

Cell Determination

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In an early embryo a cell has the potential to generate many different cell types. During development cells generally lose this potential (or 'potency'), and become restricted to making one or a few cell types. This process by which cells become progressively restricted in their potency is referred to as determination.

Determination of a cell or tissue is an operational concept, and is analyzed by experiments in which the cell or tissue is isolated or placed in an abnormal environment. If the cell's fate does *not* change as a result of the experiment, then the cell can be said to be determined with respect to that manipulation. However, it is possible that other experiments could cause alterations in the cell's fate. Thus, a cell cannot be said to be absolutely 'determined' but only determined relative to experimental tests. Evidence that a cell is not determined can also come from cell marking (clonal analysis) experiments: if a marked cell gives rise to multiple cell types in its progeny, then the marked precursor can not have been determined to make any one cell type.

From analyses of cell fate determination in many organisms, the following general rules have emerged. First, determination is a gradual process, in which a cell's potency is progressively restricted during development. Second, the 'determined state' is heritable through somatic cell divisions, an example of 'cellular memory.' Third, determination is usually but not always irreversible; in some situations a cell can revert to an apparently undetermined state, or can '*trans-determine*' to a different stable state.

Although determination is a multistep process, two basic phases can be distinguished: an initial phase in which a cell is specified to a particular developmental pathway ('cell fate specification'), and a more extended process of commitment, in which the specification is fixed and made largely irreversible. It is now well

established that cell fate specification in embryos can involve both cell-autonomous mechanisms and inductive signals from a cell's surroundings. Combinations of these influences result in progressive alterations in the gene expression patterns of embryonic cells. The later process of commitment is less well understood – for example, why the determined state is stable and heritable, and why it is unstable in some situations.

Cells can become undetermined in special circumstances. In amphibian limb regeneration, cells lose their differentiated characteristics and form a 'regeneration blastema,' which can generate all the tissues of a mature limb. Certain cultured cell lines behave as if undetermined, such as the embryonic stem cells (ES cells) used in generating transgenic mice. Germ-line cells are also exceptional in that they retain the potency to generate an entire organism when they combine to form a zygote.

The distinction between cell fate specification and determination is exemplified by *Drosophila* genes known as selector genes. Genetic analysis in *Drosophila* identified homeotic mutants, in which the fates of certain body regions were altered. These homeotic mutants defined the homeobox-containing selector genes, which function to specify region-specific cell fates. For example, cell fates in the third thoracic (T₃) segment of *Drosophila* are specified by the homeobox gene *Ultrabithorax* (*Ubx*).

The specification of cells to the T₃ identity occurs during embryogenesis and involves the localized activation of *Ubx* by transcription factors that are transiently expressed in the embryo. *Ubx* expression is activated in the future T₃ segment and then persists in these cells throughout development. If *Ubx* function is removed from cells later in development, they lose their T₃ identity and become transformed in fate, indicating that *Ubx* activity is required *continuously* to maintain the cells in their determined state. The stable activation of *Ubx* in T₃ cells and its stable repression in other cells involves chromatin-associated proteins required for the maintenance of active and inactive states of gene expression. Thus, the stability of the determined state may in part reflect stable patterns of chromatin. In vertebrates, DNA methylation could provide an additional heritable mechanism for stable patterns of gene expression.

See also: 0421