

Stem Cells: Biology, Types, Polarity, and Asymmetric Cell Division: A Review

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Abstract

Applicability of stem cells in cell-based therapy and regenerative medicine provided hope for untreatable diseases; subsequently, stem cells bioengineering has become a promising scientific research topic. Different types of stem cells possess different characteristics; certain types are superior to others according to their advantages. Cell bias toward asymmetric division is the first step regarding tissue regeneration and homeostasis, and this event is stimulated by chemical and mechanical cues arising from the surrounding microenvironment. Inappropriate asymmetric cell division (ACD) consequently results in organ disrupt morphogenesis. Intracellular events including polar distribution of regulatory proteins and fate determinants are of significant importance to prepare cells toward asymmetric division. The assembly of polarity proteins on opposite sides of the cell would induce downstream signaling pathway, and this forms a fundamental mechanism to establish cell asymmetric division. This review addresses the current understanding regarding stem cells biology, niche-raised cues, and polarity of regularity proteins and fate determinants of ACD.

Keywords: Asymmetric cell division, stem cells, stem cells polarity

STEM CELLS BIOLOGY

Stem cells are defined as unspecialized cells that have the ability of potential self-renewal, giving rise to more stem cells having the same features and identity of the mother cell. They are also capable of differentiating into progenitors that will ultimately give rise to more specialized cells. This feature is defined as “stemness” or “potency”; by this mechanism, it will be possible to maintain stem cells pool and homeostasis and preserve regeneration of damaged tissues through life time.^[1]

Stem cells evolve in multicellular organisms with many conserved features between vertebrates and invertebrates. Stem cells are considered as prerequisites for multicellularity, coloniality, and regeneration.^[2] Mammals respond to organ damage through compensatory growth of remaining tissues via induction of precursors represented by resident stem cells proliferation or scarring. Bias toward certain process is decided by different factors including age, species, and presence of stem cells repertoire.^[3]

Stem cells are located in a specific matrix that saves them from depletion or superabundant proliferation. The

interaction between stem cells and their extracellular matrix is highly dynamic and necessary for the participation of stem cells in tissue renewal, maintenance, and repair.^[4]

Both chemical and mechanical cues from the extracellular matrix are combinatorially processed by stem cells through a variety of membrane-bound chemical- and mechanosensors, resulting in an intracellular signal transduction activation, and they subsequently control differentiation into phenotypes of various stem cells.^[5]

Chemical factors include soluble biological factors such as secretions of surrounding tissues including growth factors, cytokines, transcriptional factors, cell–cell regulators, and small molecules. In addition to the types of chemical factors, their dose and spatial distribution affect stem cell maintenance and differentiation.^[5]

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Physical signals include contact with neighboring cells or other surrounding molecules, stress, rigidity, topography, and electrical conductivity. The fate of stem cells is highly controlled by the elasticity of the matrix in which cells are cultured. The extracellular matrix is composed of different constituents, proteins, carbohydrates, and peptidoglycans. This architecture forms sheets in basal lamina rich in fibronectin and collagen fibers, and this nanotopographical feature of the extracellular matrix influences stem cells fate via cellular membrane mechanosensors.^[6]

Replenishment of damaged cells is unlimited as long as the organism is alive; however, the activity of stem cells depends on the organ itself, for instance, in bone marrow the cell division is continuous, whereas in pancreas stem cells division occurs under certain physiological conditions only.^[7] Neurogenesis mostly ends at the time of birth, but this process continuously and restrictedly occurs in two specialized areas in the adult brain, which are the ventricular-subventricular zone in the lateral ventricles and in the subgranular zone of the hippocampus.^[8]

STEM CELLS TYPES

Stem cells are classified as follows according to their origin.

1. Embryonic stem cells (ESCs)

These are the prototypical stem cells derived from the inner cell mass of the blastocyst that is formed 4–5 days following fertilization. They have the potency to differentiate all cell types of the three germ lines (endoderm, mesoderm, and ectoderm). The blastocyst has also an outer layer of cells called trophoblasts and will eventually form extra-embryonic supportive structures such as placenta and umbilical cord.^[9]

However, ethical issues, immunological rejection, and teratoma formation limit ESC therapeutic applications in regenerative medicine. Cells derived from the morula are considered as totipotent cells, and they possess the capability to differentiate into three germ layers and are derived from the supportive extra-embryonic structures.^[10]

2. Embryonic germ line cells

These are derived from the gonadal ridge (primordial germ cells that give rise to eggs and sperms in adults) from a 5-to-10-week-old embryo. They are pluripotent cells and significantly require feeder layer during their *in-vitro* growth.^[11]

3. Fetal stem cells

These are derived from the fetus body or the supportive extra-embryonic structures which are normally discarded after birth, such as umbilical cord and placenta. They are described as multipotent, since they have the potency to differentiate into limited types of cells.^[11]

4. Adult stem cells (ASCs)

These are found in a very low number and in a quiescent phase of all body tissues. They are called unipotent cells since they are capable of differentiating into a single phenotype of the tissue they are found in. Although ASCs are present in nearly all tissues, the most widely used ones are mesenchymal stem cells, which are generally derived from bone marrow and adipose tissues. The second most applicable ASCs are the hematopoietic stem cells.^[10]

5. Induced pluripotent stem cells (IPSCs)

These cells are produced by the epigenetic reprogramming of somatic cells into embryonic-like pluripotent state. This is achieved via the transient overexpression of certain genes that are normally expressed only in the pluripotent cells.^[9]

This revolutionary strategy has enabled to secure cells very close to the ESCs in a broad spectrum of features such as morphology, growth pattern, and high sensitivity to growth factors and signaling molecules. IPSCs resemble ESCs mainly in the criteria of unlimited self-renewal and differentiation to the three forms of primary germ lines. IPSCs are explored in the creation of chimeric animals via their injection into the blastocyst. This strategy will pave the way to bypass the ethical concerns routinely faced through ESC employment.^[11]

IPSCs are also similar to ESCs but with a disadvantage, in that they result in teratoma formation (tumor-disorganized structure containing cells representing the three germ lines) following injection given subcutaneously in immune-deficient mice. Teratoma formation mediated by IPSCs occurs in a more aggressive manner compared with ESCs, and this is represented by shortening the rate of latency significantly when compared with ESCs. *In-vivo* teratoma formation in immunocompromised mice is the gold standard assay to assure bona fide pluripotent stem cells.^[12]

It is of significant importance to reach the maximum standards for safe cell culturing and differentiation. The safe application of IPSCs requires the treatment of those cells with specific methodologies that guarantee the minimization of possibility of the mutating cell genome during *in-vitro* cultivation, thus minimizing the probability of malignant transformation after *in-vivo* injection^[13] [Figure 1].

Stem cells could be applied in cell-based therapy in different patterns, and it could be administered systemically or directly to the target organ where it will be differentiated into the desired cell type as a response to the surrounding milieu signaling. The second pattern involves administration of differentiated cells before being transplanted. The injections of pancreatic islet cells and cardiomyocytes that were formerly differentiated from

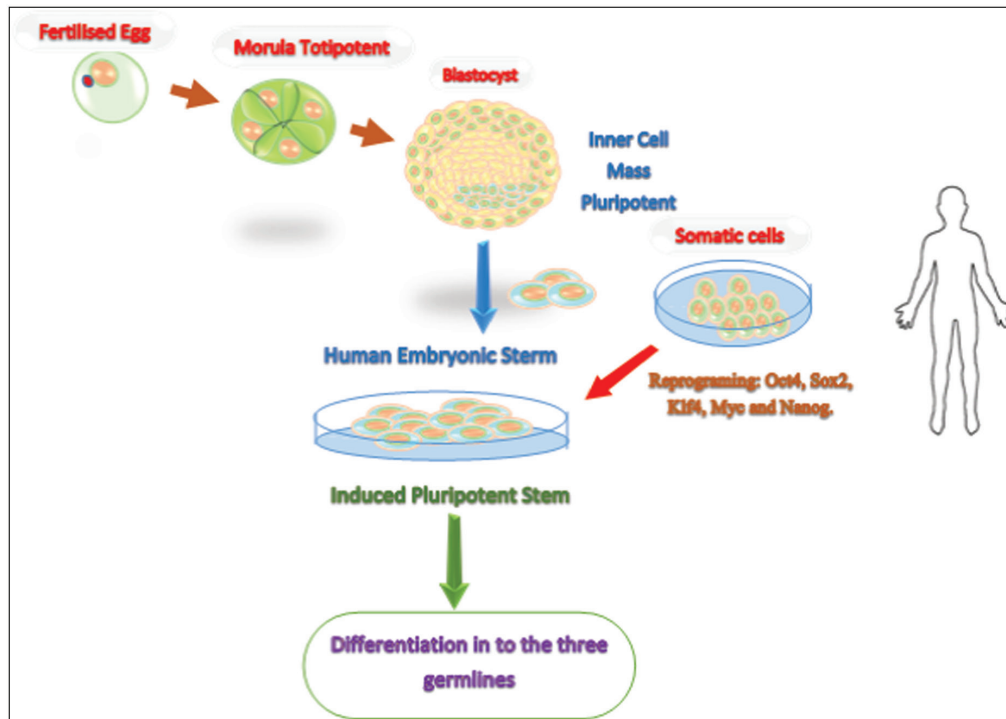


Figure 1: Stem cells types and origin

stem cells before being transplanted are used to treat diabetes and ischemic heart disease, respectively. The third pattern is through the stimulation of endogenous stem cells to promote tissue repair that could be accomplished through an injection of appropriate cocktail of cytokines, chemokines, growth factors, and chemical therapy. This cocktail is specifically designed to differentiate stem cells into the desired cell types.^[14]

STEM CELLS POLARITY AND ASYMMETRIC DIVISION ESTABLISHMENT

Cell polarity is an intrinsic property which refers to the spatial arrangement of cellular compartments such as organelles, cytoskeleton, and plasma membrane, which would ultimately be translated into variation in function, fate, and structure of cells.^[15]

There are two main types of cells division: symmetric cell division (SCD) that implies production of two identical daughter cells and ensures proliferation and population expansion of cells. The second type is the asymmetric cell division (ACD), which is a hallmark of stem cells and implies the generation of identical copies of stem cells simultaneously with differentiated progeny. ACD refers to the asymmetry in the fate of daughter cells, which either keeps their stemness identity or differentiates into their final identity. ACD ensures tissue homeostasis through the balance of stem cells renewal and differentiation. Stemness failure results in tumorigenesis and/or tissue degeneration.^[16]

ACD is achieved through a sequential coordinated process, with the aid of regulatory proteins and fate-determining factors.^[15]

Polarization is a critical process that precedes ACD. It occurs as a response to extracellular stimuli and leads to redistribution of intracellular components asymmetrically, such as polar distribution of organelles, mRNA, miRNA, regulatory proteins, and fate determinants at certain membrane regions. Centrosomes activity and positioning control organelles positioning and polarity. This temporal and spatial assembly is accompanied by proper mitotic spindle orientation in parallel to the polarity axis to ensure polar segregation of fate determinants into one daughter cell and subsequently ACD achievement.^[17,18]

Despite the increasing complexity along evolution, establishment and maintenance of polarity are mainly controlled by three master regulatory complexes, Par complex, Crumbs complex, and Scribble complex. The Par complex consists of PAR-3 (Bazooka)/PAR-6/atypical protein kinase (aPKC) proteins. The Crumbs complex consists of CRUMBS/protein associated with Lin71 (PALS1)/PALS1-associated tight junction protein (PATJ), and the Scribble complex consists of SCRIBBLE/*Drosophila* discs large tumor suppressor gene/lethal giant larva (LGL) proteins. They were first described in *Caenorhabditis elegans* and *Drosophila melanogaster* and found to be evolutionarily conserved in both vertebrates and invertebrates. All those complexes are crucial to the formation of apical junctions such as

tight junctions in mammalian epithelial cells, and among those complexes, the Par complex is the most conserved one throughout the animal kingdom.^[17,19]

The Par complex is the first regulatory protein to be asymmetrically assembled apically, controlling the apical assembly of Crumbs and the basolateral assembly of Scribble.^[20]

Upon entry into mitosis and to coordinate spindle orientation, the action of several serine/threonine protein kinases is required. For instance, Cdk-1 activation is important for mitosis entry, whereas its inhibition is essential for the anaphase onset.^[21]

Another enzyme, Polo-like kinase, controls spindle assembly and chromosome alignment, and its deficiency causes arrest in pro-metaphase. Aurora-A kinase activity is required for centrosome maturation and separation, thus important for regulating spindles assembly and stabilization. Aurora-B action is required for the metaphase checkpoint, for chromosome condensation by phosphorylation of histone H3, and for cytokinesis mitotic spindles orientation and stabilization^[22] [Figure 2].

Another evolutionary conserved tripartite regulatory complex consists of partner of Inscuteable (Pins), the vertebrate orthologous of which is Leu-Gly-Asn repeat-enriched protein (LGN); Mushroom body defective (Mud), the mammalian ortholog of which is the nuclear mitotic apparatus (NuMA); and the heterotrimeric G-protein subunit Gai which plays an important role in mitotic spindles orientation in both SCD and ACD.^[23]

Notch, which is a cell signaling pathway, plays a substantial role in multiple developmental processes in an

evolutionary conserved manner. This pathway is widely used in cell-cell communication triggering the pleiotropic effect, and its correct regulation allows efficient regulation of genes controlling cell fate decision.^[24] The notch pathway mediates tissue homeostasis and gene expression regulation and determines stem cells fate. In mammals, there are four types of NOTCH receptors, namely, from NOTCH-1 through NOTCH-4; it regulates embryonic development and is inhibited by the Numb protein. Notch ligands are members of the Delta/Serrate/LAG-2 family in *Drosophila*; there are two ligands Delta and Serrate, whereas in mammals they are named delta-like, Jagged ligands, and others.^[25]

Upon binding of any of the Notch ligands on the sending cells like DSL ligands to their specific receptors on the receiving cell, a subset of proteolytic cleavage cascades begins, gamma-secretase-mediated release and translocation of Notch intracellular domain (NICD) from its site on the cellular membrane to the nucleus, where it binds to the DNA-binding protein of the CSL family, which are transcriptional factors regulating the NOTCH pathway in both positive and negative manner, a fully functional transcriptional activator complex assembled with other co-activators to modify chromatin and induce target gene expression.^[24]

Mitotic spindle orientation is mediated by the microtubule-binding protein Mud. Mud is recruited apically by Pins and Gai, which in turn associate with Inscuteable and Par. Lgl phosphorylation by aPCK will facilitate localization of fate determinants at the opposite side of the Par complex, and then telophase involves recruitment of Kinesin (Khc)-37 and Discs-Large protein. Adaptor

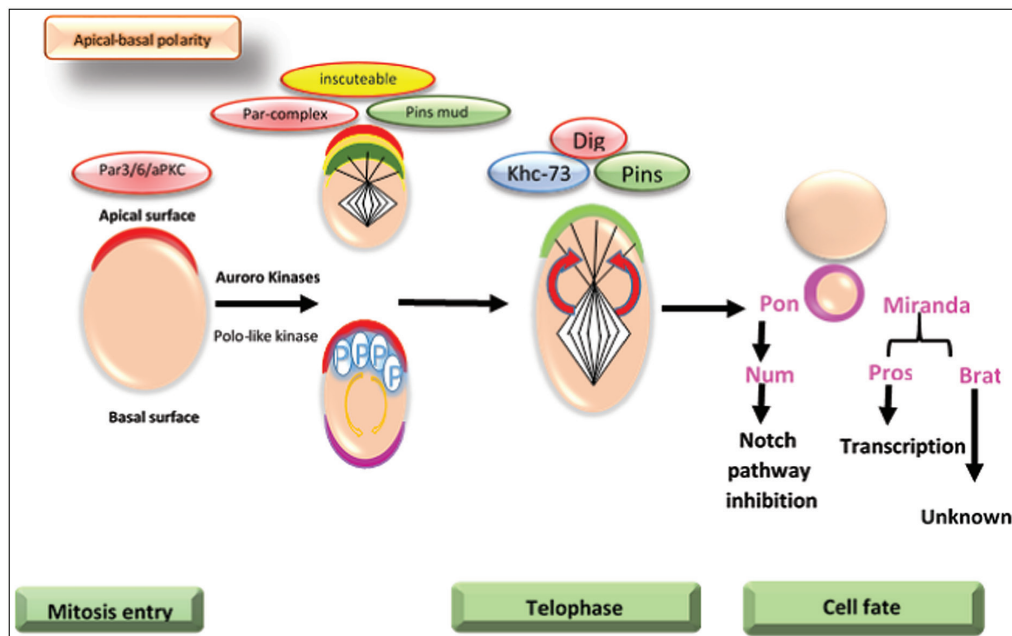


Figure 2: Stem cells undergo asymmetric cell division

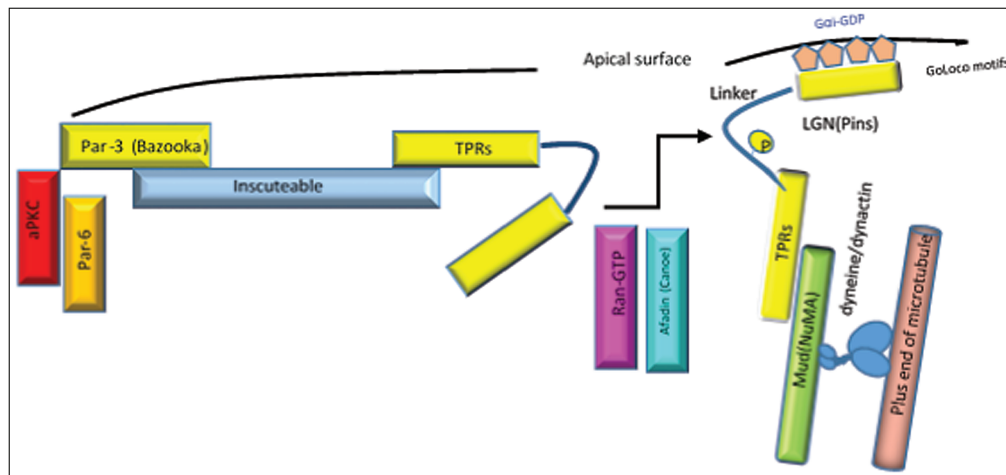


Figure 3: Regulatory proteins polarization

proteins Pon and Miranda facilitate the localization of fate determinants such as Numb, Pros, and Brat.^[15]

Pins acts as an adaptor protein linking the dynein and the cytoplasmic membrane by binding to the Mud via its N-terminal end and to the cell membrane-bound Gai via its C-terminal end. The Pins complex controls ACD by recruiting dynein to the cellular cortex where it captures astral microtubules that will reorient and pull the spindles in parallel to the polarity axis. Pins recruitment requires Inscuteable apical positioning which in turn requires (Par-3) Bazooka. Inscuteable recruits Pins and replaced by Mud that binds to the Pins N-terminal end. Both Canoe and Ran-GTP also bind to the Pins N-terminal end to cooperate in Mud recruitment^[23] [Figure 3].

Insc binds to the N-terminus of the Pins through three motifs at its C-terminus end, named GoLoco. Those motifs are unique in their ability to bind to the G- α subunit in their GDP-bound form. The Pins binds directly to the microtubule-binding protein Mud that will bind to the microtubules and enhance their polymerization.^[26]

GoLoco motifs allow the Pin/LGN to act as a guanine dissociation inhibition factor, thus facilitating the release of GDP from the Gai. This inhibiting activity is thought to positively regulate mitotic spindle orientation. The direction at which the cell divide is determined by the mitotic spindle orientation at the metaphase. This process is controlled via an evolutionary conserved machine that mediates pulling force on the astral microtubules.^[27]

Canoe, in vertebrates named Afadin, acts as an accessory factor to control spindle orientation by facilitating interaction between Pins and Mud, and it is thought to act as a downstream step from Pins localization.^[27]

CONCLUSION

Operationally, stemness is defined as cells capable of both continuous self-renewal and differentiation into

at least one phenotype. Stem cells maintenance in the undifferentiated form or its differentiation into certain phenotypes is dictated by chemical and physical signals from the extracellular matrix through sensors located on the stem cells surface that will subsequently activate downstream transcriptional pathway to specify cells identity. All multicellular organisms require the presence of molecular mechanisms to accomplish cell diversity for both embryonic development and tissue homeostasis. ACD is the conserved mechanism that will ensure this diversity through binary cell fate specification. Polarization is the mechanism that stem cells use to establish asymmetry and give rise to subcellular functional domains. The common theme in stem cells polarization establishment is the recruitment and local condensation of cellular components and organelles, and the purpose of this mechanism is to prepare cells to the next developmental step, i.e., differentiation.

Ethical consideration

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Conflicts of interest

Authors declare no conflict of interest.

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