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CANCER

# Molecular mechanisms of stem-cell identity and fate

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Stem cells are characterized by extensive self-renewal. Many have multi-lineage differentiation potential. These properties enable them to generate functional tissues during development and to regenerate these tissues following injury or degenerative processes. Stem-cell fate is regulated by the combination of extrinsic and intrinsic signals, many of which are poorly understood. An understanding of the molecular mechanisms that govern stem-cell fate and the identification of specific stem-cell markers is of fundamental significance in cell and developmental biology and has important biomedical applications. Cancer researchers have been particularly interested in stem cells as recent data have indicated that several tumour types, including germ-cell, breast, brain, haematopoietic and prostate tumours, are probably maintained by cancer stem cells. It is now the goal of several cancer research laboratories to identify definitive markers of tumour stem cells and to find therapeutic targets that will specifically eradicate these cells.

## A glossary for stem-cell biology*

**Cancer cell of origin**
Precancerous cell that gives rise to a cancer stem cell. May be a mutated stem cell, or a committed progenitor that has acquired self-renewal capacity through mutation.

**Cancer-initiating cell**
General term that encompasses both cancer cell of origin and cancer stem cell.

**Cancer stem cell**
Self-renewing cell responsible for sustaining a cancer and for producing differentiated progeny that form the bulk of the cancer. Cancer stem cells identified in leukaemias and certain solid tumours are critical therapeutic targets.

**Commitment**
Engaging in a programme leading to differentiation. For a stem cell, this means exit from self-renewal.

**Embryonic stem cell**
Pluripotent stem-cell lines derived from early embryos before formation of the tissue germ layers.

**Founder/ancestor/precursor cell**
General terms for cell without self-renewal ability that contributes to tissue formation. In some cases they generate tissue stem cells.

**Label-retaining cell**
Candidate for adult tissue stem cell because of slow division rate and/or immortal strand retention. Interpret with caution.

**Lineage priming**
Promiscuous expression in stem cells of genes associated with differentiation programmes.

**Niche**
Cellular microenvironment providing support and stimuli necessary to sustain self-renewal.

**Plasticity**
Unproven notion that tissue stem cells may broaden potency in response to physiological demands or insults.

**Potency**
The range of commitment options available to a cell.

**Totipotent**
Sufficient to form entire organism. Totipotency is seen in zygote and plant meristem cells; not demonstrated for any vertebrate stem cell.

**Pluripotent**
Able to form all the body's cell lineages, including germ cells, and some or even all extraembryonic cell types. Example: embryonic stem cells.

**Multipotent**
Can form multiple lineages that constitute an entire tissue or tissues. Example: haematopoietic stem cells.

**Oligopotent**
Able to form two or more lineages within a tissue. Example: a neural stem cell that can create a subset of neurons in the brain.

**Unipotent**
Forms a single lineage. Example: spermatogonial stem cells.

**Progenitor cell**
Generic term for any dividing cell with the capacity to differentiate. Includes putative stem cells in which self-renewal has not yet been demonstrated.

**Reprogramming**
Increase in potency. Occurs naturally in regenerative organisms (dedifferentiation). Induced experimentally in mammalian cells by nuclear transfer, cell fusion, genetic manipulation or *in vitro* culture.

**Self-renewal**
Cycles of division that repeatedly generate at least one daughter equivalent to the mother cell with latent capacity for differentiation. This is the defining property of stem cells.

**Stem cell**
A cell that can continuously produce unaltered daughters and also has the ability to produce daughter cells that have different, more restricted properties.

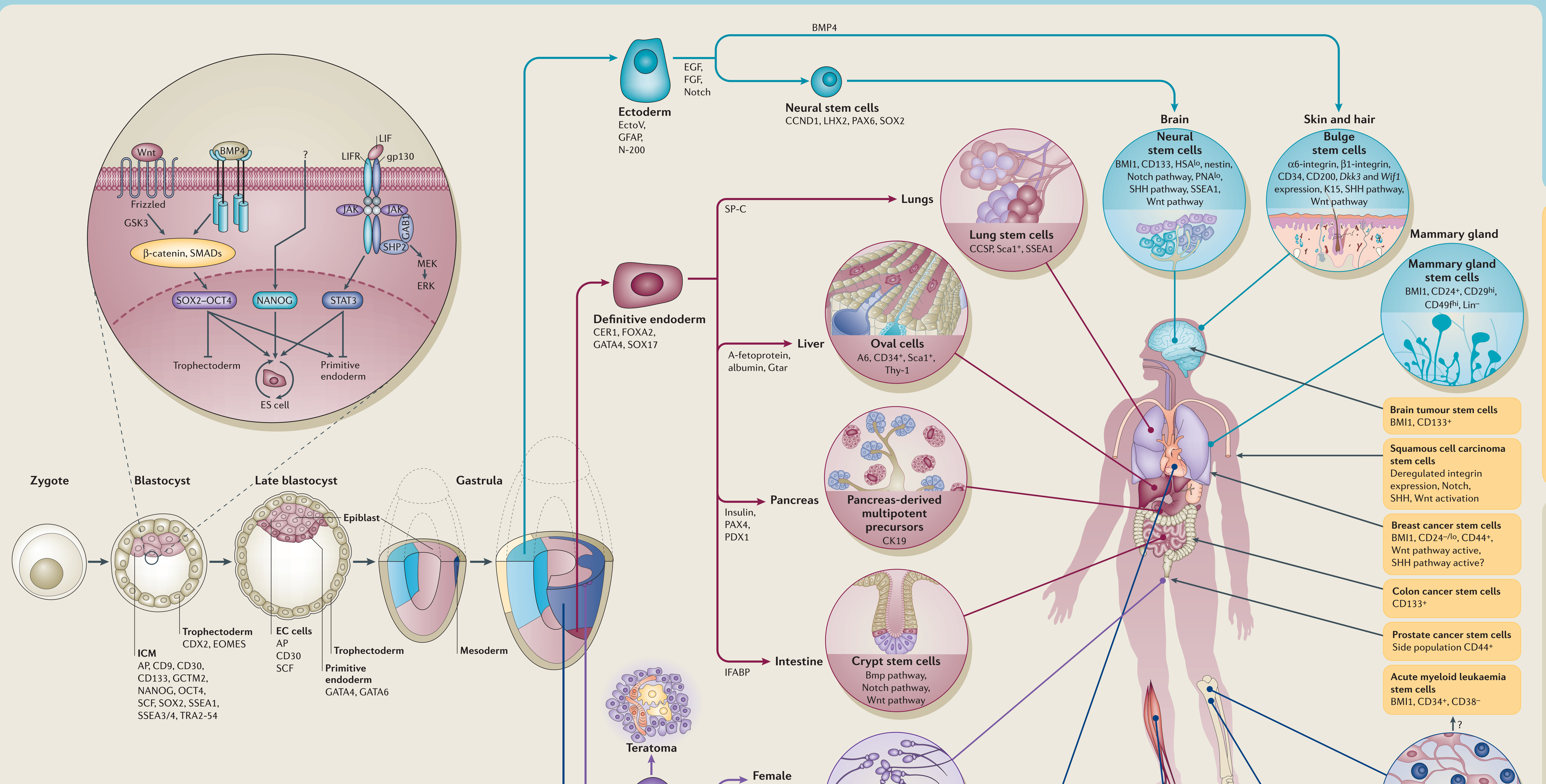
**Stem-cell homeostasis**
Persistence of tissue stem-cell pool throughout life. Requires balancing symmetric self-renewal with differentiative divisions at the population level, or sustained asymmetric self-renewal.

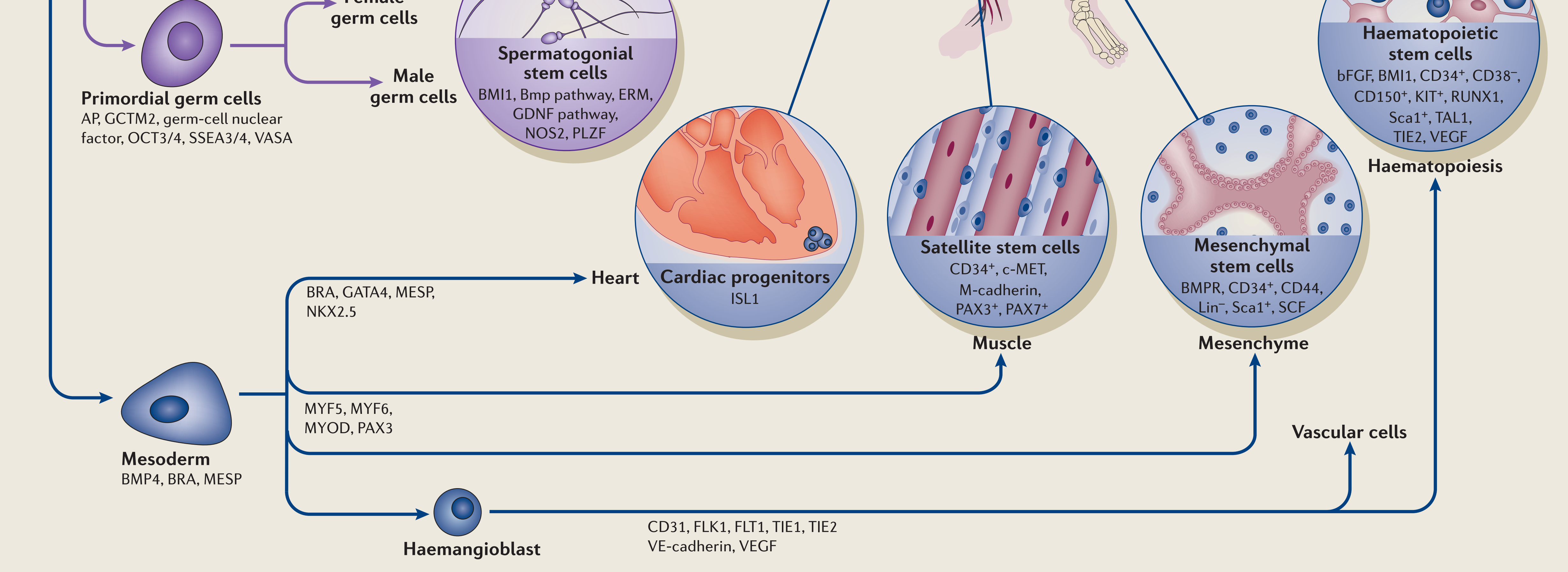
**Stemness**
Unproven notion that different stem cells are regulated by common genes and mechanisms.

**Tissue stem cell**
Derived from, or resident in, a fetal or adult tissue, with potency limited to cells of that tissue. These cells sustain turnover and repair throughout life in some tissues.

**Transit-amplifying cell**
Proliferative stem-cell progeny fated for differentiation. Initially may not be committed and may retain self-renewal.

*We are grateful to Austin Smith for his permission to reproduce the stem-cell glossary, which was produced in association with the European Consortium for Stem Cell Research. For the full glossary, see: Smith, A. A glossary for stem-cell biology. *Nature* **441**, 1060 (2006).




## Abbreviations

AP, alkaline phosphatase; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; BMPR, BMP receptor; BRA, brachyury; CCND1, cyclin D1; CD, cluster designation; CER1, cerberus-1; CK19, cytokeratin-19; EC cell, embryonic carcinoma cell; EGF, epidermal growth factor; EOMES, eomesodermin; ERK, extracellular signal-regulated kinase; ERM, ETS-related molecule; ES cell, embryonic stem cell; FGF, fibroblast growth factor; FLK1, fetal liver kinase-1; FLT1, fms-related tyrosine kinase-1; GAB1, GRB2-associated binder-1; GCTM2, podocalyxin-like precursor isoform-2; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GSK3, glucogen synthase kinase-3; hi, high; ICM, inner cell mass; IFABP, intestinal fatty-acid-binding protein; ISL1, islet-1; JAK, Janus kinase; LHX2, LIM-homeobox protein-2; LIF, leukaemia inhibitory factor; LIFR, LIF receptor; lo, low; M-cadherin, muscle cadherin; MEK, mitogen-activated protein kinase and extracellular signal-regulated kinase; MESP, mesoderm posterior; NOS2, nitric oxide synthase-2; OCT, octamer-binding transcription factor; PDX1, pancreatic and duodenal homeobox gene-1; PLZF, promyelocytic leukaemia zinc-finger protein; Sca1, stem-cell antigen-1; SCF, stem-cell factor; SHH, sonic hedgehog; SHP2, Src-homology-2 domain-containing protein tyrosine phosphatase-2; SOX2, SRY-related high mobility group (HMG)-box protein-2; SSEA, stage-specific embryonic antigen; STAT, signal transducer and activator of transcription; TAL1, T-cell acute lymphocytic leukaemia; VE-cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor.

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## Cancer stem cells

Although the existence of cancer stem cells is now generally accepted for both blood and solid tissue tumours, the definitive identification of markers for cancer stem cells is still in its infancy. Several genes and signalling pathways that are known to regulate tissue and embryonic stem cells, such as *BMI1* and the SHH, Notch and Wnt/β-catenin pathways, are deregulated in cancer. Surface markers can be used in conjunction with assays such as self renewal *in vitro* or transplantation *in vivo* to identify potential tumour stem cells, although in isolation they are not definitive. The six yellow boxes show some of these attributes and the tumours with which they have been associated. They are not intended to show definitive cancer stem-cell markers.