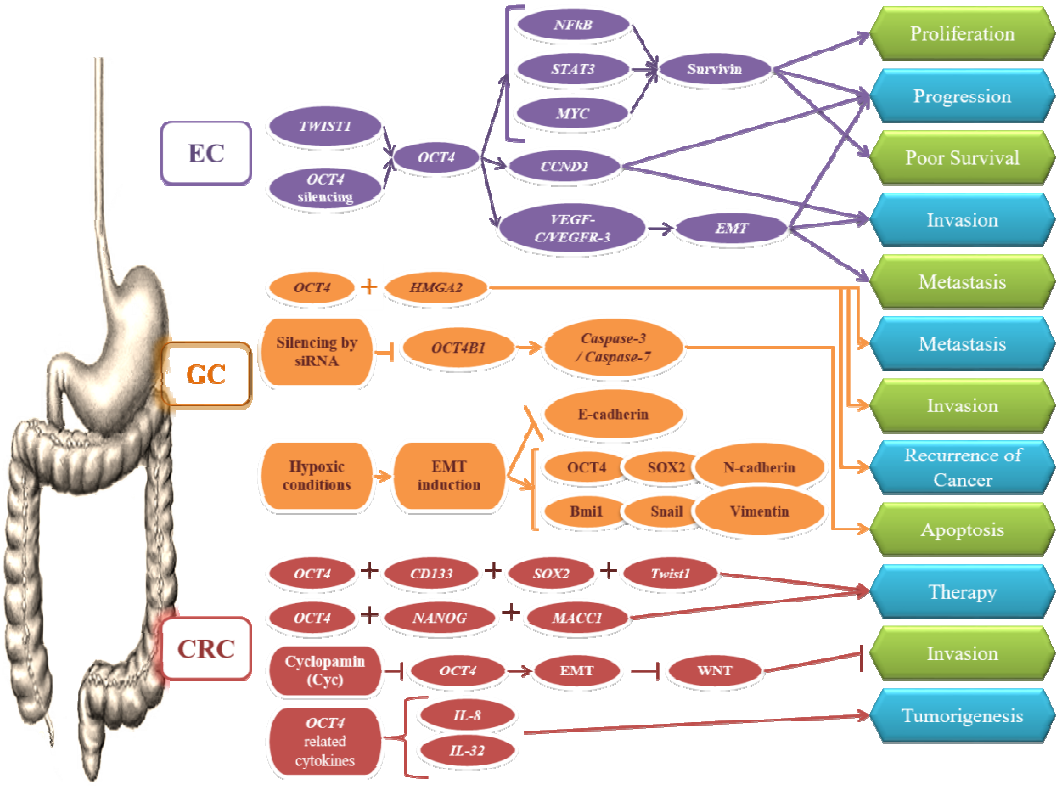

Figure 3. The cross-talk of OCT4 with different transcription factors and main mechanisms in esophageal cancer cells, gastric cancer cells, and colorectal cancer.

regard, Zhou et al discovered that Hippo signaling molecules such as Transcriptional enhancer factor domain family member 1 (TEAD1), OCT4, yes-associated protein 1 (YAP1), macrophage stimulating 1 (MST1), Large tumor suppressor kinase 1 (LATS1), Tafazzin (TAZ), and caudal-related homeobox transcription 2 (CDX2) are involved in the progression, development, and metastasis of human gastric cancer; therefore these markers may be a probable therapeutic target for gastric cancer. They also showed that the mRNA expression level of OCT4 has an association with the tumor-node-metastasis (TNM) stage and lymphatic metastasis in gastric malignancy.[90] On the other hand, Zhang et al revealed that close correlation between lactate dehydrogenase A (LDH-A), as an energy production metabolism-related enzyme, and OCT4 could be considered as a helpful therapeutic strategy for intestinal-type gastric cancer (ITGC)[91] (Figure 3).

Based on these mechanisms, it is suggested by a comprehensive understanding of the nuclear translocation and expression pattern of OCT4 in gastric carcinogenesis would be useful in planning novel modalities for the initial diagnosis and finally targeted therapy of gastric cancer.[92]

Colorectal Cancer

Nowadays, colorectal cancer (CRC) is one of the main public health challenges, the third diagnosed malignancy and the fourth reason of worldwide cancer mortality. There are several risk factors for CRC in diverse geographic areas; therefore, the frequency of this type of cancer is very variable in different regions of the world. It is noted that colorectal cancer has remained to be a healthy challenge in developed countries, but incidence rates have been increasing in

developing countries.[93]

Several studies, in 2007, revealed that there are CSCs in colorectal cancer and these cells play key roles in this malignancy.[94-96] It was afterward discovered that colorectal cancer stem cells have exposed certain surprising properties, including high degrees of plasticity and heterogeneity.[97] However, a growing body of studies have been done on the identification and characterization of colorectal CSCs and also focused on the possible importance of CSC-associated molecular profiles and especially the determined CSC surface markers.[98-100] Determining a unique marker or a specific panel for identification of colorectal cancer stem cells have been challenged recently; For instance, it was first thought CD133+ is a reliable marker for this issue, however, it was clarified that both CD133+ and CD133- in colon cancer cells were able to start and recruit tumors.[95] Further studies showed that colorectal CSCs can characterize by the expression of OCT-4^{+}, leucine-rich repeat-containing G-protein coupled receptor 5 ($LGR5^{+}$), $CD44v6^{+}$, ephrin type-B receptor 2 ($EphB2^{+}$), and aldehyde dehydrogenase ($ALDH^{+}$).[101-106] However, the main stemness-related genes such as OCT4, NANOG, and SOX2 have overexpression levels in human colorectal cancer stem cells.[107,108] In this regard, Liu and colleagues verified that OCT4 and SOX2 are potential markers for colorectal CSCs through extra polation on the expression of these markers in $CaCO_2$ and HT-29.[109] Checking the expression of embryonic stem cell markers including OCT4, NANOG, SOX2, KLF4 and c-Myc in the colon adenocarcinoma metastasis to the liver (CAML) demonstrated that there are some assumed subpopulations of cancer stem cells in this condition, which include $OCT4^{+}/SOX2^{+}/NANOG^{+}/KLF4^{+}/c\text{-}Myc^{+}$ subpopulation, $OCT4^{-}/SOX2^{+}/NANOG^{+}/KLF4^{+}/c\text{-}Myc^{+}$ subpopulation within the tumor nests (TNs) and $OCT4^{-}/SOX2^{+}/NANOG^{+}/KLF4^{+}/c\text{-}Myc^{+}$ subpopulation within the peritumoral stroma. It is assumed the only expression of OCT4 in the peritumoral stroma cells indicates the most primitive CSC subpopulation within CAML.[110] Very recent study on cancer stem cell subpopulations in primary colon adenocarcinoma also verified then OCT4+/NANOG stromal subpopulation in this type of cancer.[111]

In various reports, the relationship between OCT4 expression and its downstream or upstream genes in CRC have been studied.[112-114] For instance, it has been shown that OCT4 has a co-expression with TWIST1, CD133, SOX2 which the panel of these genes can be valuable for predicting the response to CRC therapy.[115] Moreover, Litwin et al revealed that community association was observed between OCT4 and human P-element Induced WImpy test is in Drosophila (HIWI) mRNA level in colorectal cancer tissues and also confirmed the interaction of different cancer stem cell markers in CRC development.[113] Furthermore, Lemos et al discovered that metastasis-associated in colon cancer 1 (MACC1) induces tumor progression in CRC via the MACC1/NANOG/OCT4 axis, therefore the association of MACC1 with OCT4 and NANOG would be a preferred option for therapeutic goals.[116]

The previous report showed that developmental pluripotency-associated protein 2 (DPPA2) has significantly high expression levels in CRC cells and this protein can help in the maintenance of self-renewal and stemness state of CRC cells in the format of possible regulatory transcriptional network of SALL4/OCT4/DPPA2/NANOG.[114] Moreover, several studies focused on the expression of Zinc finger protein 281 (ZNF281) and its correlation with OCT4, NANOG, and SOX2, and all of which with consensus confirmed that ZNF281 directly regulates NANOG expression in coordination with SOX2 and OCT4, as well asZNF281 as an important biomarker is up-regulated in CRC.[117-120] Among cytokines, Interleukin 8 (IL-8) and Interleukin 32 (IL-32), as OCT4-related cytokines, have an important role in stimulating tumorigenesis and regulating stem-like features in CRC.[121] On the other hand, Gazouli, and colleagues by scrutinizing OCT4B1 isoform in CRC tissues showed that OCT4B1 is up-regulated in all poorly and moderately differentiated CRC tissues, therefore it can be a reliable biomarker for the initiation, progression, and differentiation of colorectal cancer[122] (Figure 3).

By the advent of next-generation sequencing (NGS), revealing the signaling pathways and the interaction of markers together is a hot topic and interestingly the interaction of OCT4 with other markers in colorectal cancer is a notable topic for researchers. It was discovered that OCT4 knockdown in CRC leads to repressing colorectal cancer cell invasion and motility (*in vitro*) and reduces the hepatic colonization (*in vivo*). In addition, its knockdown induced changes in EMT and decreased wingless-INT (WNT) pathway activity in CRC cells.[22,122] It has also been noted that the OCT4 expression in patients with

liver metastasis from CRC is meaning fully higher than in cases without liver metastasis. These pieces of evidence verify that OCT4 can help to CRC cell invasion via EMT differentiation and can be considered as a hopeful biomarker for identifying CRC patients at high risk for liver and lung metastases.[123-125] Furthermore, it has been revealed that the hedgehog (Hh) signaling is critical for several stemness-related events in CRC, such as tumor metastasis, EMT differentiation, and expression of OCT4, SOX2 and NANOG genes. Cyclopamine (Cyc), as a sonic hedgehog (Shh) pathway inhibitor decreases the expression of OCT4 and NANOG in human colon cancer-derived oncospheres.[126,127] Furthermore, the Hippo signaling pathway has different key targets including OCT4 and CDX2 that interestingly is strictly correlated with the TNM stage, lymph node metastasis and tumor differentiation in CRC, which suggests this pathway may be considered as a proper prognostic marker for CRC patients.[128] OCT4 also plays a key role in conserving the survival of drug-resistant cells in CRC, which can be partly related to the STAT3/Survivin pathway.[129] In addition, OCT4 has a variable subcellular localization in different conditions in CRC cells.[122] For instance, in sporadic CRC and ulcerative colitis-associated colorectal cancer (UC-CRC) cells, has diffuse cytoplasmic OCT4 staining.[16]

Several studies have shown that OCT4 expression in CRC can be correlated with the clinic-pathological features of the patients. In this regard, it demonstrated that OCT4 overexpression in rectal cancer is associated with a high recurrence rate after chemo-radiotherapy.[29,130] Besides, it was recommended that OCT4 expression is a poor prognostic marker in CRC patients.[130-132] In additions, Talebi et al by investigation in the expression of OCT4 in main types of colorectal tissues (normal, polyp, and cancer) showed there is a significant association between the expression of this marker and kinds of tissues in both number and intensity of stained tissues.[133]

Targeted Therapy

For targeting in tissue-specific, there are a variety of methods have been introduced in recent decades. Among these methods using small interfering RNA, siRNA in *in vivo*, and CRISPR/Cas9 for knockdown and knock out, respectively, are more practical and common. Long et al showed that using CRISPR-Cas9 based targeted knock out on plant homeodomain finger containing protein 20 (PHF20) inhibited neuroblastoma cell proliferation and stem-like characteristic through inhibition Oct4 and Sox2 expression.[134] We also used lentiviral siRNA for stable knocking down in developmental genes like Enhancer of zeste homolog 2 (EZH2) and myeloid ecotropic viral integration site 1 (MEIS1) that they had significant effects on stem cell markers especially Sox2.[135,136] In this aspect, Liu et al indicted that knocking down of OCT2 by siRNA improve cisplatin effect in non-small-cell lung cancer which suggested that the OCT4 as targeted therapy mechanism are effective in adjuvant therapy.[137] According to this literature review, it is noted that different targets in signaling pathways are controlled by OCT4, therefore, these signaling pathways are worth assessing after targeting OCT4.

CONCLUSION

In this review, we highlighted the recent extrapolations for OCT4 expression level effects on different signaling pathways in gastrointestinal cancers. By the advent of RNAseq and concept of system biology, it is most important to find the master gene in cancers and their correlation with other pathways in specific tissues, and then select the target therapies for related cancer. Here, we concise the role of OCT4 on its downstream gene that how it influences in poor prognosis, recurrence after treatment, invasion, and metastasis of ES, GC, and CRC. It is suggested to study deeper on signaling pathways by RNAseq and have more consideration to recognize master genes for targeted therapies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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