

Rapid progress in the field of adult cells reprogramming back into a stem cell-like fate revealed shared mechanisms of action with tumoural reprogramming. A hallmark of stem cells – self-renewal and differentiation potential – seems to be tightly interlaced with large proliferation capacity and cellular plasticity of cancer cells. In this review, we briefly summarise the core transcription factors critical to maintenance of ES cell signature and overexpressed in many types of cancer, as well as signalling pathways involved in both induced pluripotency and oncogenesis, with particular regard to the role of tumour suppressor p53.

**Key words:** cancer, stem cells, reprogramming, induced pluripotent stem cells, p53.

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# Oncogenesis and induced pluripotency – commonalities of signalling pathways

Marta Klimczak<sup>1,2,3</sup>

<sup>1</sup>The International Institute of Molecular and Cell Biology, Warsaw, Poland

<sup>2</sup>Postgraduate School of Molecular Medicine, Medical University of Warsaw, Poland

<sup>3</sup>Gene Therapy Laboratory, Department of Cancer Immunology, Greater Poland Cancer Centre, Poznan, Poland

## Introduction

The multiple similarities between embryonic stem (ES) cells and cancer cells have led to widespread interest of researchers to discover molecular mechanisms that link these two cell types. Embryonic stem cells and cancer cells share certain common characteristics, such as the ability to self-renew and block in differentiation [1]. Interestingly, upon transplantation into immunodeficient mice, both ES cells and cancer cells form benign and malignant tumours, respectively. Moreover, both cell types have a rapid cell cycle and high telomerase activity, which result in uncontrolled proliferation [2]. The scientific breakthrough of Takahashi and Yamanaka in creating induced pluripotent stem (iPS) cells opened the door to broad stem cell research to understand the mechanisms involved in dedifferentiation. Importantly, the cocktail of four reprogramming factors is composed of two well-known proto-oncogenes, c-Myc and Klf4, which further connect induced pluripotency and oncogenesis. Here, we present a current understanding of transcriptional regulators that are critical to maintenance of self-renewal and are overexpressed in many human cancers. We also discuss the commonalities in signalling pathways and the role of tumour suppressor p53 in the regulation of reprogramming and tumorigenesis.

## Transcriptional regulation of dedifferentiation in tumorigenesis and induced pluripotency

The connection between oncogenesis and induced pluripotency is commonly discussed by the fact that the core pluripotency genes involved in the reprogramming process also play a central role in tumourigenicity. The cocktail of Yamanaka factors [3] that enables the dedifferentiation of somatic cells to a stem cell-like fate is actually composed of well-known oncogenes, such as c-Myc and Klf4, or genes that exhibit high expression in various types of cancer, such as Oct3/4 and Sox2.

### Oct3/4

Oct3/4, besides being a master player in induced pluripotency, plays a leading role in embryogenesis, and its correct level of expression is a critical requirement for initial formation of mammalian embryo. Not only knock-down, but also overexpression of Oct3/4 activates the differentiation to trophoectoderm and primitive endoderm or mesoderm, respectively [4]. The upregulation of Oct3/4 is characteristic of several types of human cancers, including pancreatic cancer, gastric cancer, oral squamous cell carcinoma, seminoma, and bladder cancer [5–7]. Furthermore, it has been demonstrated that Oct3/4 positively regulates the progression of carcinomas by stimulating dedifferentiation of cancer cells and acquiring cancer stem cell

(CSC)-like phenotype, that in consequence leads to epithelial-mesenchymal transition (EMT), and development of tumour-initiation abilities, promoting metastases and formation of drug-resistant phenotype [8]. In agreement with this, Oct3/4 correlates with poor prognosis of human gliomas [9], melanoma [10], and lung adenocarcinoma [11].

### Sox2

Another key factor in ES cell self-renewal, Sox2, is closely associated with many types of cancer. Overexpression of Sox2 imposes cancer stem cell-like properties, further influencing the tumour formation capacity and tumour aggressiveness in several types of cancer, such as squamous skin tumours [12], lung cancer [13, 14], and serous ovarian carcinoma [15]. Furthermore, Sox2 has been demonstrated to be involved in mechanisms of chemoresistance [13, 15, 16]. It was recently shown that a high level of Sox2 is associated with tamoxifen resistance, which develops by Sox2-dependent activation of Wnt signalling pathway in cancer stem/progenitor cells [16].

### Klf4

Besides being part of the Yamanaka factors, Klf4 is also a bifunctional player in the process of carcinogenesis – it has been suggested that it acts both as an oncogene and a tumour suppressor depending on the different cellular context [17]. For example, Klf4 inhibits cancer cell invasion in primary lung cancer by suppressing the expression of SPARC, which is an extracellular matrix protein involved in tumour development and metastasis [18]. Tumour suppressing function of Klf4 in some types of cancer is also associated with its capacity to prevent epithelial-mesenchymal transition, a critical process in cancer progression and metastasis. It functions through repression of key mesenchymal markers, such as Slug and Snail in hepatocellular carcinoma and breast cancer, respectively [19, 20]. Klf4 maintains also the expression of E-cadherin, preventing EMT in mammary epithelial cells and supporting its metastasis suppressive role in breast cancer [21]. On the other hand, Klf4 was found to play a potent oncogenic role in colon cancer by enriching spheroid cells with cancer stem cell (CSC) markers and mesenchymal markers [22]. Similarly, Klf4 is believed to act as an oncogene in mammary tumorigenesis by maintaining stem cell-like features that seem to be inconsistent with its tumour suppressing role described in ref 21.

### c-Myc

c-Myc, one of the first proto-oncogenes discovered, is activated in nearly 70% of all human cancers [23]. Undoubtedly, it plays a crucial role in tumorigenesis as well as being partially responsible for teratoma formation in iPS-derived grafts [24]. Being one of the Yamanaka reprogramming factors, c-Myc has given rise to a lot of controversy as it carries a risk of oncogenic transformation that excludes cells with exogenous expression of c-Myc from potential clinical application. Although it is possible to generate iPS cells without c-Myc, the process is highly inefficient [24]. Moreover, c-Myc has an essential positive

effect upon iPS cell formation in terms of achieving mature iPS cells that are more prone to form chimeric mice [25]. Further studies have suggested that c-Myc is actually not a critical member of the core pluripotency network as its targets are involved more in cellular metabolism, cell cycle, and protein synthesis than in developmental and transcription-associated processes [26]. It has been proposed that the transcription regulatory mechanism that controls ES cell fate can be divided into three modules: core, Polycomb, and Myc [27]. These three regulatory units are functionally separable; therefore, the overall ES cell transcription network is composed of distinct units. In ES cells, the Polycomb module was inactive but the core and Myc modules were upregulated, whereas in cancer cells the Myc module was active but the core unit that underlies the ES cell fate was not overexpressed [1, 27]. These findings suggest that similarities in gene expression signature of ES cells and cancer cells can be a result of the prevalent contribution of Myc regulatory network rather than that of an ES-cell specific network [1].

## Signalling pathways in cancerogenesis and acquisition of pluripotency

### Wnt/ $\beta$ -catenin signalling

The Wnt signalling pathway is implicated in a wide range of cell behaviours that occur throughout development. It plays a vital role in cell proliferation, cell movement, establishment of tissue polarity, cell fate decisions, as well as in stem cell maintenance [28]. The Wnt pathway has two distinct signalling branches: the canonical Wnt pathway that is characterised by stabilisation and accumulation of  $\beta$ -catenin, which then translocates to the nucleus and participates in a transcriptome regulation; and the noncanonical pathway that is  $\beta$ -catenin-independent [28, 29]. The canonical branch of the Wnt pathway has been shown to share molecular targets involved in regulation of self-renewal in the context of both stem cells and cancer [29, 30]. The unquestionable role of Wnt signalling in embryogenesis has been supported by its contribution in the maintenance of pluripotency in mouse and human ESCs [31–33] as well as in the self-renewal of adult stem cells in multiple types of tissues [34]. Wnt signal enhances the effect of LIF in maintenance of the self-renewal of mouse ES cells [32] and upregulates Stat3 thus helping to inhibit the ES cell differentiation even in the absence of LIF [35]. Furthermore, studies of a terminal component of canonical Wnt pathway, Tcf3, revealed that this factor co-occupies promoter regions throughout the genome associated with ESC-specific transcription factors such as Oct3/4 and Nanog [36]. Paracrine and autocrine Wnt signals also inhibit the differentiation to EpiSCs, so they prevent the transition from naïve to primed pluripotency [37]. Additionally,  $\beta$ -catenin regulates the expression of the telomerase subunit TERT through interaction with Klf4 and Wnt target gene c-Myc, uncovering the next link between stem cells and oncogenic potential [38]. Taking into consideration the fact that signalling pathways involved in ES cell self-renewal and those that contribute to somatic cell reprogramming often overlap, the role of Wnt pathway

in induced pluripotency was expected to be predictable. However, there are still some contradictions that make it unclear [39]. It has been shown that  $\beta$ -catenin might promote reprogramming of fibroblasts to pluripotency [3]. These data were supported by the fact that reprogramming can be triggered by accumulation of  $\beta$ -catenin in a dose-dependent manner, and activation of Wnt pathway noticeably enhances the ability of ES cells to reprogram somatic cells by fusion [40]. Further studies shed light on the biphasic effect of Wnt pathway in reprogramming. It has been suggested that Wnt signalling has an inhibitory role in the early stage of dedifferentiation but stimulates the process of induced pluripotency in its late stage. These changes are also accompanied by the requirement of different transcriptional effectors from among Tcf1, Lef1, Tcf3, and Tcf4 [41]. Very recent work has confirmed the fact that  $\beta$ -catenin is crucial for reprogramming because it stimulates the endogenous pluripotent gene expression. However, this effect is transient and  $\beta$ -catenin activation occurs only at the initial stage of reprogramming and is no longer required for pluripotent stem cell maintenance [42].

#### Hedgehog signalling

The Hedgehog (Hh) pathway is a major mediator of many fundamental processes regulating development, mainly through the control of cell fate, proliferation, survival, and differentiation [43, 44]. Aberrant Hh pathway activity is associated with aetiology of basal cell carcinoma and a subset of medulloblastoma [45]. A variety of other human cancers such as pancreas, lung, prostate, breast, brain, and gastrointestinal cancers could also be dependent on this pathway [44, 45]. Hedgehog signalling is often involved in the stimulation of cancer stem cell growth and promotion of an embryonic stem cell-like gene expression signature [46]. Therefore, it has a critical impact on tumour growth, survival, recurrence, and metastasis in many types of human cancer [47]. It has been discovered that activity of Gli, a central player in Hh pathway, is enhanced by loss of tumour suppressors, including p53 and PTEN, and by several oncogenic proteins, such as Ras, Myc, and Akt [47, 48]. Gli also upregulates the expression of Nanog by binding to its cis-regulatory sequences. Additionally, loss of p53, a key event promoting cell stemness and oncogenesis, leads to the activation of Hh signalling and consequently contributes to further Nanog upregulation [49]. Activators of Hh pathway in combination with Oct3/4 have been described to be capable of iPS generation from mouse embryonic and adult fibroblasts, indicating that they can replace Sox2, c-Myc, and Klf4 in reprogramming process [50].

#### Notch signalling

The Notch signalling pathway is evolutionarily conserved and plays a critical pleiotropic role in the proliferation, self-renewal, and differentiation of many distinct progenitor cell and stem cell types [51]. It acts differentially in a tissue- and dose-dependent manner. As an example, Notch can both promote and suppress the proliferation of mammary gland epithelial cells depending on its

activity level. Additionally, Notch activation can promote both tumour suppression and oncogenesis, depending on the cell lineage, even within the same tissue. Such completely opposite biological effects have been described in several solid tumours including breast, prostate, lung, and oral squamous cell carcinoma [52]. Recent studies revealed that Notch signalling is an essential regulator of pluripotency and self-renewal of iPS cells. It activates ROCK implicated in keratinocyte differentiation leading to impaired self-renewal of human induced pluripotent stem cells and cellular differentiation [53]. Furthermore, signalling through Notch pathway is a major obstacle in an early stage of dedifferentiation of both mouse and human keratinocytes into iPS cells. Finally, inhibition of Notch enables production of human iPS cells without Klf4 and c-Myc by suppressing p21 in a p53-independent manner [51].

#### Dysregulation of p53 pathway in cancer formation and reprogramming

The p53 transcription factor, encoded by the human gene *TP53*, is a key tumour suppressor and regulator of genetic stability. It plays a critical role in cell cycle arrest, DNA repair, programmed cell death, senescence, and differentiation. The activation or repression of differentiation by p53 is dependent on the cell type and cell fate and acts through control of cell cycle and apoptosis as well as through direct transcriptional regulation [54]. A poorly differentiated phenotype has been shown to be associated with the most aggressive human tumours and occurs frequently as a result of ES-like signature [2]. Reprogramming induced by a set of Yamanaka factors also represents a clear example of dedifferentiation process starting from terminally differentiated cells such as fibroblasts and finally reaching the pluripotent state [54]. It has been reported that p53 serves as a potent barrier to somatic cell reprogramming and dramatically reduces the efficiency of dedifferentiation. Therefore, to improve the reprogramming capacity, many groups have been evaluating the effect of p53 signalling disruption by deleting or silencing the expression of genes involved in this pathway or expressing a mutated version of p53 [55, 56]. Lower p53 level profoundly facilitates the reprogramming process, but it also leads to generation of iPS cells with chromosomal abnormalities and genome instability [56]. Additionally, mutant-p53-expressing cells exhibit higher potential to initiate malignant tumour formation than cells expressing wild-type p53 [57]. Therefore, there seems to be a striking commonality between improved reprogramming process and increased predisposition to cancer formation in the absence of p53. Here, we examine recent findings to evaluate the mechanisms of action of p53 involved in maintaining genomic integrity and regulating mesenchymal-to-epithelial transition, which are critical in both tumorigenesis and reprogramming.

#### p53-mediated DNA damage response

Genomic instability is a major characteristic of most cancers, which probably develops as a combined effect of DNA damage and failure in DNA damage response (DDR)

[58]. In response to various abnormalities, such as telomere attrition, high level of reactive oxygen species (ROS), or oncogene-induced unscheduled replication, DNA damage response is activated. It is coordinated by cell-cycle checkpoint kinases, including ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related), which orchestrate p53-dependent repair pathways. Germline and somatic mutations in components of this checkpoint machinery constrain DNA damage repair enabling cells with genomic defects to proceed through the cell cycle intact, increasing the risk of mutagenesis and predisposing to cancer formation [58].

A p53-dependent DNA damage response is also a key modulator of reprogramming as it prevents the acquisition of the pluripotent state of cells with various types of DNA damage, such as DNA repair defects, dysfunctional telomeres, or damage caused by exogenous agents. In cells with alterations in DNA structure, the process of dedifferentiation is usually terminated in its initial stage by p53-mediated activation of senescence genes, such as Cdkn1a, and also by inhibition of ES cell-enriched genes, such as Oct3/4, Sox2, Myc, and Esrrb, and activation of differentiation-associated genes [59].

#### The role of p53 in regulation of epithelial-mesenchymal transition

Changes between epithelial and mesenchymal states, defined as epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET), significantly regulate cellular plasticity. They are hallmarks of embryonic development and tumour progression. The term EMT refers to a process by which polarised cells lose their ability of cell-cell adhesion and gain the mesenchymal phenotype characterised by mobility, increased resistance to apoptosis, and the ability to leave the primary tumour site and migrate to distant sites. Therefore, both EMT and MET have pivotal roles in tumorigenesis: EMT contributes to invasion, tumour dissemination, and development of resistance to commonly used therapies; MET, in a reverse process to EMT, is associated with formation of distant metastases [60].

Interestingly, recent work has suggested that p53 restricts MET by inhibition of Klf4-dependent activation of epithelial transcriptional genes [54]. In addition, the repressive effect on the transcription of epithelial genes has been observed as early as one day after infection of cells with ectopic reprogramming factors, indicating that p53-mediated inhibitory effect on MET is not a result of its ability to modulate proliferation, senescence, cell cycle arrest, or apoptosis. These data also provided a mechanistic insight into the oncosuppressive role of p53 as it influences the genome-wide inhibition of Klf4-transcriptional program and can even restrict the oncogenic potential of Klf4.

Additionally, it has been suggested that p53 modulates changes between epithelial and mesenchymal states by regulation of miRNA. For instance, p53-dependent activation of miRNA-34 serves to antagonize Snail1, a transcriptional repressor which is linked to cancer cell EMT process, as well as to inhibit Snail1 regulatory molecules such as  $\beta$ -catenin,

LEF1, and Axin2, which are commonly known to be involved in Wnt signalling pathway [61]. Interestingly, miRNA-34 and p21 are cooperative regulators of somatic reprogramming and act downstream of p53 [62]. It has been demonstrated that enhanced activity of miR-34 leads to repression of reprogramming factors including Nanog, Sox2, and n-Myc, consequently inhibiting the process of acquisition of pluripotency. p53 also plays a role in regulation of EMT through transcriptional activation of other miRNA, such as miRNA-200c, which indirectly modulates the expression of E-cadherin, a known epithelial cell marker [63]. miRNA-200c was shown to inhibit ZEB1/2, which is a transcriptional repressor of E-cadherin; therefore, it acts as a p53-dependent factor involved in maintaining epithelial character and preventing development of stem cell properties.

#### Conclusions

In this review we discussed the latest findings in the area of biological parallelisms between induced pluripotency and oncogenesis. Through the large effort of researchers around the world, the molecular mechanisms of cellular stemness have been evaluated and light has been shed on the understanding of tumour formation as a process of dedifferentiation and acquisition of stem cell-like features. This concept has provided the starting point of new therapeutic approaches in which disruption of common signalling pathways involved in both normal and pathological dedifferentiation could have potential value in the treatment of cancer. However, there are still some unresolved aspects, like differences between normal and tumoural reprogramming, which have to be precisely understood in order to develop rational and effective therapies.

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**Address for correspondence****Marta Klimczak**

Laboratory of Gene Therapy  
Department of Cancer Immunology  
Greater Poland Cancer Centre  
Garbary 15  
61-866 Poznan, Poland  
e-mail: m.klimczak01@gmail.com