Chapter 1

The Role of an NFκB-STAT3 Signaling Axis in Regulating the Induction and Maintenance of the Pluripotent State

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1. Introduction

Induced pluripotent stem cells (iPSC) are generated by reprogramming differentiated somatic cells to a pluripotent cell state that highly resembles embryonic stem cells (ESC) [1]. Fully reprogrammed iPSC can differentiate into any adult cell type [2-6]. Takahashi and Yamanaka generated the first iPSC in 2006 by transfecting fibroblasts with four defined factors: SOX2, OCT4, KLF4, c-MYC (SOKM; also referred to as Yamanaka factors) [7]. The clinical use of iPSC offers great potential for regenerative medicine as any cell type can be generated from true pluripotent cells [8-10]. However, human clinical iPSC applications are currently limited by inefficient methods of reprogramming that often generate incompletely reprogrammed pluripotent states that harbor potentially cancerous epigenetic signatures, and possess limited or skewed differentiation capacities [11-13]. Many standard iPSC lines do not fully resemble pluripotent ESC, and often retain an epigenetic memory of their cell of origin [14, 15]. Such incompletely reprogrammed iPSC also display limited differentiation potential to all three germ layers (e.g., endoderm, ectoderm, mesoderm) [16, 17].

To avoid integrating retroviral constructs that may carry mutagenic risks, many non-viral methods have been described for hiPSC derivation [18, 19]. For example, one successful approach is to transiently express reprogramming factors with EBNA1-based episomal vectors [20-22]. It was initially intuitive to reprogram skin fibroblasts due to their easy accessibility. However, standard episomal reprogramming in fibroblasts occurs at even lower efficiencies (< 0.001-0.1%) than reprogramming with retroviral vectors (0.1%–1%) [23-25]. Subsequent studies revealed that various cell types possess differential receptiveness for being reprogrammed to pluripotency [26-30]. One highly accessible human donor source is blood, which has been demonstrated to reprogram with significantly greater efficiency than fibroblasts [4, 20, 31-33].

The innate immune system possesses highly flexible cell types that are able to adapt quickly to various pathogens by eliciting defense responses that protect the host [34-36]. Innate immune cells derived from the myeloid lineage (eg, monocyte-macrophage, dendritic cells, neutrophils) are able to reactivate some unique features of pluripotent stem cells that may give them greater flexibility for being reprogrammed to a pluripotent cell state than other differentiated cells [37]. Additionally, the differentiation state of the cell seems to be of critical importance for its reprogramming efficiency [38].

Our group established a reprogramming method that solves many of the technical caveats cited above (Figure 1). We have generated high-fidelity human iPSC (hiPSC) from stromal-primed (sp) myeloid progenitors [20]. This system can reprogram >50% of episome-expressing myeloid cells to high-quality hiPSC characterized by minimal retention of hematopoietic-specific epigenetic memory and a molecular signature that is indistinguishable from bona fide human ESC (hESC). The use of bone marrow-, peripheral-or cord blood (CB)-derived myeloid progenitor cells instead of fibroblasts, and a brief priming step on human bone marrow stromal cells / mesenchymal stem cells (MSC) appeared to be critical for this augmented reprogramming efficiency. In this system, $CD34^+$ - enriched cord blood cells (CB) are expanded with the growth factors (GF) FLT3L (FMS-like tyrosine kinase 3 ligand), SCF (stem cell factor) and TPO (thrombopoietin) for 3 days, subsequently nucleofected with non-integrating episomes expressing the Yamanaka factors (4F, SOX2, OCT4, KLF4, c-MYC), and then co-cultured on irradiated MSC for an additional 3 days. Cells are then harvested, and passaged onto MEF (mouse embryonic fibroblasts), and hiPSC are generated via standard methods and culture medium. The initial population of enriched $CD34^+$ CB progenitors quickly differentiates to myeloid and monocytic cells in this system, and reprogrammed cells arise from $CD34^-$ myeloid cells. The first iPSC colonies appear around day 10, and stable mature iPSC colonies can be established after ~21-25 days. The episomal constructs are partitioned after relatively few cell divisions (e.g., 2-9 passages) to generate high quality non-integrated hiPSC.

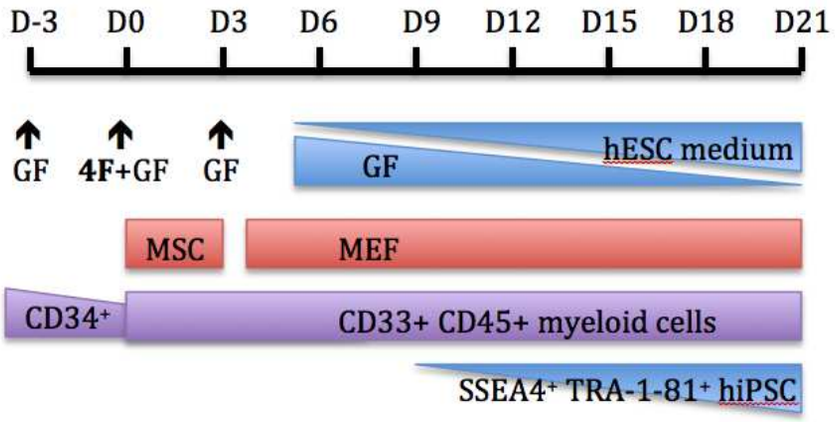

Figure 1. Schema of the stromal-primed myeloid reprogramming protocol for the generation of high quality human iPSC. 4F: four Yamanaka factors, GF: hematopoietic growth factors.

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A proteomics and bioinformatics analysis of this reprogramming system implicated significant activation of MSC-induced inflammatory TLR-NFκB and STAT3 signaling [20]. A combination of cell contact-dependent and soluble factors mediate these effects. A recent study similarly implicated inflammatory TLR3 signaling as a novel trigger for enhanced fibroblast reprogramming, albeit at much lesser efficiencies than observed in our myeloid reprogramming system. TLR3 signaling leads to epigenetic modifications that favor an open chromatin state, which increases cell plasticity and the induction of pluripotency [39]. Lee *et al.* termed this novel link between inflammatory pathways and cell reprogramming 'Transflammation' [40].

In this chapter we will discuss hypotheses why inflammation-activated myeloid cells may be highly receptive to factor-mediated reprogramming. Specifically, we will explore the role of the NFκB-STAT3 signaling axis in mediating the unique susceptibility of myeloid cells to high-quality human iPSC derivation.

2. Overview of the canonical and non-canonical NFκB pathway

Multipotent myeloid progenitors are derived from hematopoietic stem cells and differentiate to monocytes macrophages, dendritic cells, and granulocytes, which elicit the initial innate immune response toward pathogens [41]. NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a central transcription factor that regulates these innate immune responses during microbial infections [42-44]. The NFκB system belongs to a group of early-acting transcription factors that are present in the cytoplasm in an inactive state but can be quickly activated by multiple inflammatory stimuli [45, 46].

2.1. The canonical NFκB signaling pathway

The NFκB family consists of 5 members; p65 (RelA), p50 and c-Rel are involved in canonical signaling, and p52 and RelB are involved in non-canonical signaling. Canonical NFκB signaling is characterized by activation of the IκB kinase complex (IKK), which contains two kinases, IKK1/α and IKK2/β along with a non-catalytic subunit called IKKγ (NEMO) [47, 48]. Unstimulated NFκB is sequestered in the cytoplasm by IκBα protein. In contrast, activation of the IKK complex (e.g., by TLRs) leads to IKKβ-mediated serine phosphorylation of IκBα triggering its proteasome-mediated degradation and its dissociation from NFκB [49, 50]. This activates the p65:p50 dimer through p65 phosphorylation and leads to NFκB translocation into the nucleus where it induces target gene expression. Subsequent acetylation keeps p65 in the nucleus [51]. This can be reverted by HDAC3 (histone deacetylase 3)-induced deacetylation of p65, which increases the affinity of NFκB proteins for IκBα and nuclear export [52, 53]. Canonical NFκB signaling is a fast and transient process that regulates complex inflammatory processes that includes the initial pro-inflammatory phase, the induction of apoptosis, and even tumorigenesis [54]. It can be activated by toll-like receptors (TLR), which recognize characteristic pathogenic molecules to activate innate immune responses [55-57].

2.2. The non-canonical NFκB signaling pathway

Non-canonical NFκB signaling is stimulated via the NFκB-inducing kinase (NIK), which leads to phosphorylation of the p100 precursor protein and generation of the p52:RelB dimer that translocates to the nucleus to activate gene transcription. This pathway is uniquely dependent on steady state levels of *NIK* expression, which are controlled under normal conditions through TRAF3-directed ubiquitination and proteasomal degradation. Non-canonical NFκB signaling is slow but persistent and requires de novo NIK protein synthesis and NIK stabilization [58]. It is activated by receptors that belong to the TNFR (tumor necrosis factor receptor) superfamily like BAFF (B-cell-activating factor), CD40 or lymphotoxin β-receptor (LTβR) [59-62].

The common feature of these receptors is the possession of a TRAF-binding motif, which recruits TRAF members (e.g., TRAF2 and TRAF3) during ligand ligation [63, 64]. Receptor recruitment of TRAF members triggers their degradation, and leads to NIK activation and p100 processing [65]. Additionally, BAFF is an important component of pluripotency-supporting growth media for the culture of ESC and a regulator of B-cell maturation [66]. It predominantly activates non-canonical NFκB signaling due to its possession of an atypical TRAF-binding sequence, which interacts only with TRAF3 but not with TRAF2 [67]. TRAF3 degradation is sufficient to trigger non-canonical NFκB signaling, whereby activation of the canonical NFκB pathway requires TRAF2 recruitment [68].

2.3. CD40 stimulates both NFκB pathway components

Another receptor associated with NFκB signaling is CD40, which is expressed on various cell types including B cells and monocytes. The CD40 receptor interacts with its ligand CD40L, which is primarily expressed on activated T cells. This signaling is majorly involved in B-cell activation, dendritic cell maturation, antigen presentation and acts as a co-stimulatory pathway of T-cells [69]. Upon ligation by CD40L, CD40 targets both the canonical and non-canonical NFκB pathways via proteolysis of TRAF2 and TRAF3 [70-72]. Non-canonical NFκB signaling regulates hematopoietic stem cell self-renewal via regulating their interactions with the microenvironment [73]. The deregulation of non-canonical hematopoietic NFκB signaling is associated with auto-immunity, inflammation and lymphoid malignancies [58, 74].

2.4. NFκB subunit functions

A third NFκB signaling pathway is activated following response to DNA damage that results in IκB degradation independent of IKK. This results in dimerization of free NFκB subunits that are mobilized similarly to canonical NFκB signaling [47]. Unlike RelA, RelB, and c-Rel, the p50 and p52 NFκB subunits do not contain transactivation domains in their C-terminus. Nevertheless, the p50 and p52 NFκB members play critical roles in modulating the specificity of NFκB functions and form heterodimers with RelA, RelB, or c-Rel [75]. Cell contact-dependent signals are crucial during immune responses and can be mediated through NFκB signaling [76]. This can be augmented by co-stimulatory signals like CD40 or CD28 that directly bind to NFκB proteins like p65 [77-81].

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3. Functional role of NFκB signaling in stem cells

3.1. Differential roles of canonical and non-canonical NFκB signaling in embryonic stem cells

TLR activation is not only important for mediating innate immune responses, but also for stem cell differentiation. For example, hESC are characterized by the expression of pluripotency genes and markers such as OCT4, NANOG, alkaline phosphatase (AP) and telomerase [82-86]. NFκB signaling has been demonstrated to be crucial for maintaining ESC pluripotency and viability, and drives lineage-specific differentiation [87, 88]. A balance of canonical and non-canonical NFκB signaling regulates these opposing functions; non-canonical pathway signaling maintains hESC pluripotency, and canonical pathway signaling regulates hESC viability and differentiation [89, 90]. For example, non-canonical NFκB signaling has to be silenced during cell differentiation, which allows this pathway to act like a switch between hESC self-renewal and differentiation. RelB positively regulates several key pluripotency markers and represses lineage markers by direct binding to their regulatory units. RelB down-regulation reduces the expression of pluripotency genes like *SOX2* and induces differentiation-associated genes like *BRACHYURY* (mesodermal marker), *CDX2* (trophoectodermal marker) and *GATA6* (endodermal marker) [89].

3.2. Canonical NFκB signaling in hematopoietic stem cells

RelB/p52 signaling also positively regulates hematopoietic stem-progenitor cell (HSPC) self-renewal in response to cytokines (e.g., TPO and SCF) and maintains osteoblast niches and the bone marrow stromal cell population. It negatively regulates HSPC lineage commitment through cytokine down-regulation in the bone marrow microenvironment, although it is able to direct early HSC commitment to the myeloid lineage [73, 91].

Canonical p65 signaling also regulates hematopoietic stem cell functions and lineage commitment by controlling key factors involved in hematopoietic cell fate [92-94]. Canonical NFκB signaling is positively regulated by Notch1, which facilitates nuclear retention of NFκB proteins and promotes self-renewal [95-98]. FGF2 (fibroblast growth factor 2) is important for hESC self-renewal and preserves the long-term repopulating ability of HSPC through NFκB activation [99-102]. Deletion of p65, p52 and RelB dramatically decreases HSC differentiation, function and leads to extramedullary hematopoiesis [103]. NFκB pathway components and FGF4 are highly expressed in $CD34^+$HSPC from cord blood, where they regulate clonogenicity. Nuclear p65 can be detected in 90% CB-derived $CD34^+$ cells but only in 50% BM-derived $CD34^+$ cells [104]. The important role of NFκB in regulating myeloid cell lineage development has been most potently revealed via genetic deletion of IKKβ, IκBα, and RelB, which resulted in granulocytosis, splenomegaly and impaired immune responses [73, 103].

3.3. Canonical NFκB signaling during ESC differentiation

Canonical NFκB signaling is very low in the undifferentiated pluripotent state, where it maintains hESC viability. However, it strongly increases during lineage-specific differentia-

tion of pluripotent stem cells. p65 binds to the regulatory regions of similar differentiation genes as RelB with opposing effects on their activation or silencing. It regulates cell proliferation by direct binding to the CYCLIN D1 promoter [89]. There are different levels of inhibiting canonical NFκB signaling: first, p65 translational repression by the microRNA cluster miR-290 to maintain low p65 protein amounts and second, the inhibition of translated p65 by physical interaction with NANOG. Similarly, *OCT4* expression is reversely correlated with canonical NFκB signaling [105]. In contrast to most observations in mouse ESC, NFκB probably plays a more important role in the maintenance of human ESC pluripotency [106]. Finally, active TLRs are expressed on embryonic, hematopoietic and mesenchymal stem cells (MSC), thus implicating their roles in a variety of stem cell types [107-110].

4. Role of NFκB signaling during reprogramming to pluripotency

Undifferentiated human iPSC have elevated NFκB activities, which play important roles in maintaining *OCT4* and *NANOG* expression in pluripotent hiPSC [111]. Innate immune TLR signaling was recently shown to enhance nuclear reprogramming probably through the induction of an open chromatin state, and global changes of epigenetic modifiers [39]. This normally increases cell plasticity in response to a pathogen, but may also enhance the induction of pluripotency, transdifferentiation and even malignant transformation [112-116].

The EBNA (Epstein-Barr virus nuclear antigen) is a virus-derived protein that is not only a critical component of episomal reprogramming vectors, where it mediates extra-chromosomal self-replication, but it is also known to activate several TLRs [117-119]. These include TLR3, which is known to augment reprogramming efficiencies through the activation of inflammatory pathways [39, 120]. TLR3 recognizes double-stranded RNA from retroviruses and signals through TRAF6 and NFκB [121-123]. The TLR3 agonist poly I:C was shown to have the same effect as retroviral particles in enhancing Yamanaka factor-induced iPSC production. TLR3 causes widespread changes in the expression of epigenetic modifiers and facilitates nuclear reprogramming by inducing an open chromatin state through down-regulation of histone deacetylases (HDACs) and H3K4 (histone H3 at lysine 4) trimethylations [38, 39, 124]. These epigenetic modifications mark transcriptionally active genes, whereas the H3K9me3 (Histone H3 at lysine 9) modification marks transcriptionally silenced genes [125, 126]. Histone deacetylation is generally associated with a closed chromatin state and HDAC inhibitors were shown to enhance nuclear reprogramming [127, 128]. Histone acetylation favors an open chromatin state, and is maintained by proteins containing histone acetyltransferase (HAT) domains, such as p300 and CBP [129, 130]. Interestingly, p300/CBP is able to interact with NFκB [131, 132]. RelB directly interacts with the methyltransferase G9a to mediate gene silencing of differentiation genes [133]. Epigenetic changes that allow an open chromatin state are crucial for giving the Yamanaka factors access to promoter regions necessary for the induction of pluripotency. Epigenetic chromatin modifications by TLRs are normally involved in the expression of host defense genes during infections [134-136]. This capability can be deployed to enable nuclear reprogramming as TLR3 was shown to change the methylation status of the *Oct4* and *Sox2* promoters. Interestingly, changes in these methylation marks were

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not observed with TLR3 activation alone but only in the presence of the reprogramming factors. Although TLR3 by itself promotes an open chromatin configuration, the reprogramming proteins are likely necessary to direct the epigenetic modifiers to the appropriate promoter sequences [137]. Lee *et al.* described the potential of inflammatory pathways to facilitate the induction of pluripotency as 'transflammation' [40, 138].

5. Overview of the JAK/STAT pathway

The JAK/STAT pathway (Janus kinase/signal transducer and activator of transcription) integrates a complex network of exterior signals into the cell, and can be activated by a variety of ligands and their receptors [139]. These receptors are associated with a JAK tyrosine kinase at their cytoplasmic domain. The JAK family consists of the four members JAK1, JAK2, JAK3 and TYK2 [140, 141]. Many cytokines and growth factors signal through this pathway to regulate immune responses, cell proliferation, differentiation and apoptosis [142-146]. Ligand binding induces the multimerization of gp130 receptor subunits, which brings two JAKs close to each other inducing trans-phosphorylation. Such activated JAKs phosphorylate their receptor at the C-terminus and the transcription factor STAT at tyrosine residues. This allows STAT dimerization and their nuclear translocation to induce target gene transcription. [147, 148] STAT3 acetylation is critical for stable dimer formation and DNA binding [149]. From the 7 mammalian STATs, STAT3 and STAT5 are expressed in many cell types, are activated by a plethora of cytokines and growth factors, and integrate complex biological signals [150, 151]. The other STAT proteins mainly play specific roles in the immune response to bacterial and viral infections. STAT3 is an acute phase protein with important functions during immediate immune reactions [152-154]. STAT3 can be recruited by receptor tyrosine kinases that harbor a common STAT3 binding motif in their cytoplasmic domain (e.g., GCSF (granulocyte colony-stimulating factor), LIF (leukemia inhibitory factor), EGF (epidermal growth factor), PDGF (platelet-derived growth factor), interferons (IFNγ) and interleukins (IL-6, IL-10)) [155-158]. Many cytokines signal through IL-10/STAT3 to achieve an immunosuppressive function or anti-apoptotic effect [159, 160]. IL-10 is also required during terminal differentiation of immunoglobulins [161]. STAT3 can be phosphorylated at tyrosine or serine residues. The phosphorylation site can play distinct roles in the regulation of downstream gene transcription [162]. Stat3-deficient mice die during early embryogenesis due to Stat3 requirement for the self-renewal of ESC [163].

Negative feedback regulation of the JAK/STAT circuitry is mediated by the SOCS family of target genes (suppressors of cytokine signaling) in a way that activated STAT induces SOCS transcription [164, 165]. SOCS proteins can bind to phosphorylated JAKs as a pseudo-substrate to inhibit JAK kinase activity and turn off the pathway [166, 167]. SOCS are negative regulators of the immune response [168, 169]. A small peptide antagonist of SOCS1 was shown to bind to the activation loop of JAK2 leading to constitutive STAT activation and TLR3 induction. This boosts the immune system to exert broad antiviral activities [170]. The JAK/STAT pathway also interacts with many other signaling pathways in a complex manner to regulate cell homeostasis and immune reactions [149, 171].

6. Functional role of the JAK/STAT pathway in stem cells

6.1. Stat3 maintains naïve pluripotency in mouse embryonic stem cells

ESC pluripotency is regulated by transcriptional networks that maintain self-renewal and inhibit differentiation [172-174]. Stat3 and Myc are necessary to maintain mouse ESC (mESC) self-renewal and bind to many ESC-enriched genes [175]. Their target genes include pluripotency-related transcription factors, polycomb group repressive proteins, and histone modifiers [176, 177]. The transcription factor Stat3 is a key pluripotency factor required for ESC self-renewal [178, 179]. Mouse ESC require LIF-Stat3 (leukemia inhibitory factor) and Bmp4 (bone morphogenic protein 4) to remain pluripotent in *in vitro* cultures, whereas human ESC require FGF2/MAPK (fibroblast growth factor / mitogen-activated protein kinase) and TGFβ/Activin/Nodal (transforming growth factor β) [180-183]. Nevertheless, the core circuitry of pluripotency is conserved among species and includes OCT4, SOX2 and NANOG [174].

6.2. The LIF-IL6-STAT3 circuitry

LIF belongs to the IL-6 family of cytokines and acts in parallel through the Jak/Stat3 and PI3K/Akt (Phosphatidylinositide 3-kinase) pathways to maintain *Oct4, Sox2* and *Nanog* expression via Kruppel-like factor 4 (Klf4) and T-box factor 3 [184, 185]. Lif and IL-6 are necessary for STAT3 phosphorylation mediated by Jak1 [186]. Stat3 phosphorylation positively regulates *Klf4* and *Nanog* transcripts and facilitates Lif-dependent maintenance of pluripotency in a signaling loop [106]. Stat3 directly binds to genomic sites of *Oct4* and *Nanog*, regulates the Oct4-Nanog circuitry and is necessary to maintain the self-renewal and pluripotency of mESC [187-189]. Overexpression of *Stat3* maintains mESC self-renewal even in the absence of Lif [190]. Withdrawal of LIF up-regulates the NFκB pathway and results in ESC differentiation as well as STAT3 disruption [191-193]. The interleukin 6 (IL-6) response element (IRE) is activated by STAT3, vice versa IL-6 stimulation leads to STAT3 phosphorylation and transactivation of IRE- containing promoters providing a positively regulated STAT3-IL6 loop. STAT3 directly associates with c-Jun and c-Fos in response to IL-6 [194]. c-Jun and c-Fos are DNA binding proteins and components of the AP-1 (activation protein-1) transcription factor complex [195]. AP-1 can be activated by TLR2/4, IL-10 or STAT3 to regulate inflammatory responses or drive keratinocyte differentiation in interplay with STAT3 and c-MYC [196]. Tlr2 also plays an important role in the maintenance of mESC [107]. STAT3 is important to tune appropriate amounts of AP-1 proteins required for proper differentiation. DNA binding sites for both *AP-1* and *STAT3* have been found in many gene promoters [194, 197]. It is important to note that c-Jun is able to capture or release the NuRD (nucleosome remodeling and deacetylation) repressor complex, an important epigenetic modulator of gene silencing [198, 199]. STAT3 is able to bind to bivalent histone modifications enabling a quick switch between the activation of pluripotency genes during ESC maintenance and their inhibition during cell differentiation [193].

6.3. STAT3 signaling in immune cells

STAT3 also has complex functions during hematopoietic development, immune regulation, cell growth, and leukemic transformation [200-202]. It is critically important for the survival and differentiation of lymphocytes and myeloid progenitors [171]. STAT3 signaling can be

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activated in a cell contact-dependent way, which is distinct from its cytokine activation. Co-cultures of MSC (human mesenchymal stem cells) and APC (antigen-presenting cell) increase STAT3 signaling in both cell types in a cell contact-dependent way, which mediates the immune-modulatory effects of MSC to block APC maturation and induce T-cell tolerance [203]. MSC are high-proliferative non-hematopoietic stem cells with the ability to differentiate into multiple mesenchymal lineages [204-206]. They accumulate in tumor environments in response to NFκB signaling and produce cytokines [207]. MSCs are FDA-approved for the treatment of severe acute GVHD, due to their immunomodulatory properties [208]. STAT3 phosphorylation is induced by cell-cell contacts and inhibited in postconfluent cells that consequently become apoptotic. Therefore, STAT3 may represent a molecular junction that allows cell proliferation or growth arrest depending on the state of the cell. Increased STAT3 activity may promote cell survival during cell confluency [209].

6.4. Cell contact-dependent STAT3 signaling during cell transformation

Constitutive STAT3 activation can by itself result in cellular transformation [210-214]. For example, contact-dependent STAT3 activation is known to play a promoting role in the interactions between tumor cells and their environment [215-218]. Cell transformation and the induction of pluripotency may share very similar signaling processes, and it is possible that STAT3 may represent a common axis [219, 220]. During early tumor development, certain cells have to acquire stem cell-like features that allow them to self-renew (tumor-initiating cells) and to produce cell progeny (tumor bulk) [221-224]. These tumor-initiating cells are very difficult to eradicate during chemotherapies and often re-establish the tumor seen as clinical relapse [225-227]. Tumor-initiating cells display strong inflammatory gene signatures with elevated IL6-STAT3-NFκB signaling to sustain their self-renewal [228-231]. A better understanding of the mechanism by which STAT3 and NFκB regulates the acquisition of pluripotency and self-renewal might also give us crucial insight about tumor development, and may lead to future novel therapies [171, 232].

7. The role of STAT3 signaling during reprogramming

7.1. STAT3 is a master reprogramming factor

Activation of Stat3 is a limiting factor for the induction of pluripotency, and its over-expression eliminates the requirement for additional factors to establish pluripotency [233]. These key properties have positioned Stat3 signaling as one of the master reprogramming factors that dominantly instructs naïve pluripotency [175]. Elevated Stat3 activity overcomes the pre-iPSC reprogramming block and enhances the establishment of pluripotency induced by SOKM [234]. Stat3 and Klf4 co-occupy genomic sites of *Oct4, Sox2* and *Nanog*. Klf4 and c-Myc are downstream targets of Stat3 signaling and part of the transcriptional network governing pluripotency. The Stat3 effect is combinatorial with other reprogramming factors, which implies that additional targets of Stat3 play a pivotal role [235].

7.2. STAT3 is an epigenetic regulator

Stat3 activation regulates major epigenetic events that induce an open-chromatin state during late-stage reprogramming to establish pluripotency [236-238]. For example, Stat3 signaling stimulates DNA methylations to silence lineage commitment genes and facilitates DNA demethylations to activate pluripotency-related genes [106, 239, 240]. Other chromatin modifications include histone acetylation and deacetylation, which are catalyzed by enzymes with histone acetyltransferase (HAT) or histone deacetylase (HDAC) activities. Histone acetylation is associated with an open chromatin state that allows active gene transcription. HDAC inhibitors are known to significantly improve the efficiency of iPSC generation by allowing promoter accessibility [128, 241, 242]. STAT3 suppresses HDAC expression and repressive chromatin regulators to establish an open-chromatin structure giving full access to transcriptional machineries. The key pluripotency factor Nanog cooperates with Stat3 to maintain ESC pluripotency [173]. Interestingly, HDAC inhibitors but not *NANOG* over-expression rescues complete reprogramming in the presence of STAT3 inhibition.

Finally, DNA demethylation is regulated in mammalian cells by Tet proteins (tet methylcytosine dioxygenase), which convert 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). Tet1 suppresses ESC differentiation and Tet1 knockdown leads to defects in ESC self-renewal. Tet1 up-regulation is positively regulated by Stat3 during the late-reprogramming stage [243-246].

8. Interactions between NFκB and STAT3 signaling

8.1. Synergistic NFκB and STAT3 signaling

The NFκB and STAT3 pathways are closely interconnected in regulating immune responses [247, 248]. STAT3 activation itself induces further STAT3 phosphorylation. Un-phosphorylated STAT3 that accumulates in the cell can bind to un-phosphorylated NFκB in competition with IκB. The resulting STAT3/NFκB dimer localizes to the nucleus to induce NFκB-dependent gene expression [249]. STAT3 associates with the p300/CBP (CREB-binding protein) co-activator enabling its histone acetyltranferase activity to open chromatin structures, which allows chromatin-modifying proteins to bind the DNA and activate gene transcription. [250, 251] Tyrosine-phosphorylated and acetylated STAT3 additionally binds to the NFκB precursor protein p100 and induces its processing to p52 by activation of IKKα. STAT3 then binds to the DNA-binding p52 complex to assist in the activation of target genes [252]. Both, the NFκB and STAT3 pathway synergize during terminal B-cell differentiation [253]. Phosho-p65/STAT3 dimers and phospho-STAT3/NFκB dimer complexes can bind to κB motifs. Also, phospho-STAT3 and phosho-p50 interact with each other. Soluble CD40L rapidly activates NFκB p65 and up-regulates IL10 receptors on the cell surface. This renders STAT3 more susceptible to IL-10 induced phosphorylation [161]. Macrophage activation is regulated by Toll-like receptors, JAK/STAT signaling and immunoreceptors that signal via ITAM motifs [254, 255]. These pathways have low activity levels under homeostatic conditions but are strongly activated during innate immune responses. ITAM-coupled receptors cooperate with TLRs in driving

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NFκB signaling and inflammation during infections, whereas extensive ITAM activation inhibits JAK/STAT signaling to limit the immune reaction [256, 257]. Pleiotropic cytokines like interferons and IL-6 regulate the balance of pro-and anti-inflammatory functions by activating variable levels of STAT1 and STAT3 [258].

8.2. NFκB and STAT3 synergies in stem cells

NFκB and STAT3 are also part of an important stem cell pathway axis [259, 260]. A functional link between NANOG, NFκB and LIF/STAT3 signaling was shown in the maintenance of pluripotency [228]. Non-canonical NFκB signaling is activated by STAT3 through activation of IKKα and p100 processing [58]. Conversely, STAT3 inhibits TLR-induced canonical NFκB activity probably through up-regulated SOCS3. C-terminal binding of NANOG inhibits the pro-differentiation activities of canonical NFκB signaling and directly cooperates with STAT3 to maintain ESC pluripotency. NANOG and STAT3 bind to each other and synergistically activate STAT3-dependent promoters [106, 261].

The STAT3 pathway also interacts with many signaling pathways that are critically involved in the reprogramming process. For example, STAT3 signaling activates the MYC transcriptome and signals in loop with LIN28 [229]. LIN28 is expressed in undifferentiated hESC and is able to enhance the reprogramming efficiency of fibroblasts. It is down-regulated upon ESC differentiation [262-265]. Proto-oncogene tyrosine-protein kinase Src activation triggers an inflammatory response mediated by NFκB that directly activates *IL6* and *Lin28B* expression through a binding site in the first intron. IL6-mediated activation of STAT3 transcription is necessary for monocyte activation and tumorigenesis. IL6 itself further activates NFκB, thereby completing a positive NFκB-STAT3-IL6 feedback loop that links inflammation to cell transformation [229]. Constitutive STAT3 signaling maintains constitutive NFκB activity in tumors by inhibiting its nuclear export through p65 acetylation, although STAT3 signaling inhibits NFκB activation during normal immune responses [52].

9. The role of epigenetic regulators during the induction of pluripotency

9.1. The NuRD complex

A panoply of chromatin remodelers play active, regulatory roles during the reprogramming process [266, 267]. For example, the Mbd3/NuRD complex is an important epigenetic regulator that restricts the expression of key pluripotency genes [268]. MBD3 (Methyl-CpG-binding domain protein 3) is part of the NuRD (nucleosome remodeling and deacetylation) repressor complex, which mediates chromatin remodeling through histone deacetylation via HDAC1/2 and ATPase activities [269-271]. The NuRD complex interacts with methylated DNA to mediate heterochromatin formation and transcriptional silencing of ESC-specific genes. Whereas MBD2 recruits NuRD to methylated DNA, MBD3 fails to bind methylated DNA as it evolved from a methyl-CpG-binding domain to a protein–protein interaction module [272]. Mbd3 antagonizes the establishment of pluripotency and facilitates differentiation [273].

9.2. MBD3 suppression is a rate-limiting step in factor-mediated reprogramming

Recent evidence suggested that efficient reprogramming may require NuRD complex down-regulation [274]. The reprogramming factors OCT4, SOX2, KLF4 and MYC bind to MBD3, a critical component of the NURD complex. In the absence of MBD3, *SOKM* over-expression induces pluripotency with almost 100% efficiency [275]. Such reprogramming occurs within seven days in mouse cells. Once pluripotency is established, MBD3 does not appear to compromise its maintenance. The MBD3/NuRD repressor complex is probably the predominant molecular block that prevents the induction of ground-state pluripotency. Several reprogramming factors directly interact with the MBD3/NuRD complex to form a potent negative regulatory complex that restrains pluripotency gene reactivation. Thus, chromatin de-repression is of critical importance for the conversion of somatic cells into iPSC.

9.3. Bivalent histone modifications

Embryonic stem cells are not only able to maintain their undifferentiated state indefinitely, but also need to retain their ability to differentiate into various cell types [276]. The co-existence of these two features requires the combined action of signal transduction pathways, transcription factor networks, and epigenetic regulators [277]. Pluripotent gene expression has to be maintained in a way that it can be rapidly silenced upon receiving differentiation signals. The NuRD complex maintains this ESC flexibility by inducing variability in pluripotency factor expression that results in a low-expressing subpopulation of ESCs primed for differentiation [268, 278]. The control of gene expression by juxtaposition of antagonistic chromatin regulators is a common regulatory strategy in ESC, called bivalent histone modification [279, 280]. Individual promoters exhibit trimethylation of two different residues of histone H3: lysine 4 (H3K4me3) and lysine 27 (H3K27me3) [281, 282]. H3K27me3 is a repressive histone modification, whereas H3K4me3 is an activation-associated mark [283]. Both epigenetic markers have opposing effects and allow quick adjustments between ESC self-renewal and differentiation. Bivalent genes are generally transcriptionally silent in ESCs but are prone for rapid activation. MBD3 binding is enriched at bivalent genes characterized by 5hmC modifications. STAT3 binds to bivalent histone modifications and is able to switch between cellular pluripotency and differentiation [236, 284, 285].

9.4. MBD3 may prevent completion of the reprogramming process

MBD3 plays key roles in the biology of 5-hydroxy-methylcytosine (5hmC) [286]. 5hMC is an oxidation product of 5-methylcytosine (5mC) [287, 288]. MBD3 silences pluripotency genes like *Oct4* and *Nanog* through 5-hydroxy-methylation of their promoters. MBD3 binds to 5hmC in cooperation with Tet1 to regulate 5hmC-marked genes, but does not interact with 5mC. Mbd3 interaction with 5hmC recruits NuRD to its targets resulting in gene repression. Knockdown of the MBD3/NuRD complex affects the expression of 5hmC-marked genes [289]. Mbd3 acts upstream of Nanog and may block the transition from partially to fully reprogrammed iPSC by silencing Nanog. *Nanog* overexpression was dominant over Mbd3 knockdown in the induction of efficient reprogramming and is in general sufficient to maintain mESC pluripotency. Mbd3 depletion facilitates the transcription of *Oct4* and *Nanog* and leads to the

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generation of iPSC and chimeric mice even in the absence of Sox2 or c-Myc [290]. The depletion of Mbd3/NuRD does not replace Oct4 during iPSC formation as reprogramming did not occur with Klf4 and c-Myc alone. Mbd3-dependent silencing of pluripotency factors occurs during ESC differentiation. This involves NuRD-dependent deacetylation of H3K27 required for the binding of the polycomb repressive complex two. NuRD-dependent silencing of pluripotency genes prevents the de-differentiation of somatic cells. In the absence of Mbd3, NuRD disassembles, which lowers this epigenetic barrier and allows the activation of pluripotency genes. Drug-induced down-regulation of Mbd3/NuRD may greatly improve the efficiency and fidelity of reprogramming [291].

9.5. STAT3-MBD3 counteractions

Stat3 promotes the expression of self-renewal transcription factors and opposes NURD-mediated repression of several hundred target genes in ESCs. The opposing functions of Stat3 and NuRD maintain variability in the levels of key self-renewal transcription factors. Stat3, but not NuRD, is the rate-limiting factor for pluripotency gene expression. Self-renewing ESC face a barrier that prohibits differentiation. NuRD constrains this barrier within a range that can be overcome when self-renewal signals are withdrawn [268, 278, 292]. Mbd3/NuRD-mediated gene silencing is a critical determinant of lineage commitment in embryonic stem cells and allows cells to exhibit pluripotency and self-renewal. Mbd3-deficient ESC show

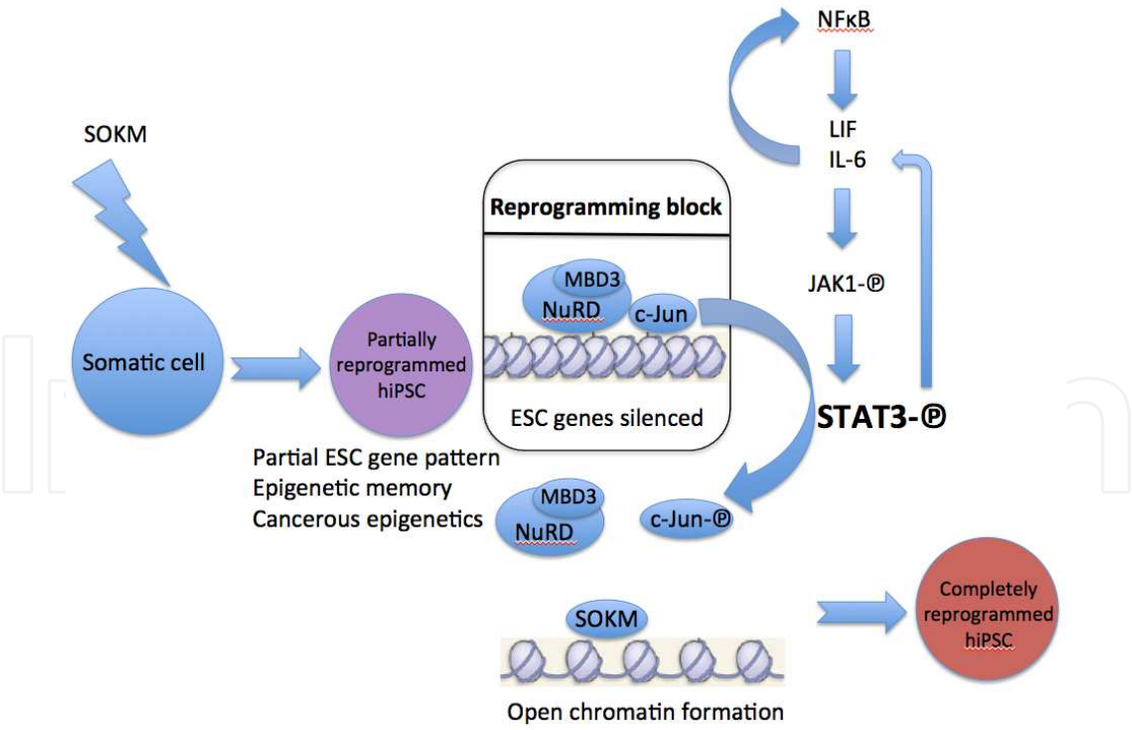

Figure 2. The master reprogramming factor STAT3 may overcome an unknown reprogramming block by inducing an open chromatin formation that facilitates the pluripotency factors SOKM to bind to ESC gene promoters. We hypothesize that upstream inflammatory signals mediated by NFκB signaling may facilitate STAT3 to de-repress the NuRD complex via c-Jun.

persistent self-renewal even in the absence of Lif. They are able to undergo the initial steps of differentiation, but their ability for lineage commitment is severely compromised. They fail to downregulate undifferentiated cell markers as well as upregulate differentiation markers [293]. Stat3 has many downstream effectors like the proto-oncogene c-Jun that is part of the AP-1 complex [194]. The transactivation domain of un-phosphorylated c-Jun recruits Mbd3/NuRD to AP-1 target genes to mediate gene repression. This repression is relieved by c-Jun N-terminal phosphorylation or Mbd3 depletion. Upon JNK activation, NuRD dissociates from c-Jun, which results in de-repression of target gene transcription. Termination of the JNK signal induces Mbd3/NuRD re-binding to un-phosphorylated c-Jun and cessation of target gene expression (Figure 2) [199].

10. Conclusions

In this review, we have discussed a potentially novel link between inflammatory pathways and efficient cell reprogramming. In this context, our group reported that bone marrow stromal-primed human myeloid cell progenitors are significantly more receptive to reprogramming stimuli than other cell types [20]. Myeloid cells harbor a unique epigenetic plasticity that allows them to quickly respond to a plethora of pathogens. They are innately equipped to transcriptionally and epigenetically activate key inflammatory pathways via an interconnected NFκB and STAT3 signaling machinery [294]. Both pathways act as epigenetic modifiers during normal inflammation stimulation, and both are also known to promote ESC pluripotency by inducing an open chromatin state that allows other transcription factors to regulate cell fates [236]. This epigenetic remodeling may prove crucial for efficient reprogramming, as well as the generation of high quality iPSC that resemble ESC without excessive epigenetic memory of their cell of origin [295].

Moreover, Stat3 is a master reprogramming factor that is able to dominantly instruct pluripotency, yet is also inherently interconnected with inflammatory signaling cascades (Figure 2). It binds to bivalent histone modifications, and allows rapid transitions between pluripotency and differentiation [193]. The NFκB pathway acts in synergy with downstream STAT3 signaling, whereby non-canonical NFκB signaling maintains pluripotency through epigenetic silencing of differentiation genes and canonical NFκB signaling promotes cell differentiation [296]. Finally, recent evidence suggests that strong chromatin repression by the NuRD complex is a key rate-limiting factor during reprogramming to pluripotency. This important complex may normally function to ensure that differentiated cells do not reactivate pluripotency genes, which might enable tumorigenesis [268]. We propose the hypothesis that NuRD complex silencing might be more easily achieved through the activation of inflammatory pathways in receptive cells such as those from the myeloid lineage.

It remains to be elucidated how all these processes are inter-regulated. It will be especially important to link reprogramming efficiency with the resulting quality of the pluripotent state achieved in hiPSC. We hypothesize that epigenetic plasticity in inflammatory cells that normally allows chromatin accessibility to the transcriptional machinery, could be manipu-

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lated to facilitate a complete erasure of the donor epigenetic memory during factor-mediated reprogramming. Additionally, preventing cancerous epigenetic patterns in iPSC via more accurate high-fidelity reprogramming methods will be the foundation for future clinical applications [13]. Finally, the basic understanding of pluripotency induction may also give us a better understanding of how tumor-initiating cells arise and how they can be eradicated to prevent tumor relapse, thus potentially opening a new era of cancer treatments.

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