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The Oct1 transcription factor and epithelial malignancies: Old protein learns new tricks

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Abstract

The metazoan-specific POU domain transcription factor family comprises activities underpinning developmental processes such as embryonic pluripotency and neuronal specification. Some POU family proteins efficiently bind an 8-bp DNA element known as the octamer motif. These proteins are known as Oct transcription factors. Oct1/POU2F1 is the only widely expressed POU factor. Unlike other POU factors it controls no specific developmental or organ system. Oct1 was originally described to operate at target genes associated with proliferation and immune modulation, but more recent results additionally identify targets associated with oxidative and cytotoxic stress resistance, metabolic regulation, stem cell function and other unexpected processes. Oct1 is pro-oncogenic in multiple contexts, and several recent reports provide broad evidence that Oct1 has prognostic and therapeutic value in multiple epithelial tumor settings. This review focuses on established and emerging roles of Oct1 in epithelial tumors, with an emphasis on mechanisms of transcription regulation by Oct1 that may underpin these findings.

Keywords

Oct1/POU2F1; NuRD; Jmjd1a/KDM3A; Gastric cancer; Cervical cancer; Breast cancer; Colorectal cancer; Prostate cancer; Lung adenocarcinoma; Thyroid cancer

1. Introduction

Gene transcription is orchestrated by sequence-specific DNA binding transcription factors. A mammalian genome encodes several thousands of these transcription factors, which have varied expression patterns, upstream regulatory mechanisms and downstream modes of action. Typically the ultimate consequence of transcription factor activity is to enable or inhibit functional RNA polymerase II (Pol II) complexes at target genes, thus augmenting or attenuating transcription rates and gene expression.

The functions of transcription factors have been most commonly delineated in one of three ways: 1) forward genetic screens, often in model organisms such as *C. elegans* and *D.*

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melanogaster, 2) reverse-genetic approaches, and 3) identification of regulatory sites in genes with particular function, followed by the identification of transcription factors that associate with the sites. It was through this latter method that Oct1 was first described.

One of the earliest described mammalian transcription factors, Oct1 was identified as a protein associated with regulatory DNA binding sites in animal viruses that were used to study gene regulation during the 1980s: adenovirus, SV-40 and herpes simplex virus-1 [1–3]. These binding sites consist of a recurring 8-bp sequence (5'ATGC(A/T)AAT) that came to be known as the octamer motif. Oct1 was also identified through its ability to bind conserved binding sites in endogenous cellular genes, including the cell type-specific immunoglobulin heavy and light chain and *Interleukin-2* genes, and widely expressed genes such as those encoding histones and U snRNAs [4–9]. In cell-free transcription assays, or when overexpressed with plasmids containing artificial reporter genes, Oct1 could enhance transcriptional output. However, the augmentation of transcription was typically weak compared to other transcription factors such as AP-1 and NF- κ B [10]. This weak activity suggested that in order to function, Oct1 might require chromatin contexts not recapitulated in these classic assay systems.

These early findings on Oct1 are linked, via a circuitous route, to later work implicating Oct1 as a potent tumor promoter, most prominently in epithelial malignancies, and to a recent crop of biochemical, genomic and in vivo findings further supporting a pro-tumorigenic role. A brief description of that route, with its stopovers and waypoints, and a summation of what is known currently regarding Oct1's roles in malignancy, is the focus of this review.

2. Oct1 Molecular characterization and DNA binding

The Oct1 gene contains a bipartite DNA binding motif consisting of two distinct sub-motifs [11]. The N-terminal motif is distantly related to a homeobox, while the C-terminal motif resembles a classic homeobox. The full DNA binding domain came to be known as the POU domain, and the two sub-motifs were termed POU_S (for POU-specific domain) and POU_H (for POU-homeodomain). POU is an acronym that stands for the founding members of the family, Pit-1, Oct1/2, and UNC-86 [12]. In humans and mice, there are some 13 POU transcription factors, 8 of which display specificity for the octamer motif and are hence referred to as Oct proteins [13]. Oct1 is the only Oct protein, and only POU family protein, that is widely expressed. Analysis of Oct1 mRNA expression, e.g. with GeneAtlas (<http://biogps.org/dataset>), reveals little variance in human or mouse expression among organs such as kidney, pancreas, lung, thyroid and prostate. In contrast, other Oct proteins such as Oct2/POU2F2, Oct11/Skn-1/POU2F3, Oct6/POU3F1, Brn2/POU3F2, Brn1/POU3F3, Brn4/POU3F4 and Oct4/POU5F1 do not appear to be significantly expressed in these organs, or in epithelial cells generally. Therefore Oct1 is the predominant, if not sole, Oct transcription factor in many epithelial tissues. One exception is the expression of Oct2, the most closely related Oct1 paralog, in mouse and human normal and malignant mammary gland epithelial cells [14, 15].

Structural studies revealed that Oct1, as predicted by sequence and biochemical analysis, recognizes DNA through the two independently folded DNA binding subdomains. The POU_H and POU_S domains are separated by a flexible ~20 amino acid linker [16]. The classic Oct1 binding sequence is the octamer motif, though several changes are tolerated. Even greater deviation can be tolerated in the context of dual or compound binding sites. In these cases, DNA binding to sub-optimal sequences is stabilized by the presence of a second Oct1 protein (Fig. 1A). The heptamer-octamer sequence in immunoglobulin genes is the oldest example [17]. The “heptamer” sequence is a degenerate octamer motif. Another example is a dyad octamer sequence identified in the imprinted *H19/Igf2* locus between *Igf2* and the *H19* lncRNA [18]. For many of these sequences structural information on DNA binding is scarce, however dual sites have been described in two structurally defined configurations: the PORE (Palindromic Octamer Related Element, ATTTGAAATGCAAAT) and MORE (More PORE, ATGCATATGCAT). The PORE is essentially two octamer motifs inverted with respect to one another. *Osteopontin* (*Spp1/Opn*) is a classic PORE-containing Oct1 target gene [19, 20], with the PORE located in the first intron. In contrast, binding to the MORE (Fig. 1A) rearranges the spatial distribution of the DNA binding subdomains relative to each other such that rather than binding major grooves on opposite sides of the DNA helix, the two domains bind adjacent major grooves on the same face of the DNA [21]. Oct1 binding to MOREs is inducible by oxidative and genotoxic stress, through phosphorylation of a conserved Ser385 residue in the POU_H DNA binding sub-domain [22].

Although originally described as a synthetic element, MORE-like elements were identified in several endogenous target genes, through inducible Oct1 binding as determined by ChIPseq (Fig. 1B). One of the strongest described is a dyad MORE sequence (binding four Oct1 molecules) located about 2 kb upstream of *Polr2a*, which encodes the large subunit of Pol II [20, 22]. This element is conserved across the mammalian lineage. Aside from *Polr2a*, MORE-like sequences were also described in *Ahcy* (S-adenosyl methionine metabolism), *Ell* (Pol II elongation factor), *Bmp4* (cancer-associated signaling protein), *Hmgb3* (HMG-box DNA binding transcription factor), *Blcap* (imprinted oncoprotein), *Kdm2b/Jhdm1b/Fbx110* (oncogenesis-associated lysine demethylase), *Rras* and *Rras2* (signal-transducing oncoproteins), and *Abcb1* (stem cell-associated efflux transporter) [22, 23]. A different element termed TMFORE (*Taf12*, *Mili*, *Foxo4* Octamer Related Element, AAATTATGCTTCCGAAATCTCTTGATGTC) was found in the eponymous mouse genes rather than through structural studies. This element is well-conserved in mammals and is composed of octamer half-sites in paired and inverted combinations distinct from either a PORE or a MORE. It also displays stress-inducible Oct1 binding. Complex binding sites such as the PORE, MORE and TMFORE easily bind Oct proteins and may represent a significant fraction of in vivo binding sites, especially in situations where there is no match to known weight matrices [24]. In addition to Oct1 homodimers, heterodimers with Oct2, Oct4 or Oct6 can assemble cooperatively on multimeric sequences in vitro [25–27]. Oct1 has been shown to form a complex with Oct2 at the inducible nitric oxide synthase *Nos2* (*iNos*) promoter, inhibiting recruitment of Pol II. In the absence of Oct2, Oct1 binds the iNOS promoter allowing recruitment of Pol II and transcription initiation [28]. The rules governing which Oct proteins assemble at which elements have not been systematically

explored, though in a few cases simultaneous binding of Oct1 and Oct4 has been demonstrated at target genes in embryonic stem cells [26, 25].

Outside of the Oct transcription factor family, described Oct1 cooperative transcription factor binding partners (Fig. 1A, lower right) include C/EBP β [29, 30], SP-1 [31], STAT-5 [32, 33], CREB [34], glucocorticoid receptor [32, 35, 36], androgen receptor [37], thyroid hormone receptor beta-1 [38], retinoid X receptor [39] and NF- κ B/RelA [40]. In summary, Oct1 behaves similarly to other transcription factors in that it can recognize with high affinity and specificity strong matches to its consensus binding site, and can partner with itself, Oct1 paralogs and other classes to transcription factors to recognize more degenerate binding sites.

3. Oct1 Knockout phenotypes

Because Oct1 is widely expressed, and because it associates with multiple critically important genes such as histones, U snRNAs, RNA polymerase II subunits and TBP-associated factors (TAFs), a reasonable hypothesis would be that loss of Oct1 is incompatible with cell growth and viability. Such a result would assign Oct1 the function of a “housekeeping” transcription factor that is necessary for the expression of essential targets. The alternative would be that Oct1 plays a more nuanced role. Oct1 disruption in mice and cells supports the alternative model. Loss of Oct1 in untransformed cells for example does not appear to affect growth or morphology. Additionally, whole body knockout embryos survive to mid-gestation. Three disrupted *Pou2f1* (*Oct1*) mouse alleles have been generated:

- i. A severely hypomorphic germline-deficient allele [41] results in mid-gestation embryonic lethality (embryonic day 11.5–12.5). Runting and anemia with pale fetal liver are present at these time points, though with variable penetrance. The animals live long enough to derive mouse embryonic fibroblasts (MEFs) and to obtain fetal liver hematopoietic progenitors. Surprisingly, Oct1 is dispensable for proliferation of primary cells in this system. Oct1 deficient MEFs proliferate normally in standard conditions [41], while Oct1 deficient hematopoietic progenitors efficiently transplant recipient animals and give rise to stably-engrafted blood cells [42, 23]. Oct1 deficient fetal liver cells do however show poor engraftment potential when used in serial or competitive transplant situations, or following brief culture [23].
- ii. A germline-null allele [43] implants but dies after gastrulation. Importantly, the early embryonic lethality can be rescued by tetraploid complementation, indicating that it is not embryo-intrinsic. Further investigation revealed that the extra-embryonic restriction is due to defects in trophectoderm stem cells. Tetraploid-complemented embryos survive to embryonic day 8.5–9.5. MEFs taken from these embryos also proliferate normally, but following glucose or amino acid starvation fail to arrest at the G1 phase of the cell cycle [44].
- iii. A recently developed conditional-null allele [45] thus far only has been used for deletion in T cells. In this model, T cell development and activation are normal but defects manifest in CD4 memory T cells. Whole body deletion of this allele is embryonic lethal [45], but careful staging has not been performed. As with many

conditional alleles, incomplete deletion is an issue that needs to be taken into account in future studies. However there are equally important issues with using a severe hypomorph allele (above) and the residual protein product typically seen with RNAi (below).

Acute RNAi-mediated Oct1 knockdown results in similar conclusions: cancer cell lines such as A549 (lung), MCF-7 (breast) and MDA-MB-231 (breast) engineered with doxycycline-inducible shRNAs show no growth defects upon induction of Oct1 shRNA [23, 46]. Cumulatively, these results indicate that Oct1 is not critical for the expression of many target genes (such as histones and U snRNAs) under standard conditions. The mouse phenotypes also indicate that Oct1 is dispensable for many developmental pathways. These findings are seemingly paradoxical given the conservation of Oct1 binding elements in critical genes, and the demonstrated binding of Oct1 to these elements using ChIP/ChIPseq, however discarding the naïve expectation that a transcription factor bound to a target gene necessarily contributes to its baseline expression easily solves this conundrum (below).

4. Oct1 revisited

The lack of cellular lethality upon loss of Oct1 raises three significant questions: 1) What is the function of Oct1 at “housekeeping” genes such as histones, U snRNAs, RNA polymerase II subunits and TAFs? 2) What is its role at cell type-specific genes? 3) What is Oct1’s physiological function? Regarding the third question, one insight came with the discovery that Oct1 deficient cells are hypersensitive to genotoxic and oxidative stress generated using ionizing radiation, doxorubicin or hydrogen peroxide [47]. Oct1 had already been shown to regulate the induction of *Gadd45a* in response to DNA damage [48–50], suggesting that the hypersensitive phenotype of Oct1 deficient cells may stem from Oct1 responding to stress signals and altering target gene expression.

A second insight came from the 2009 finding that Oct1 controls cellular metabolism. Although Oct1 deficient MEFs grow at normal rates in rich media and are morphologically normal as assessed by light microscopy [41, 51], they have reduced glucose uptake and increased mitochondrial genome number, membrane potential, respiratory rate and reactive oxygen species (ROS) concentrations [46, 51]. Electron micrographs of these same cells reveal increased mitochondrial articulation, while metabolomic analysis indicates increased TCA intermediates and decreased lactate. Consistent with these changes, amino acid uptake and oxidation are greatly increased in Oct1 deficient cells. Similar results were observed using whole mouse knockout embryos, primary B and T cells isolated from Oct1 deficient fetal liver transplant recipients, and RNAi in cell lines. The opposite result – a more glycolytic phenotype – was observed in cells overexpressing Oct1. Wild-type immortalized MEFs (3T3 cells) die after 5–6 days in culture medium lacking glucose, whereas Oct1 deficient MEFs arrest but remain viable [44, 46, 52]. Consistent with these changes, multiple Oct1 targets, including stress- and signal-responsive target genes, encode metabolic regulators [46, 47, 53, 54]. Examples include *Gpx3*, *Pcx*, *Pdk4* and *Hmgcl*.

A final insight, inconsistent with the notion that Oct1 is a monolithic factor that maintains baseline target gene expression, is the finding that Oct1 is a signal integrator. Oct1 is

modified in multiple ways, including by phosphorylation, *O*-GlcNAcylation, and ubiquitylation (Fig. 2). Of these modifications, the best studied is phosphorylation. Oct1 Ser385 phosphorylation in the POU_H DNA binding subdomain allows the protein to adopt a configuration that allows it to bind more favorably to genes containing a MORE-like sequence [22] (Fig. 1B). Phosphorylation at Ser335 in the other DNA binding subdomain, POU_S, abrogates DNA binding. NEK7 catalyzes this modification during M-phase [55], but AMPK can also phosphorylate Ser335 in response to glucose deprivation [56]. Finally, the Oct1 N-terminus is phosphorylated in vitro by DNA-PK at multiple residues in a manner that dampens transcriptional activity, though these modifications have not been confirmed in cells [57]. Information on other Oct1 modifications is scarce. Other Oct1/POU2F1 phosphorylation events have been documented in large screens but are not functionally annotated [58, 59]. Mass spectroscopy indicates that the protein is both ubiquitylated and *O*-GlcNAcylated [52]. The ubiquitin ligase(s) and deubiquitinases are unknown, as is the significance of the ubiquitylation events, but it is known that Oct1 is stabilized at the protein level in stem cells (see below). *O*-GlcNAcylation appears to control Oct1 transcriptional activity at the level of association with the nuclear periphery (below).

To summarize this section, the last ten years have seen the identification of roles for Oct1 in stress responses and metabolic control, and provided evidence that Oct1 integrates multiple signal inputs through multiple post-translational modifications.

5. Oct1 transcriptional mechanisms

Early studies of Oct1's transcriptional properties relied on plasmid-based reporter systems in which octamer elements coupled to reporter genes were used with transiently transfected and overexpressed Oct1. Like other Oct/POU family members such as Oct4, Oct1 is not very robust in these classic transcription activity assays. These findings run counter to both the high conservation of Oct1, and the conservation of its binding sites in important target genes. Multiple labs have undertaken to better understand its transcriptional properties, with the idea that mechanistic insights may result in a more sophisticated and biologically accurate view of its functions. Oct1 can interact with components of the core transcription machinery [60, 61], suggesting that when localized to the core promoter it can regulate gene expression by recruiting transcription complex components. In breast cancer cell lines, Oct1 regulates rapid induction of *Nos2* (*iNOS*) through a binding site that must be positioned close to the TATA box in the proximal promoter. Prior to induction, this gene has an engaged Pol II, indicating that Oct1 likely regulates this gene at the level of transcript elongation [62]. Oct1 activation of *Nos2* can be inhibited by expression of, and association with, Oct2 [28].

Additionally, new models for Oct1 transcription regulation have emerged in which Oct1 can associate with different cofactors – and with the nuclear periphery – to mediate either transcription activation, repression or a third output – termed “gene poisoning.” Oct1 can switch between different modes via the action of upstream regulatory inputs (for example MAPK signaling), even at the same gene. These contrasting transcriptional modalities may underpin its many functions in malignancy, delineated in section 6.

5.1 Gene activation and repression by Oct1

The action of Oct1 on chromatin has been primarily studied using HeLa cells, fibroblasts, T cells and colon cancer cells lines [45, 63]. Affinity purification/mass spectroscopy studies have shown that Oct1 interacts with a multi-subunit repressive chromatin complex known as NuRD (Nucleosome Remodeling and Deacetylase). NuRD mediates transcriptional repression through ATP-dependent nucleosome remodeling, histone deacetylase and DNA methylation mechanisms [64–66]. NuRD recruitment by Oct1 is closely associated with target gene silencing (Fig. 3).

In response to MAPK signaling, Oct1 can dissociate from NuRD and recruit Jmjd1a/KDM3A to target sites in chromatin [63]. Jmjd1a is a histone lysine demethylase with specificity for H3K9me2 and me1. These modifications repress transcription and thus by removing them Jmjd1a potentiates gene expression (Fig. 3). Association with Jmjd1a correlates with loss of the repressive H3K9me2 mark [45, 63] and with either active gene expression, or with a silent but poised state in which a gene is held in a readily inducible configuration (below). The Oct1 interaction with NuRD and Jmjd1a is mutually exclusive, suggesting a molecular switch in which Oct1 can switch from repressive to permissive potentialities in response to upstream signals.

5.2 “Gene poising” by Oct1

Gene regulation is often viewed from the standpoint of “on/off switches”, but the maintenance of genes in silent but readily inducible configurations is important for many biological systems. Stem cells and memory immune cells for example must maintain cohorts of genes in a transcriptionally silent state that must be induced upon reception of the correct developmental and immunological cues. Mechanistically, one way to establish poised gene expression states is by the maintenance of chromatin free of repressive modifications. H3K9me2 is one such modification, and the H3K9me2 demethylating enzyme Jmjd1a is an Oct1 cofactor [63]. Investigation of Oct1, Jmjd1a and other cofactors in T cells showed that Oct1 can maintain target genes in a poised configuration for later induction by antigen re-encounter [64]. The chromatin at these target genes is free of H3K9me2 and free of DNA methylation. In these absence of Oct1 these marks accumulate and the target gene is induced only poorly. In vivo, loss of Oct1 in CD4+ T cells specifically ablates the memory phase [45]. This poising mechanism also may be important in stem cells, which have similar characteristics to memory cells including long life, low-level homeostatic proliferation and homing to specific niches.

5.3 Oct1 target gene regulation via nuclear organization

Cell biology-based methods have identified Oct1 regulation by sub-nuclear localization, and by the tethering of distant binding sites together in space. One early study showed that Oct1 dissociation from the nuclear periphery correlated with cellular aging and regulation of the target gene *Mmp1* (*Collagenase*) [67]. Another study indirectly associated Oct1 with the nuclear periphery, and with nuclear lamins, by a strong enrichment of octamer elements in lamin-associated chromatin domains or LADs [68]. Oct1 and B-type lamins interact [53, 55], supporting these findings. LADs are associated with gene repression, and may thus correlate with complexes of Oct1 bound to NuRD (Fig. 3). Subsequent work tied Oct1

association with the nuclear periphery to oxidative stress sensing [53]. In this study, Malhas and Vaux showed reduced Oct1 association with the nuclear periphery in cells lacking functional lamin B1. Oct1 binding to oxidative stress-responsive target genes such as *Gpx3* and *Rdm1* increases in these cells, which like Oct1 deficient cells have elevated ROS levels and are hypersensitive to oxidative stress. The association of Oct1 with the nuclear periphery may be regulated by *O*-GlcNAcylation, as mutation of *O*-GlcNAcylated sites within the protein affects both association with the nuclear periphery and association with the stress-responsive Oct1 target gene *Gadd45a* [52]. Regulation of Oct1 by nuclear-cytoplasmic shuttling has also been identified in response to oxidative stress and cAMP [69, 70].

Recent findings in T cells show that Oct1 interacts with CTCF, a protein involved in nuclear organization and intra-/inter-chromosomal interactions between widely spaced regions of DNA [71]. This same study showed that Oct1 can cross-regulate T cell-specific target loci located on different chromosomes, maintaining one locus in a more repressed configuration following T cell stimulation. Maintenance of these loci together in space during a specific temporal window is dependent on Oct1. These findings have yet to be extended to epithelial cells.

6. Role of Oct1 in Tumor Initiation/Progression

Mechanism-oriented studies have identified a pro-tumorigenic role for Oct1. Loss of Oct1 in primary *Tp53*^{-/-} MEFs for example blocks transformation by activated H-Ras and growth on soft agar. Oct1 has no effect on immortalization by serial passage, suggesting specific inhibition of oncogenic transformation [46]. Consistent with these findings is the observation that reduced Oct1 levels protect mice from p53-generated tumors in a mouse model of thymic lymphoma [46]. Pro-tumorigenic functions of Oct1, emphasizing its metabolic functions, have also been described in non-epithelial tumors including glioblastoma, Hodgkin's lymphoma, thymic lymphoma and melanoma [46, 54, 72–74]. Adding to this literature, recent reports continue to build on the idea that Oct1 has potential prognostic and therapeutic significance for multiple cancer types, in particular cancers of the GI tract, lung and breast. Combined, these malignancies account for the majority of cancer incidence and deaths in much of the developed world [75, 76]. Documented Oct1 alterations in different tumor types are summarized in Fig. 4. Collectively, these data indicate that Oct1 can be a powerful facilitator of epithelial tumor potential.

6.1 Oct1 Deletion

Deletion of tumor suppressor genes is common in cancer. Due to Oct1's pro-tumorigenic functions, in the simplest models recurrent deletion of the *Pou2f1* gene encoding Oct1 would not be expected in tumors. Indeed, data available in the Broad Institute Tumorscape database [77] indicate that *Pou2f1* is not deleted at a significant rate in any of the 10844 tumors of different types available in the dataset, or located in a focal peak region of deletion. Cancer types studied in this survey include breast, prostate, lung and many others. To our knowledge, no reports of *Pou2f1* spontaneous deletion exist in the literature.

6.2 Oct1 focal amplification

A common somatic alteration leading to tumorigenesis is the focal amplification of chromosomal regions containing genes encoding oncoproteins. In a recent study, Qian *et al.* performed copy number variation analysis in gastric cancer tissues using data from the TCGA, the Singapore dataset and the VU University Medical Center (VUMC) cohorts [78]. They showed Oct1 to be focally amplified in 10% of primary diffuse-type gastric cancer samples. Supporting these findings, data available from Tumorscape show that *Pou2f1* is significantly focally amplified across the entire dataset consisting of 10844 tumor types [77]. In addition to genomic amplification, Oct1 expression is frequently increased in certain tumors, as will be discussed below, suggesting that much of the Oct1 overexpression observed in malignancy may stem from transcriptional or post-transcriptional mechanisms.

6.3 Increased Oct1 mRNA levels

Gene expression profiling of cancer cells compared to normal cells is a common way of identifying genes which when overexpressed might contribute to tumor generation, progression or maintenance. Reports focused on epithelial malignancies demonstrate significant increases in Oct1 gene expression. For example, several studies analyzing global gene expression changes in gastric cancer compared to normal gastric tissues have identified elevated levels of *Pou2f1* mRNA [79–81]. In a recent study on colorectal cancer (CRC), Wang *et al.* identified increased *Pou2f1* levels in 50% of the 38 total primary CRC tissues, compared to paired normal tissues [82]. Multiple studies as well as TCGA data sets show that *Pou2f1* expression is modestly increased in both infiltrating and superficial bladder carcinoma, compared to levels in normal bladder [83–86]. In breast cancer, gene expression profiling studies reveal increases in *Pou2f1* expression (between 1.3- and 1.4-fold, averaged across all samples, though some samples vary by more than 5-fold) in invasive ductal as well as lobular breast carcinoma [83, 87–89]. A recent study by Xiao *et al.* found that *Pou2f1* was expressed at almost 6-fold higher levels in cervical cancer tissues compared to paired non-cancerous controls [90]. *Pou2f1* mRNA was also detected at higher levels in head and neck squamous cell carcinoma (HNSCC) cell lines compared to normal keratinocytes, and in primary HNSCC tissues compared to normal tissues [91]. In this study, the authors demonstrate that Oct1 acts as a transcriptional activator of the HOX genes *Hoxd10* and *Hoxd11*, both of which are overexpressed in HNSCC.

6.4 Increased protein levels

Although the nature of DNA and RNA makes them more amenable to relatively inexpensive, high-throughput analysis, it is usually the activity of functional proteins that controls cell physiology. Increased levels of a particular protein associated with tumor initiation or progression may be due to overexpression of the gene, but it is also possible that post-transcriptional and/or post-translational events increase protein levels while leaving transcription of the gene unchanged. The majority of epithelial cancers discussed in this review report increased levels of Oct1 protein. Some of the most robust reports associate elevated Oct1 with gastric cancer. For instance a recent study by Xu *et al.* finds that Oct1 is elevated in gastric cancer tissue and is also regulated by the AKT pathway, leading to the induction of epithelial-to-mesenchymal transition (EMT) [92]. EMT is a cellular process

observed in cancer progression and metastasis in which biochemical changes in epithelial cells allow them to become more migratory as they acquire mesenchymal cell characteristics [93]. Another study, which focused specifically on intestinal-type gastric cancer, showed that 74% of the 42 gastric cancer samples analyzed showed increased Oct1 protein levels [94]. In contrast, Jeong *et al.* reported a smaller percentage, 36.5% of 332 tested gastric cancer patient samples, displaying Oct1 protein overexpression, while the other 63.5% showed reduced Oct1 expression compared to matched non-cancerous tissue [95]. However, this study also identified a positive correlation between Oct1 protein levels, advanced tumor invasion and lower survival rate, suggesting that Oct1 is involved in gastric tumor progression. This possibility is further supported in a recent study by Qian *et al.*, which confirmed elevated Oct1 protein levels in gastric cancer tissues, and identified a role for Oct1 in the regulation of synbindin, a protein involved in ERK signaling [78]. This latter study additionally showed that Oct1 expression offers superior prognostic power compared to the widely used AJCC staging.

A study by Hernández *et al.* presented a comprehensive analysis of the somatic genetic mutations in breast cancer. Here the authors identified genes with mutations that contribute to the neoplastic process as well as those with “passenger” mutations, or mutations that occur too infrequently to be directly linked to the neoplastic process. Hernández *et al.* then performed an interactome network analysis in order to determine functional interactions between proteins. Although Oct1 was not identified in the somatic mutation analyses in this study, Oct1 protein was identified in the interactome network analysis as part of a large component connecting validated and/or benchmark proteins which contribute to malignancy [96]. Protein analyses in primary tissues from breast cancer patients has also revealed higher levels of Oct1 protein compared to normal breast tissues, in the absence of mRNA alteration [23].

Oct1 protein up-regulation has also been shown in colorectal, prostate and cervical cancer. A study by Li *et al.* demonstrated elevated Oct1 protein levels in over 75% of the total 136 primary CRC tumors tested [97]. In addition, Wang *et al.* showed elevated Oct1 protein expression in ~60% of the 98 CRC tissues analyzed, and further showed that high Oct1 protein correlated with reduced disease-free and overall survival [82]. Obinata *et al.* showed increased Oct1 protein in prostate cancer cell lines and primary tumor tissue [98]. They identified a positive correlation between Oct1 protein levels and high Gleason scores in tissues from 102 prostate cancer patients. Survival analyses showed that patients with low Oct1 immunoreactivity had better cancer-specific survival compared to patients with high Oct1 immunoreactivity. Based on their results, the authors concluded that Oct1 may have prognostic significance for prostate cancer. Oct1 protein was also increased in cervical cancer tissues compared to normal cervical tissue [90], however this study analyzed tissues from only 10 cervical cancer patients, and more work in this area is needed to firmly conclude that Oct1 protein levels are upregulated in this cancer type.

6.5 Increased Oct1 activity

Because there are multiple Oct1 post-translational modifications, and because Oct1 association with transcription cofactors and the nuclear periphery is regulated by multiple

mechanisms (above), there are many possible ways in which transcription of Oct1 target genes can be modulated without altering the levels of Oct1 protein. In a few cancer types there is evidence for increased Oct1 transcriptional activity without increased Oct1 mRNA or protein levels. In these cases, augmented Oct1 function was detected indirectly, by the tendency of coordinately regulated genes associated with malignancy to have binding sites for Oct1. The products of these genes may contribute to tumor initiation and progression.

A recent report by Kalamohan *et al.* [99] implicated Oct1 in coordinate regulation of gene expression associated with gastric cancer. In this study, co-expressed genes in 200 gastric cancer tumors were categorized into 21 modules. One module was considered to be the major driving force of diffuse type gastric cancer, and one of the features in this module was higher frequency of Oct1-mediated transcription, with an Oct1 binding site occurrence of over 21%, the highest identified enrichment frequency for transcription factor binding sites. For intestinal-type gastric cancer, the authors identified the genes and gene hubs in another module as the major drivers, and Oct1 was among the top 5 transcription factors whose binding sites were enriched, with over a 12% occurrence [99].

A study of c-Myc-driven lung adenocarcinoma identified a statistically enriched Oct1 binding sites in the deregulated genes. Here the authors performed transcriptional profiling on lung adenocarcinomas of female c-Myc transgenic mice, identifying a cohort of transcriptionally induced genes in order to identify regulatory gene networks [100]. Oct1 binding site enrichment was found in a set of genes indirectly controlled by c-Myc. Two other studies identify enrichment in Oct target sites in breast cancer and other malignancies without specifically implicating Oct1 [93, 101]. Sometimes these sites are identified as Oct4 target sequences or parts of “pluripotency signatures”, despite the lack of obvious Oct4 expression in these tissues. The overlapping specificity of Oct proteins makes it difficult to conclusively identify one particular Oct protein in this analysis, making it possible that the widely expressed Oct1 protein underlies these differences in expression.

Another case in which Oct1 activity is increased leading to pro-tumorigenic effects is a recent study which identified the circadian gene Period2 (PER2) as a tumor suppressor frequently downregulated in breast cancer. PER2 was shown to act as a transcriptional corepressor by recruiting EZH2 and SUZ12 as well as HDAC2 to Oct1 binding sites in target genes including *Twst1*, *Snai1* (*Snail*) and *Snai2* (*Slug*). Downregulation of PER2 removes this inhibitory effect and allows for the transcriptional activation of *Twst1*, *Snai1* and *Snai2* by Oct1 [93].

Oct1 transcription activity is signal-responsive. For example, MAPK signals can regulate Oct1 association with cofactors (see section 5). Recent findings demonstrate an involvement for Oct1 downstream of BRAF in thyroid cancer, where BRAF-V600E mutation is the most common genetic alteration. In this study, which analyzed the role of thyroid hormone T3 in papillary thyroid cancer, the authors found that T3 binds to and activates a complex consisting of the thyroid hormone receptor TR β 1 and Oct1, leading to the translocation of this complex to the nucleus where it binds to Oct1 sites on the cyclin D1 (*Ccnd1*) promoter, inducing cell proliferation [38]. When the levels of T3 are increased, as in the case of hyperthyroidism, the TR β 1/Oct1 complex is over-activated, leading to overexpression of

cyclin D1 and the promotion of thyroid cancer. Interestingly, Oct1 was also recently found to be activated by BRAF in order to promote expression of target genes in melanoma, a non-epithelial cancer [54]. Constitutively active BRAF-V600E activates Oct1 in melanoma cells in order to promote the expression of the metabolic/ketogenic enzyme 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL), leading to accumulation of the HMGCL product acetoacetate (AA). AA promotes binding of mutant but not wild-type BRAF to MEK1, promoting MEK-ERK activation. Although active BRAF activates Oct1 in order to induce *Hmgcl* expression in normal cells, only in cells harboring the BRAF-V600E mutant is there a metabolic advantage in having increased accumulation of AA, and because BRAF-V600E is constitutively active, Oct1 activity is higher compared to normal cells. It will be interesting to analyze the expression and activity of Oct1 in other cancer types where BRAF mutation occurs, including breast, lung, ovarian and colorectal cancers [102]. Cumulatively, these studies identify augmented Oct1 protein activity, rather than augmented Oct1 mRNA levels, as an important correlate of tumor gene expression patterns.

Recently, a pathway by which increased Oct1 expression could lead to activation of the MAPK/ERK pathway was observed in gastric cancer cells [78]. Oct1 was found to act as a transactivator of *Synbindin*, a gene encoding a regulator of the MEK/ERK pathway. Synbindin binds to both ERK and MEK on the Golgi apparatus, facilitating ERK phosphorylation by MEK [78]. Because Oct1 has previously been shown to be regulated by MEK/ERK, taken together these findings suggest a complex interaction between Oct1 and MAPK signaling.

6.6 Mutation

The Sanger Institute Catalogue of Somatic Mutations in Cancer (COSMIC) database [103] reports that out of 22997 samples analyzed, only 120 Oct1 mutations have been identified. These include missense mutations and small number of frameshift events. However there has not been as yet any direct association between these mutations and epithelial cancers. In aggregate, the published findings indicate that Oct1 can contribute to malignancy at multiple levels, but is most strongly implicated post-transcriptionally including at the level of protein concentration and activity.

7. Mechanisms and target genes potentially underlying Oct1's pro-tumorigenic role

What are the critical Oct1 targets and pathways that help to drive malignancy? This question remains incompletely answered, mostly because systematic Oct1 genomic target analyses in different tumor types have yet to be performed. However, both anecdotal results from various malignancies and systematic ChIPseq results from nonmalignant cells have identified targets that may contribute to disease. The described functions of Oct1 are numerous, and identifying those functions that allow Oct1 to promote tumorigenicity in specific malignancies may help in categorizing and treating these diseases. Based on the known target genes, and knowing that given genes can function in more than one area, the functions of Oct1 can be broadly classified into six categories: control of cell growth,

cellular stress response, metabolic regulation, regulation of stem cell identity, invasion and metastasis and immune regulation (Table 1).

7.1 Control of cell growth

Growth-associated Oct1 target genes include targets needed for cell proliferation and viability. Examples include histones, U snRNAs, Pol II subunits and TAFs. Additionally, growth regulators such as *Ccnd1* (*Cyclin D1*), *Rras* and *Rras2* are Oct1 target genes [22, 104, 33, 34]. *Ccnd2* was also recently revealed to be an Oct1 target in T cells [45]. At the *Ccnd1* locus, Oct1 has been described both as a directly bound transcription factor and as a transcriptional co-activator [33, 34]. In papillary thyroid cancer, where T3 levels are increased, Oct1 has been shown to form a complex with TR β 1. This complex binds T3 and translocates to the nucleus, leading to the expression of *Ccnd1* and the initiation of thyroid tumors [38].

Interestingly and as mentioned above, loss of expression of many of these genes would be expected to cause cell lethality, inconsistent with the Oct1 knockdown/knockout phenotype. More likely and consistent with current findings, Oct1 modulates the expression of these genes in response to upstream signals. For example, Oct1 may regulate these genes under conditions of stress, buffering them from inappropriate repression [22, 63]. This anti-repression mechanism works by recruitment of Jmjd1a to target genes to prevent the accumulation of repressive H3K9me2 marks. In MEFs, Oct1 deficiency causes this mark to accumulate at two tested target genes, *Polr2a* and *Ahcy*. Following hydrogen peroxide exposure, these broadly expressed target genes become strongly repressed in Oct1 deficient cells [63].

7.2 Cellular stress response

When exposed to oxidative stress, Oct1 can be modified by phosphorylation at Ser385. This modification alters the binding specificity of Oct1 at target sites, allowing Oct1 to additionally bind more complex sites, such as the MORE motifs described in section 2 [22]. Target genes containing MORE sites include the high mobility group-box 3 gene *Hmgb3* and the oncogenes *Rras* and *Rras2* [23]. HMGB3 protein expression is frequently elevated in gastric cancer and is associated with poor prognosis [105].

The best-characterized stress-associated Oct1 target is *Gadd45a*. Gadd45 proteins are induced by endogenous and exogenous stress signals including oncogenic stress, ionizing radiation and ultraviolet light. Gadd45a's functions are not completely understood but it is known to regulate cellular stress responses via interactions with p21, PCNA, Cyclin B1 and the p38 and JNK signaling kinases to regulate cell cycle arrest, apoptosis and DNA repair [106, 107]. Studies have shown that *Gadd45a* is induced through both p53-dependent and -independent mechanisms. NF-Y and Oct1 mediate p53-independent induction [48–50, 108]. The tumor suppressor BRCA1 may collaborate with Oct1 in *Gadd45a* regulation [109] and act as an Oct1 cofactor at the *Esr1* promoter [110]. *Esr1* encodes ER α and is an Oct1 target gene [111]. Oct1 and BRCA1 have been documented to interact [109, 112, 113]. Interestingly, BRCA1 is also implicated in Oct1 regulation of other targets, including *Mad2* [113], and several targets involved in base excision DNA repair, *Ogg1*, *Nth1*, *Ref1* (*Ape1*)

[114]. Precisely how this pathway works has not been fully delineated. Other defined stress-inducible Oct1 targets include *Pdrg* and *Cdkn1b/Kip1* [44, 115].

7.3 Metabolic regulation

The metabolic activities promoted by Oct1 described in section 4, including the switch from aerobic glycolytic metabolism, are consistent with changes observed in tumor cells [116], suggesting that Oct1 may have cancer-promoting effects via metabolic mechanisms. Consistent with this hypothesis, experiments have associated Oct1's metabolic functions with its action in cancer. In *Tp53* deficient MEFs, Oct1 deletion eliminates soft agar colony formation following transformation with H-Ras. Transformation of fibroblasts by serial passage is unaffected, suggesting that the effects are specific to Ras-induced oncogenic transformation [46]. Loss of Oct1 mimics the effects of dichloroacetate (DCA), a known inhibitor of transformation that promotes oxidative metabolism [117]. Combining DCA with Oct1 loss produces no additive effect, suggesting that DCA and Oct1 loss act in the same pathway [46]. Another study, focused on glioblastoma, identified a pathway by which Oct1 controls the expression of its direct target, miR-451, via the activity of AMPK in a manner controlled by glucose availability. Oct1 Ser335 phosphorylation by AMPK dampens its activity and reduces miR-451 expression, resulting in increased expression of repressed miR-451 targets such as CAB39 [56]. Finally a study focused on melanoma and leukemia identified Oct1 at the center of a pathway linking mutant BRAF and oncogenic MAPK signaling to lipid metabolism, through the direct Oct1 target *Hmgcl* [54]. Although none of these studies focuses on epithelial tumors, the players are widely expressed. Targeted studies are required to reveal whether the increased Oct1 activity consistently observed in epithelial tumors drives malignancy through these pathways.

7.4 Regulation of stem cell identity

Loss of Oct1 has been shown to decrease tumor size in xenograft models of colon cancer [82] and lung cancer [46]. In the latter model, A549 cells with inducible Oct1 knockout were used to generate subcutaneous tumors in immunodeficient recipients, yielding somewhat smaller tumors that nevertheless grew at the same rate within their hosts. These results suggested that fewer cells seed the tumor. More sophisticated limiting dilution experiments revealed that the number of cells necessary to initiate a tumor rises greatly in the Oct1 deficient condition [23]. This phenotype is frequently associated with “tumor stem cells” – cells that have been described as glycolytic and stress resistant, phenotypes also associated with Oct1. Additional work identified a direct role for Oct1 in promoting stem/progenitor cell phenotypes (e.g., dye efflux, ALDH activity), and identified relevant target genes (e.g., *Abcg2*, *Abcb1*, *Abcb4* and *Aldh1a1*) [23].

Published work from our laboratory [23] and the Clevers laboratory [118] shows that Oct1 levels are elevated, compared to surrounding cells, in stem cells of the small intestine and colon that also express high levels of the stem cell markers *Lgr5*, *Lrig1* and *Aldh1*. In the latter case, elevated Oct1 protein levels were observed without increases in Oct1 mRNA expression. Further work [23] extended these findings to malignant stem-like (CD44^{hi}CD24^{lo}) breast cancer samples: metastatic tumor samples with high stem cell content had high levels of Oct1 protein but not mRNA. The finding that Oct1 levels are

elevated at the protein but not mRNA level in normal and malignant stem cell compartments are consistent with a model in which Oct1 protein is stabilized in stem cells. Oct1 is known to be ubiquitinated [52], and more work is required to understand possible Oct1 regulation at the level of protein stability.

A pro-stem cell function for Oct1 may enhance tumor aggressiveness, as tumor cells with expanded stem cell signatures tend to be of higher grade [119]. Stem cell phenotypes are also closely linked to chemo- and radio-resistance [120–122]. Elevated expression of ABC efflux transporters on the cell surface decreases the intracellular concentration of cytotoxic therapeutics, thus conferring resistance [123]. Increased progenitor phenotypes can also cause epithelial cells to lose cell polarity, resulting in tissue disorganization and metastatic behavior [124–126].

7.5 Invasion and metastasis

Only recently have roles of Oct1 in tumor spread begun to emerge. Examples come from breast and colon cancer. Oct1 targets include *Twist1* and *Snai2* (*Slug*), genes involved in EMT. TWIST1 and SLUG are part of a group of transcription factors that induce EMT during development as well as in tumor cells. A study by Li *et al.* showed that Oct1 is overexpressed in the majority of CRC tissues analyzed, and delineated a mechanism by which Oct1 might contribute to CRC progression [97]. The authors showed that Oct1 expression correlates with the expression of N-cadherin and ZEB1, which promote EMT, and that Oct1 knockdown in CRC cell lines reduces proliferation, migration and EMT markers. These changes are consistent with a role for Oct1 in CRC progression. In breast cancer, the activation of EMT-inducing genes by Oct1 has also been observed [93]. Hwang-Versluis *et al.*, showed that the tumor suppressor PER2 acts as a transcriptional corepressor by recruiting EZH2 and SUZ12 as well as HDAC2 to Oct1 binding sites of EMT genes including *Twist1*, *Snai1* and *Snai2*, therefore repressing induction of these genes. Downregulation of PER2, which is observed in both sporadic and familial primary breast cancers, removes this inhibitory effect and allows for the transcriptional activation of EMT genes by Oct1, leading to invasion and metastasis [93].

Oct1 has also been identified as a transcriptional activator of the HOX genes *Hoxd10* and *Hoxd11*, both of which are overexpressed in HNSCC primary tissues and cell lines [91]. Overexpression of these genes in HNSCC is associated with proliferation and invasion of oral keratinocytes, leading to tumor spread.

Spp1/Opn is an Oct1 target gene [19, 20]. The product of this gene, Osteopontin, is a secreted signaling protein that has been shown to be overexpressed in breast, lung, colorectal, ovarian and gastric cancers [127]. In breast cancer, Osteopontin has been shown to play a role in metastasis and tumor progression [128].

7.6 Immune regulation

Immune-modulatory targets for Oct1 are well described and are too numerous to address completely here. Although the mechanisms and implications have not been worked out for all target genes and cell types, it is clear that Oct1 regulates multiple target genes in B cells, T cells, macrophages and NK cells. These targets include cytokines (e.g., IL-2, IL-4, IL-8) [9,

129–131], pro-inflammatory mediators (e.g., CRP, NOS2/iNOS, prostaglandin D synthase) [132–134] and immunoglobulins (heavy and light chain) [4–6]. As with other systems, Oct1 appears to be dispensable for the baseline expression of many of these genes in standard assay conditions. However it has been shown that Oct1 uses the gene poising mechanism outlined in section 5.2 to maintain silent immunomodulatory targets in a configuration that allows robust expression in memory cells. Oct1 is also required in vivo for robust helper T cell memory [45].

8. Summary and future directions for the field

After decades of being studied in other guises, a broad role is emerging for Oct1 as a tumor promoter across a range of epithelial and other tumor types. What the field requires are deep and focused studies on the role of Oct1 in specific tumors, comparing, for example, Oct1 expression to established prognostic markers for the particular tumor type. A better understanding of molecular mechanisms is also required. Surveys of common and unique Oct1 transcriptional targets in normal and malignant tissue will allow greater mechanistic insights. The availability of a conditional mouse allele [45] will allow for improved study of Oct1 in pre-clinical cancer models. Determining how Oct1 itself is regulated at the transcriptional and post-transcriptional level is necessary to identify points in different regulatory pathways that can potentially be leveraged to treat disease. The Oct1 mRNA contains a particularly long (>11 kb) 3'UTR with predicted target sites for multiple tumor suppressor microRNAs, including microRNAs expressed in epithelial cells and associated with epithelial malignancies such as let-7, miR-1, -7, -34, -128 and -218. Translational down-regulation by one or more of these microRNAs could explain the documented elevated levels of Oct1 protein in cancer cells [23]. Oct1 is regulated by the tumor suppressive microRNA miR449a in liver cancer. miR449a is also associated with tumor suppression in lung and prostate cancer, suggesting that similar mechanisms may operate [135].

Another largely unexplored area is the role that human polymorphisms in Oct1 target sites may be playing in cancer or other processes. Maurano et al. coupled genome-wide analysis of DNase I hypersensitive sites (which correspond to transcription factor binding sites) in different human cells and tissues with a meta-analysis of human genome-wide association studies to identify human disease polymorphisms co-localizing with transcription factor binding sites. Oct1 binding site polymorphisms associated with bladder cancer and a variety of autoimmune syndromes were identified in this analysis [136]. The precise molecular mechanisms underpinning these associations have yet to be followed up.

A third area ripe for exploration is the possible differential role of various Oct1 isoforms in disease. The *Pou2f1* gene locus is complex, with a heterogeneous 5' end. Multiple Oct1 isoforms have been described that vary in length and sequence at the N-terminus of the protein [137].

Fourth and finally, the two most robust recent areas of Oct1 research have been in cancer and immune biology. These studies have largely proceeded in parallel with one another. Combining these heretofore largely independent research trajectories may become an

important area of future work. For example, no work has thus far been conducted on the role of Oct1 in anti-tumor immune responses.

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Highlights

- Part of a larger set of articles pertaining to the Oct transcription factor family
- A brief history of one of these factors, Oct1/Pou2f1
- Current knowledge from the standpoint of malignancy
- First-ever comprehensive review regarding epithelial malignancy (a field that has really exploded in recent years)

Fig. 1. Different modes of Oct1 DNA binding. A) Modes of Oct1 DNA binding. The best-documented examples are shown, but clear structural information is only available for the subset on the left: canonical octamer, tandem/PORE and MORE. In many cases, such as TMFORE, conserved arrangements of half-sites are seen without knowing how Oct1 molecules are arranged on DNA. B) Expansion of one specific DNA binding modality, the MORE. Binding is inducible by stress signals. Example target genes identified by ChIPseq [22] or specific target gene analysis [23] are shown. All sites are conserved to mouse. Consensus MORE sequence is shown at the top. At the right is the position of the binding

site relative to the transcription initiation site, and functional annotation. Some target genes have been heavily studied and some much less so.

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Fig. 2.

Oct1 post-translational modifications verified to occur in cells using mass spectroscopy. A) Schematic is shown with known modifications. Not all modifications have been functionally annotated. Modifications identified in large phosphorylation screens are as follows: Daub et al. [138]: phospho-Ser267, phospho-Ser335 (annotated as the smaller POU2F2/Oct2 which would score more highly, but the peptide is identical to Oct1), phospho-Ser385, phospho-Ser441, phospho-Thr445; Dephore et al. [139]: phospho-Ser269, phospho-Thr270, phospho-Thr276, phospho-Ser278, phospho-Ser283, phospho-Ser335 (annotated as the smaller POU2F2/Oct2 which would score more highly, but the peptide is identical to Oct1), phospho-Ser385, phospho-Ser447, phospho-Ser448; Van Hoof et al. [58]: phospho-Thr270, phospho-Ser278, phospho-Thr445, phospho-Thr446, phospho-Thr448. Modifications identified in Oct1-targeted studies are as follows: Kang et al. [52]: Ub-Lys9, *O*-GlcNAc-Thr255, phospho-Ser270, phospho-Ser276, phospho-Ser278, phospho-Ser283, phospho-Ser335, phospho-Ser385, Ub-Lys403, phospho-Thr448, *O*-GlcNAc-Ser728; Segil and

Heintz [140]: phospho-Ser385. B) Complete sequence of the major isoform of human Oct1 is shown, with modifications.

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Fig. 3.

Mechanisms of transcription regulation by Oct1. Top: Oct1 has been described to repress transcription via association with the chromatin modifying complex NuRD [63]. NuRD possesses both histone deacetylase activity and ATP-dependent chromatin remodeling activity and can potentially suppress transcription. Bottom: in response to signals (including MAP kinase signaling through ERK in T cells), NuRD dissociates from Oct1 and the histone lysine demethylase Jmjd1a/KDM3A associates.

Fig. 4. Summary of the different described alterations to Oct1 status in different epithelial tumor types. References are provided at bottom. Progressing from left to right: deletion, focal amplification, increased mRNA expression, increased proteins levels, increased protein activity on target genes, point mutation. Note that Oct1 has not been described to be systematically deleted or mutated in malignancy.

Table 1

Oct1 target genes discussed in section 7¹

Pathway	Gene	Description	Function	Ref
Control of cell growth	<i>Ahcy</i>	Adenosylhomocysteinase	Threonine metabolism. S-adenosyl methionine biosynthesis.	[22, 62]
	<i>Ccnd1</i>	Cyclin D1	Component of the core cell cycle machinery. Promotes proliferation leading to tumor formation.	[33, 34, 38, 102]
	<i>Polr2a</i>	RNA polymerase II polypeptide A, 220 kDa	Protein-coding gene transcription.	[20, 22, 62]
	<i>Rras</i> , <i>Rras2</i>	Related RAS Viral (R-Ras) Oncogene Homolog; Related RAS Viral (R-Ras) Oncogene Homolog 2	Small GTPases, activate signal transduction pathways. Induce cell proliferation.	[22, 23]
Cellular stress response	<i>Cdkn1b/Kip1</i>	Cyclin-dependent kinase inhibitor 1B	Inhibitor of cell cycle progression.	[44]
	<i>Esr1</i>	Estrogen receptor 1	Encodes ERalpha. Hormone response. Mitogenic. Associated with mammary gland development.	[109,110]
	<i>Gadd45a</i>	Growth arrest and DNA damage-induced protein, alpha	Stress-inducible. Associated with cell cycle arrest.	[48–50, 52, 104–107]
	<i>Hmgb3</i>	High mobility group-box protein, B3	Transcription factor. Induces gastric cancer cell proliferation and cell cycle progression. Important for stem cell maintenance.	[23, 103]
	<i>Mad2</i>	Mitotic arrest deficient 2	Component of the mitotic spindle assembly checkpoint. Reduced expression leads to failure of cells to arrest in G2-M phase, leading to aberrant cell division.	[109]
	<i>Nth1</i> <i>Ogg1</i> <i>Ref1 (Ape1)</i>	Nth Endonuclease III-Like 1; 8-Oxoguanine glycosylase; Redox factor-1/Apurinic/Pyrimidinic endonuclease	Base excision DNA repair. Detection and repair of DNA damage.	[110]
	<i>Pdrg</i>	p53 and DNA damage regulated gene	Regulation of cell growth.	[111]
Metabolic regulation	<i>Hmgcl</i>	HMG-CoA lyase	Accumulation of acetoacetane. Facilitates activation of MEK-ERK signaling.	[54]
Stem cell identity	<i>Abcb1</i> <i>Abcb4</i> <i>Abcg2</i>	ATP-binding cassette (ABC) transporter, B1, B4, G2	Efflux activity. Chemoresistance.	[23, 119]
	<i>Aldh1a1</i>	Aldehyde dehydrogenase 1 family, member A1	Retinoic acid biosynthesis. Associated with stem cell activity.	[23]
Invasion and metastasis	<i>Hoxd10</i> , <i>Hoxd11</i>	Homeobox D10; Homeobox D11	Transcription factors. Regulate organ morphogenesis and cell differentiation during development. Promote proliferation and invasion of oral keratinocytes.	[90]
	<i>Snai1</i> <i>Snai2</i> <i>Twst1</i>	Snail family zinc finger 1, Snail family zinc finger 2 (Slug), Twist family bHLH transcription factor 1	Transcription factors. Induce EMT in malignant cells, leading to metastasis.	[92]

Pathway	Gene	Description	Function	Ref
	<i>Spp1</i> (<i>Opn</i>)	Secreted signaling glycoprophosphoprotein-1 (Osteopontin)	Induces migration in breast carcinoma cells.	[19, 20, 25, 123, 124]

¹ Immunomodulatory genes are not shown

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