22

STEM CELLS, CELL ASYMMETRY, AND REGULATED CELL DEATH

REVIEW THE CONCEPTS

1. By definition, a stem cell divides to give rise to a copy of itself and to a differentiated cell or a cell capable of differentiating into multiple cell types, such as a mutipotent progenitor cell. Totipotent stem cells can give rise to every tissue in an organism. Pluripotent stem cells give rise to multiple, but not necessarily all, cell types. Progenitor cells give rise to more than one cell type but, unlike stem cells, do not self-renew.

2. In plants, stem cells are located in meristems, such as shoot apical meristems (SAMs) and floral meristems. In adult animal cells, stem-cell populations are thought to exist in low numbers in many organs including skin, intestine, and bone marrow. SAMs in plants are embryo-like in their concentration of totipotent stem cells. However, stem cells are difficult to purify from adult animals, and the only totipotent stem cells found in animals are in very early stage embryos.

3. Because Dolly was derived from an egg containing a nucleus from an adult, differentiated cell, we know that differentiated nuclei (at least adult mammary cells) have the potential to dedifferentiate and become totipotent. Since Dolly was derived from a differentiated nucleus placed into an egg and not from an intact, differentiated cell, we can conclude nothing about the ability of a differentiated cell to become totipotent. Other than the nucleus, the organelles, including mitochondria, which also contain genetic material, were derived from a germ cell. Differentiation of cells is maintained by cytoskeletal structures, organelles that confer cell properties, particular modifications of key regulatory proteins, and accessibility of regulatory genes in the chromatin.

The Dolly experiment best indicates that the chromatin of differentiated nuclei can be remodeled from a differentiated to a totipotent state.

4. (a) pluripotent cells, (b) pluripotent cells, (c) totipotent cells, (d) multipotent cells.

5. True. Somatic cell nuclear transfer (SCNT) where the nucleus of an adult somatic cell is introduced into an enucleated egg to produce the equivalent of a zygote can, in rare cases, develop into a fully functional organism even though the source of the DNA is a differentiated somatic cell from an adult. Furthermore, induced pluripotent stem cells (from adult somatic cells) can be experimentally introduced into a blastocyst and form all of the tissues of a mouse, including germ cells.

6. Intestinal stem cells were first identified by their location in the crypts and by their expression of the G protein–coupled receptor *Lgr5*. The lineage-tracing studies in Figure 21-15 showed that the descendants of these Lgr-expressing cells indeed gave rise to all types of differentiated intestinal epithelial cells and thus that they were multipotent.

7. The key experiment was showing that a single isolated HSC was sufficient to restore the entire blood system when transferred into a lethally irradiated mouse in which all of the HSCs have been killed. That is, the cell was multipotent—generating all types of differentiated blood cells—as well as able to undergo self-renewal, in that it gave rise to multiple daughter HSCs.

8. Because *C. elegans* consists of a small, invariant number of cells, it has been possible to generate a fate map of every cell from the fertilized egg to adulthood. *C. elegans* is also very amenable to genetic manipulation. Therefore, it is possible to alter the expression of specific genes and then determine the effect of this manipulation on cell division, cell differentiation, and cell death. Because many differentiation pathways are highly conserved between *C. elegans* and mammals (e.g., the apoptotic pathway), much of the information derived from studies in *C. elegans* can be applied by analogy to mammalian systems and homologous genes can be discovered.

9. In *S. cerevisiae*, the myosin motor protein, Myo4p, localizes Ash1 mRNA to the bud that will form the daughter cell. In *Drosophila* neuroblasts, microtubules are required for assembly of the Baz/Par6/PKC3 protein complex at the apical end.

10. A complex comprising Par3, Par6, and aPKC is localized anteriorly in the developing embryo and blocks expression of members of another complex (containing Par1 and Par2) from that region of the embryo. Conversely, the Par1/Par2 complex is expressed posteriorly within the embryo and prevents members of the Par3/Par6/aPKC complex from being expressed.

11. In mutant mice in which either neurotrophins or their receptors are knocked out, specific classes of neurons die by apoptosis. These results indicate that apoptosis occurs by default unless a specific extracellular signal is transduced to block the apoptotic program.

12. In apoptosis, cells shrink and condense, and then fragment into apoptotic bodies before being phagocytosed by macro-phages. In necrosis, cells swell and burst, emptying their contents into the surroundings. Necrosis, but not apoptosis, triggers a potentially damaging infl ammatory response in the tissue.

13. Killer proteins initiate the events surrounding apoptosis. Destruction proteins digest cell components such as DNA. Engulfment proteins aid phagocytosis of dying cells.

14. (a) no cell death (since CED-9 supresses apoptosis, and CED-3, which is a killer protein, is inactive)
(b) no cell death (while Bax would induce cytochrome c release, nonfunctional caspase-9 would not be able to induce downstream apoptotic events)
(c) cell death (in the absence of active PI-3, the active unphosphorylated Bad can bind Bcl-2 and lead to the induction of downstream apoptotic events)

15. Although external signals such as TNF and Fas ligand induce apoptosis, the responding cell must still transduce the death signal through an intracellular pathway and induce its own death by activation of the caspase enzymes. The morphologic events of this death are indistinguishable from apoptosis triggered by an intrinsic pathway.

16. a.The cell should undergo apoptosis even in the presence of trophic factors.
b. The cell should not undergo apoptosis even in the absence of trophic factors.
c. The cell should not undergo apoptosis even in the absence of trophic factors. The mutations named in the question in both (b) and (c) could be found in cancer cells because either would block apoptosis even in the absence of trophic factors.

17. IAPs have zinc-binding domains that can bind directly to caspases and inhibit their protease activity, thus preventing apoptosis. SMAC/DIABLOs, a family of mitochondrial proteins, can bind to the zinc-binding domains in IAPs and pre-vent them from binding to caspases.