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REVIEW PAPER OPEN ACCESS

General features and molecular mechanisms involved in self-renewal, pluripotency, differentiation, reprogramming of stem cells

Motahhareh Tourchi-Roudsari*

Department of Medical Biology and Genetic, Gaziantep University, Turkey

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Abstract

Stem cells have identified as biological cells that exist in nearly all multicellular organisms. They are unspecialized which have the ability to self-renew as well as to differentiate into defined cellular subtypes. Moreover, stem cells have ability to return function to damaged cells in the living organism. Moreover, they have the potential to replace or repair damaged cells and or disease tissues to treat a wide spectrum of diseases and injuries. Molecular mechanism that regulate self-renewal and pluripotency is not clear exactly yet. In this review, I will summarize different types of stem cells, some their properties, potency, and applications. Also, in this paper will be focused on currently known molecular mechanism involved in self-renewal, pluripotency, differentiation, and reprogramming of Stem Cells; such as three of signal transduction pathways involving, Transcription factors and their network, cell cycle regulators, microRNA, telomerase enzyme, chromatin, Epigenetic regulators, and chromatin modification in ES cells.

* **Corresponding Author:** Motahhareh Tourchi-Roudsari ✉ Tourchi90@gmail.com

Introduction

Stem cells (SC) are biological cells with ability of self-renewal and differentiation. They have the considerable potential to develop into many different cell types in the body during early life and growth (Hima Bindu and Srilatha, 2011). Stem cells are able to differentiate into specialized cell types and also they can give rise to any mature cell type is referred to as potency (Hima Bindu and Srilatha, 2011).In fact, potency of the stem cell into different cell type determines the differentiation potential. Growth of ES cells as a pluripotent population requires a balance between survival, proliferation, and self-renewal signals. In fact Precise mechanisms that regulate stem cell self-renewal, pluripotency, differentiation, and reprogramming is not clear exactly yet. Recently, many genetic regulators have been identified that may play key roles in the self-renewal and pluripotency process of human and mouse ES cells, including extracellular signaling factors, transcription factors, cell-cycle regulators, microRNA, genes implicated in chromosomal stability, epigenetic regulation, and DNA methylation (Liu *et al.,* 2007). Stem cell therapy is an amazing modern medical advancement that goes direct to the source of the problem and treats various disorders (Ramachandran and Yelledahalli, 2011). In fact, There is not any doubt that stem cells have the ability for treating many human afflictions such as ageing, cancer, diabetes, blindness and neurodegeneration (WattDriskell, 2010). During the recent years, many important progressions have obtained in stem cell research that lead to develop in stem cell biology with providing necessary informations on this field and suggest great promise for expanding new successful stem cell-based medical therapy, further investigations show to be important to translate the basic knowledge into clinical therapeutic applications in humans (Mimeault *et al.*, 2007). Stem cell research has the ability to result advancement of novel cellular and gene therapies that can be translated into efficient and secure clinical treatments of numerous genetic and degenerative disorders in human (Mimeault *et al.*, 2007).

In this review, I will summarize different types of stem cells, some their properties, potency, and applications. Also, in this paper will be focused on currently known molecular mechanisms involved in Self-Renewal, pluripotency, differentiation, reprogramming of Stem Cells; such as three of signal transduction pathways involving, Transcription factors and their network, cell cycle regulators, microRNA, telomerase enzyme, chromatin, Epigenetic regulators, and chromatin modification in ES cells.

Classifying stem cells to 4 main types

Embryonic stem (ES) cells are most potent that derived from the inner cell mass of blastocyst. They can differentiate into any cell types of the body that derived from any of the three germ layers. ES cells also have two important properties: self-renewal and pluripotency (Kang *et al.*, 2010).

Adult stem (AS) cellshave been isolated from different tissue sources such as bone marrow, retina and skeletal muscle (Toma *et al.*, 2001).Moreover known as somatic stem cell and germline stem cells that producing gametes (BinduSrilatha, 2011). Most adult stem cells have a linage-restricted potential and they can proliferate cells inhabiting in their specific cell niche within tissues. More adult stem cells are multipotent, however pluripotent adult stem cells are rare and can be isolated from number of tissues like umbilical cord blood (BinduSrilatha, 2011).

Cancer Stem (CS) cellsare a subpopulation of tumor cells that have ability of self-renewal and differentiation just like normal stem cells. Indeed, Stem cells are able to be malignant transformation responsible as target cells; moreover disorder of stem cell self-renewal pathway can lead to tumor formation. In addition to the self-renewal ability and differentiation, other similarities have been reported between normal and cancer stem cells. For example, telomerase enzymes expresses in both normal and cancer stem cells and therefore having long lifespan (infinite replication potential) is other similar property in both of the stem cells (Dean *et al.*, 2005).

Also, expression OCT4 (Octamer-binding transcription factor 4) that is a homeodomain transcription factor of the POU family, is other similarity between them. The studies show that OCT4 have expressed in pluripotent embryonic stem and germ cells(Burdon *et al.*, 2002; Rosner *et al.*, 1990). Because of some properties both types of stem cells resistant to apoptosis and radiotherapy (Bao *et al.*, 2006; Diehn *et al.*, 2009; RaguzYagüe, 2008).

Induce Pluripotent Stem (ips) cellare pluripotent stem cells that produce from mouse and human somatic cells by reprogramming, introduction of genes (overexpression of transcription factors including Oct4 (also known as Pou5f1), Klf4, Sox2, and c-Myc (OKSM) or Oct4, Sox2, Nanog, and Lin28 (N. Liu *et al.*, 2007) that reprogram the cell and transform it into a cell that has similar ability with embryonic stem cells and therefore posses properties of self-renew and differentiation into all three of the germ layers. DNA damage can cause by reprogramming that leads to responses such as cell cycle arrest and senescence (Na *et al.*, 2010). Only a few cells can successfully pass this barrier and become iPS cells. It is important to say there is a relationship between deletion of key components of DNA damage machinery (p53 and p21) with generation rate of iPS cells. In fact, remove of p53 and p21 is associated with an increase in reprogramming efficiency (Banito *et al.*, 2009; H. Hong *et al.*, 2009; Kawamura *et al.*, 2009; Li *et al.*, 2009; Marión *et al.*, 2009; Utikal *et al.*, 2009; Zhao *et al.*, 2008). Vitamin C supplementation can cooperate with epigenetic regulators to increase reprogramming efficiency via decreasing p53-induced cell senescence (Esteban *et al.*, 2010). Although, production iPS cells in high rate via inappropriate decreasing of DNA damage pathway is not safe (Na *et al.*, 2010).

Stem Cell potential

Stem cells have a potential to differentiate based on their capacity into specialized cell types and also give rise into any mature cell type. In fact, potency of the stem cell into different cell type determines the differentiation potential.

Totipotent stem cells have ability for producing all of the differentiated cells in an organism. Morula cells that have been separated from earlier stage of the embryo are totipotent. Spores and Zygotes are examples of totipotent cells. In fact, they give rise to an entire functional organism.

Pluripotent stem cells are capable to differentiate into any of the three germ layers. Embryonic stem cells are caused as inner cell mass (ICM) cells in a blastocyst inside. In fact, they be able to give rise to all tissue types, however, cannot produce an entire organism, including placenta.

Multipotent stem cells are able to differentiate into a limited cell numbers within a tissue type. Multipotent blood stem cell as a hematopoietic cell is a good example that can differentiate to several types of blood cells like lymphocytes, monocytes, neutrophiles, etc., but not to other types of cells.

Oligopotent stem cells have capable of differentiation only into a few cells like lymphoid or myeloid stem cells. A lymphoid cell is able to differentiate to various blood cells like Band T cells but not to different blood cell type such as red blood cell.

Unipotent stem cells have capacity to differentiate only one cell type. Different between them and non-stem cells is that unipotent stem cells have capable of self-renewal.

Molecular mechanisms involved in self-renewal, pluripotency, and differentiation, reprogramming of ES cells

Three of Signal Transduction pathways involving

Signal transduction pathways have different and diverse roles in vertebrate development. The studies report cooperation between signal transduction pathways and transcription factors that can reprogram differentiated cells to a pluripotent state (Marson *et al.*, 2008)

Canonical Wnt pathway

The canonical Wnt pathway affects the proliferation, self-renewal, differentiation of both stem cells and progenitors during development. Also, it plays an important role in somatic cell reprogramming.

Some studies showed that wnt pathway can maintain pluripotency ability in both human and mouse ES cell as well as the self-renewal of undifferentiated adult stem cell in diverse tissues. Upregulated Wnt path way at any level make promotion in ES cell pluripotency and self-renewal via adding exogenous Wnt3A ligand, blocking GSK3 activity, overexpressing B-catenin or depleting TCF3 (Sokol, 2011).In fact, Wnt signaling is activated in ES cells and down-regulated in differentiated cells. Because, Wnt pathway that is activated by 6-bromoindirubin-3-oxime (BIO), inhibitor of glycogen synthase kinase-3 (GSK-3), can maintain expression of the ES cells specific markers and as a result be able to keep undifferentiated phenotype in ES cells(Sato *et al.*, 2004). Dysregulation of this pathway correlated to different cancers that cancer stem cells play important role in carcinogenesis. B-catenin interaction with reprogramming factors Klf4, Oct4, and Sox2 (OSK) increases pluripotency gene expression to promote somatic cell reprogramming. But, it is not needed for pluripotent stem cell maintenance. Wnt signaling pathway contain two different major subsets; canonical and non-canonical Wnt pathways. These two important molecular events downstream of Wnt signaling that cooperate in promoting ES cell pluripotency; one event is the stabilization and translocation of B-catenin into the nucleus and other one is inactivation of T cell factor3 (TCF3). Wnt/B-catenin signaling increases iPSCs induction at early stage of reprogramming by activation of the endogenous pluripotency network pathway. It is interesting to note that c-Myc expression also can make high reprogramming efficiencies like B-catenin. Unfortunately, iPSCs induced by c-Myc have more oncogenic/tumorigenic potential. In fact, c-Myc enhances the frequency of transformed cell during iPSCs production. In the reprogramming process, B-catenin represses endogenous c-Myc expression. Therefore, B-catenin may induce iPSCc with less tumorigenic potential. WNT3-WNT9B signaling plays important role in regulation of neural differentiation (Lee *et al.*, 2015). Switching pluripotent and differentiation control by WNT9B through noncanonical Rho/JNK signaling, while canonical WNT3/B-catenin signaling increases proliferation (Lee *et al.*, 2015). Also, WNT5A involves in promotion of cancer cell invasion (Shojima *et al.*, 2015). Wnt signaling and B-catenin stimulate expansion of stem cells and differentiation toward lineage committed cell types (Merrill, 2012).Generally the studies show that Wnt/B-catenin signaling has different roles and divergent effects in pluripotent stem cell self-renewal and somatic cell reprogramming.

Hedgehog Pathway

Hedgehog (Hh) intracellular signaling pathways has fundamental role in cell proliferation and differentiation during development. Nervous system, neurons and glia cells can be created from differentiation of mouse embryonic stem cells in vitro (Maye *et al.*, 2004). The studies show that mutated embryonic stem cell lines in components of the Hh signaling cascade cannot completely generate neurectoderm-containing embryoid bodies intact. In fact, the mutant cultures have defective capacity for differentiating into mature neurons and glia. Therefore Hedgehog (Hh) signaling is necessary for differentiation of embryonic stem cells into neurectoderm (Maye *et al.*, 2004). In mammals, there are three Hh family ligands: Sonic Hh, Indian Hh, and Desert Hh. SHH pathway is highly activated during differentiation and in contrast is minimally active in undifferentiated hES cells. Also, SHH signaling does not involved in maintain of pluripotency and proliferation (Wu *et al.*, 2010). Reports showed that PTCH1, Gli1, and Gli2 that are Hh signaling component have high-level expression in normal mammary stem/progenitor cells compared with differentiated cells (S. Liu *et al.*, 2006; Wu *et al.*, 2010). Moreover, the activated pathwayby Hh ligands increases the self-renewal and proliferation of mammary stem/progenitor cells as indicated by increased number and size of mammosphere respectively.

BMi-1, a polycomb gene that function as regulator of hematopoitic and neuronal stem cells self-renewal.Expression of Bmi-1 increases by activation of Hh signaling, and over expression and down-regulation of Bmi-1 has positive and negative effects on Hh signaling respectively, as over expressed Bmi-1 promotes self-renewal of mammary stem cell and proliferation(S. Liu *et al.*, 2006). Hh pathways and downstream transcription factor Bmi-1 play important role for regulating self-renewal of stem cell in normal mammary development (Fig. 1).

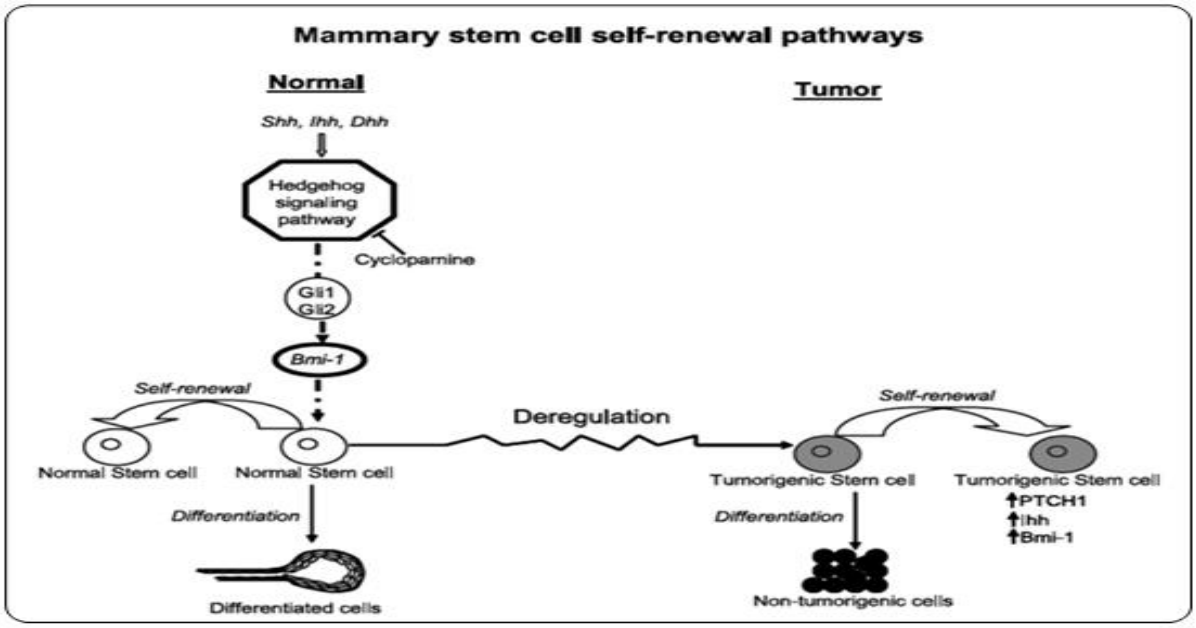

Fig. 1. Hypothetical model is shown self-renewal pathways of mammary stem cell in normal and cancer stem cells. Arrows show the activated pathways by ligands; cyclopamine acts as an inhibitor in hedgehog signaling pathway (S. Liu *et al.*, 2006).

Activation of Hh signaling and increased expression of Bmi-1 also reported in cancer stem cells. Infact, if deregulation of self-renewal pathways occur in normal cells, cancer stem cell population can be caused that then induce tumorigenesis. This study support from cancer stem cell hypothesis that demonstrate carcinogenesis results from deregulation these pathways (Fig. 1) (S. Liu *et al.*, 2006). Therefore, the studies proved that Hh signaling pathway and Bmi-1 have important role in the regulation of self-renewal of normal and malignant stem cell.

Notch signaling pathway

This pathway is a highly conserved cell signaling that plays substantial roles in cell fate determination during embryonic development and adult life (Yu *et al.*, 2008).

The studies show that Notch signaling inactive in undifferentiated hES cells in contrast; it is activated upon differentiation induction in hES cells; Because in undifferentiated hES cells, levels of Notch receptors and ligands are below the threshold of activation. The Notch signaling increases differentiation of human ES cells to produce the progeny in all three embryonic germ layers; ectoderm, mesoderm, and endoderm but not trophoblast cells. In fact, Notch signaling inhibits trophoblastic differentiation of hES cells (Yu *et al.*, 2008).Activation of Notch signaling pathway correlates with induction of protein expression OCT4 that lead to exist from the undifferentiated state and initiation of differentiation. Notch signaling plays important role in hES cell self-renewal. Although, there is not any compelling evidences based on that Notch pathway is involved in the self-renewal of mouse ES cells also (Yu *et al.*, 2008).

Transcription Factors and transcription network in ES cells

The four reprogramming factors (Oct4, Sox2, Klf4, and cMyc) have key and vital roles in early embryogenesis and ES cells (TakahashiYamanaka, 2006).The studies show that transcription factors Oct4, Sox2, Nonog, and etc, can involve and be necessary for ES cells self-renewal and differentiation. They are regulated by themselves and also signal transduction pathways. With activation of these genes, the self-renewal genes are activated that in contrast differentiated genes are repressed. As a result ES cells be able to maintain their pluripotency (N. Liu *et al.*, 2007). Oct4, Sox2, and Nanog have been identified that form an intrinsic core-regulatory circuit to keep pluripotent state of ES cells *in vitro* (N. Liu *et al.*, 2007). Nanog, sox2, and Oct4 are able to interact together to encode key differential and developmental transcription factors and in contrast are inactive in ES cells. Also, these three genes cooperate together to regulate transcriptionally active genes involved in pluripotency maintenance (Boyce *et al.*, 2005; Loh *et al.*, 2006). Oct4 interacts with Sox2 and forms complex to regulate downstream genes and *Oct4* and *Sox2* expression. Oct4/Sox2 complex also interact with Nanog as other target (Kuroda *et al.*, 2005; Rodda *et al.*, 2005). *Nanog* promoter has specific binding site for Oct4/Sox2 complex(N. Liu *et al.*, 2007). Oct4/Sox2 complex is essential for maintaining of necessary transcription factors expression in ES cells via autoregulatory and multicomponent loop network motifs (N. Liu *et al.*, 2007). C-Myc may involve in ES cells self-renewal (Miura *et al.*, 2004). The c-Myc overexpression is adequate for maintaining mouse ES cells in an undifferentiated state. In contrast, differentiation induces by blocking c-Myc expression (Cartwright *et al.*, 2005).

Oct4 (Octamer-binding transcription factor 4) also is known as Oct3, a protein in humans is encoded by the POU5F1 gene (Takeda *et al.*, 1992). Oct-4 is a homeodomain transcription factor of the POU family. It is extremely expressed in human and mouse ES cells, and when cells lose pluripotency and differentiate, its expression decreased (ChenDaley, 2008).

Lack of Oct4 leads to improper differentiation of ES cells into trophectoderm, while differentiation into primitive endoderm and mesoderm is caused due to overexpression of oct4 (Niwa, 2001; Yeom *et al.*, 1996). Oct4 and Nanog, two homeodomain transcription factors, were identified as the first proteins are necessary for both early embryo development and pluripotency maintenance in ES cells (ChenDaley, 2008).

Sox2,an HMG-family protein transcription factor , plays important role in maintaining undifferentiated embryonic stem cells self-renewal, and pluripotency. Sox2 forms a heterodimer complex with oct4 to regulate various genes in mouse ES cells. In addition to Sox2 and Oct4 in the enhancer element of target gene form a ternary complex together and regulate its expression as a binary complex. Sox2 is similar to Oct4 in expression pattern (N. Liu *et al.*, 2007).

Nanogis a transcription factor that is encoded by *NANOG* gene. It is necessary for maintaining the pluripotent cells of the inner cells mass and ES cells. Nanog expression is reported in pluripotent cells, and in contrast, differentiated cells are lacking of that (ChenDaley, 2008).Regulation of pluripotent state is one of major roles of Nanog (Chambers *et al.*, 2003; Mitsui *et al.*, 2003). Nanog disruption in ES cells leads to differentiation to endoderm lineages (ChenDaley, 2008). Nanog is able to activate Oct4 promoter (Pan *et al.*, 2006).

c-Myc/ Klf4;Kruppel-like factor 4 (KLF4) is known as a member of the KLF family of transcription factors and Myc (c-Myc) is a transcription factor that functions as a regulator gene. C-Myc/Klf4is necessary factors in somatic cell reprogramming (de-differentiation). C-Myc/Klf4 cooperate with other transcription factors like Oct4 and Sox2 to induce somatic cells to a more embryonic character. Unexpectedly, Nanog was unnecessary in the experiment (TakahashiYamanaka, 2006). These factors also are responsible for Induction of de-differentiation of somatic cells and following chromatin modification.

Chromatin modification that occurs as a result of these transcription factors, may play a key role in the reprogramming progress (TakahashiYamanaka, 2006)

Cell cycle regulators in ES cells

ES cells cell cycle has some specific features that the most important is that ES cells have a short cell cycle unlike somatic cells cycle; it is because of the short G1 phase as compared to somatic cells (Becker *et al.*, 2006; Stead *et al.*, 2002). ES cells response to DNA damage through apoptosis and differentiation instead of considering checkpoint between G1 phase and S phase after DNA damage. While, somatic cells arrest cell cycle in G1 phase to abolish DNA damage.The high level of DNA damage induces apoptosis in ES cells. Also, ES cells response to low levels of DNA damage through p53 to induce ES cells differentiation. P53 presents in ES cells and acts as a Nanog expression repressor in response to DNA damage (Lin *et al.*, 2005). Therefore, mechanisms involved in ES cells cycle are different with mechanisms involved in G1/S checkpoint in somatic cell cycle (chk1/chk2/Cdc25A and p53-p21) (Aladjem *et al.*, 1998; BartekLukas, 2001; Y. HongStambrook, 2004; Mailand *et al.*, 2000).

MicroRNA in ES cells

MicroRNA are a large family of small non-coding RNAs that comprises more than 200 known members in the mammalian genomes (N. Liu *et al.*, 2007). Unique set of microRNAs are specifically expressed in both human and mouse pluripotent ES cells, but microRNAs expression are down-regulated in differentiated embryonic bodies or in adult tissues (ChenDaley, 2008). microRNAs play a key role for both ES cell differentiation and maintaining pluripotency in ES cells. Also, suggesting microRNAs have a role in self-renewal of ES cells (N. Liu *et al.*, 2007). If one of essential factors for microRNA generation (for example, DGCR8, a RNA binding protein that is essential for microRNA processing as assists the RNase III enzyme Drosha) was knocked out in mouse ES cells, generated microRNA will be unmature (Y. Wang *et al.*, 2007).

Therefore, when induced to differentiate, DGCR8-deficient ES cells cannot fully down-regulate pluripotency markers and retain an ES cell morphology. Although, the data show that some of differentiation markers expressed and it can be a confirmation for specific role of microRNA in ES cell differentiation(Esteban *et al.*, 2010). microRNA may facilitate differentiation by down-regulation of pluripotency-associated genes (ChenDaley, 2008). microRNAs also play important role in reprogramming. Somatic cells express *Let-7* family microRNAs that these microRNAs are up-regulated upon ES cell differentiation (Pick *et al.*, 2009; RoushSlack, 2008; StefaniSlack, 2008; Urbach *et al.*, 2010). *Let-7*microRNAs are kept at low level by Lin 28, ES-cell-specific factor, via promoting *let-7* microRNA degredation(Heo *et al.*, 2008; Viswanathan *et al.*, 2008).*Lin28* overexpression abbreviates the cell cycle in monoclonal B cell and increases rate of iPS cell generation (Hanna *et al.*, 2009). Moreover, ES-cell-specific miRNA miR-294 enhances efficiency of iPS cell generation about 10-fold when present together with *Oct4, Sox2, Klf4* but not cMyc (Judson *et al.*, 2009). The studies show that miR-294 is a downstream target of *cMyc* (Judson *et al.*, 2009). Hence, microRNAs have significant roles in ES cells maintenance of pluripotency, self-renewal, differentiation, and reprogramming of ES cells.

Telomerase enzyme, chromatin, Epigenetic regulation and Chromatin modification in ES cells

Telomerase is the enzyme maintains length of telomeres, which act as the cap to protect the end of the chromosome, by addition of guanine-rich repetitive sequences to the 3' end of telomeres. Telomerase enzyme is active and essential for uninterrupted self-renewal in human and mouse ES cells (Kim *et al.*, 1994; Thomson *et al.*, 1998). Activation of telomerase enzyme is downregulated during ES cells differentiation(Miura *et al.*, 2004). Gene activity is specified via chromatin structure and interactions of chromatin-binding proteins. Some chromatin properties are different between ES cells and somatic cells, such as chromatin structure, nuclear architecture, chromatin dynamics, and histone modifications (Boyer *et al.*, 2006; MeshorerMisteli, 2006).

During induction of differentiation, the heterochromatin marker tri-methylated residue k9 of histone H3 (H3-triMeK9) is increased, and also global levels of acetylated histones H3 and H4 as a euchromatin marker is decresed (J. H. Lee *et al.*, 2004; MeshorerMisteli, 2006).ES cells chromatin is highly dynamic and more transcriptionally permissive than in differentiated cells. Moreover, pluripotent nuclei chromatin is in open conformation. In fact, they have an increased fraction of loosely bound or soluble architecture chromatin proteins such as core and linker histones (ChenDaley, 2008).Also, replication in pluripotent cells occurs earlier than differentiated cells.It is important to say that pluripotent cells have unexpectedly high level of acetylated H3K9 and methylated H3K4. However, these gene expression will be stop by H3K27 trimethylation in ES cells (Azuara *et al.*, 2006; Bernstein *et al.*, 2006; Boyer *et al.*, 2006). chromatin is subjected to different forms of epigenetic regulation that regulate activation of transcription in specific genomic regions, containing chromatin remodeling, histon modifications, histon variants, and DNA methylation. Good examples of this are H3K9 and H3K27 trimethylation that are associated with inactive regions of chromatin, while H3K4 trimethylation and H3/H4 acetylation correlate with active transcription (JenuweinAllis, 2001). pluripotency factors and epigenetic regulators are in cross-talk with one another to maintain pluripotency. Pluripotency factors such as Oct4, Sox2 and NANOG co-regulate genes encoding epigenetic control factors; for example, components of chromatin remodeling and histone modifying complexes, such as SMARCADI, MYS3 and SET(Boyer *et al.*, 2005). Moreover the studies show interaction of pluripotency factors , Nanog and Oct4, directly or indirectly with histon modifying enzymes and chromatin remodeling complexes, histone deacetylase NuRD (P66b and HDAC2), Polycomb group (YY1, Rnf2 and Rybp) and SW1/SNF chromatin remodeling (BAF155) complexes(J. Wang *et al.*, 2006). The genes of pluripotency factors are subjected to epigenetic regulation.

For example, histone demethylase gene, *Jmjd1a* that is downstream target of Oct4 positively regulate expression of pluripotency associated genes, Tcl1, Tcfcf2l1 and Zfp57via demethylating H3K9Me2 at the promoters (Loh *et al.*, 2006; Loh *et al.*, 2007). Polycomb group proteins (PcG) are essential for early developmental gene expression (Pasini *et al.*, 2004).

They are chromatin modification factors that play a key role in self-renewal and pluripotency of ES cells. PcG proteins are able to facilitate oligomerization, condensation of chromatin structure, and inhibition of chromatin remodeling activity(N. Liu *et al.*, 2007). Moreover, PcG proteins as part of an epigenetic cellular memory system regulate gene silencing through chromatin structure.

They also control dynamics and plasticity of gene regulation, particularly during differentiation via interacting with other components of the transcriptional apparatus (PreziosoOrlando, 2011) . Polycomb proteins comprise of at least two distinct repressor complexes, the Polycomb-repressive complexes 1 and 2 (PRC1 and PRC2). Reports prove over expression of some PcG proteins in variety of different tumors (Richly *et al.*, 2011). There are different mechanisms for gene silencing that DNA methylation is one. Silencing of certain genes by DNA methylation is essential for induction of differentiation of ES cells. Hypermethylation of Oct4 in promoter/enhancer region of differentiated cells is associated with gene silencing. In contrast, hypomethylation in ES cells allows cells express OC4 in high level and therefore stay in pluripotent state.

Applications of stem cells

The recent developments in basic and clinical research on different types of stem cells showed many possibilities for their potential therapeutic use in regenerative medicine and cancer therapies in humans (Mimeault *et al.*, 2007).

Stem cells have the potential to replace or repair damaged cells and or disease tissues to treata wide spectrum of diseases and injuries.

There is not any doubt that stem cells have the ability for treating many human afflictions such as ageing, cancer, diabetes, blindness and neurodegeneration (WattDriskell, 2010). The most application of stem cell is stem cell transplantation. Haemopoietic stem cell transplantation is the most well-known therapy and also this kind of treatment is currently available (Austin *et al.*, 2008; PerryLinch, 1996). Stem cells also are able to be used for studying disease. Obtaining the cells that are damage in the disease for more studying is not easy, as a result using stem cells as a model for disease process in the laboratory is very useful for better understand what goes wrong. Stem cells can be used as a resource for testing new medical treatments. Before clinical using new medications, they have to test to be ensure safety, therefore using stem cells as a resource for testing is other application as reduces need for animal testing. Moreover, other stem cells application is that stem cells can accelerate drug discovery, drug screening and toxicological evaluation.

Conclusion

The review paper is explained about 4 main types of stem cells, ES cells, AS cells, CS cells, and IPS cells. Also, Stem cells based on their potential into different cell types is divided to Totipotent, Pluripotent, Multipotent, Oligopotent, and Unipotent. The different molecular mechanisms involved stem cells such as signaling pathways, transcription factors, microRNA, epigenetic regulation, and chromatin modification that are reviewed in this paper. In addition to independent and key roles each of them in stem cells, they can also cooperative together for maintaining and causing a state in stem cells. In future, a wide range of diseases can be treated through technologies derived from stem cell research. Ultimately, understanding of the molecular mechanisms of stem cells exactly will be able to guide the way to a safe and new cell-based medicine.

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