

A Rainbow of Cell Identities

Each of the three major modes of cell specification summarized in Table 1 offers a different way of providing an embryonic cell with a set of determinants (often transcription factors) that will activate specific genes and cause the cell to differentiate into a particular cell type. Is the designation of a “cell type” the most precise way to identify a cell? To answer this question, we would have to be able to watch and analyze individual cells in an embryo over time. In Chapter 1, we discussed fate-mapping techniques, which enable the marking of a single cell with something such as a dye that can be traced through development to determine the cell’s fate (Klein and Moody 2016). A genetic approach to fate mapping has been developed to label cells with a seeming rainbow of possible colors, which can be used to identify each individual cell in a tissue or even a whole embryo (Livet et al. 2007). This method was named *Brainbow* because the initial study focused on characterizing cells of the developing mouse brain. It can be applied to any organism, however, and has been called different names, such as “Flybow” and “dBrainbow” for its use in *Drosophila*, “Rainbow” and “Confetti” for its use in mice, and “Zebrow” for its use in zebrafish (Weissman and Pan 2015).

Table 1

AUTONOMOUS SPECIFICATION

Predominates in most invertebrates.

Specification by differential acquisition of certain cytoplasmic molecules present in the egg.

Invariant cleavages produce the same lineages in each embryo of the species; blastomere fates are generally invariant.

Cell type specification precedes any large-scale embryonic cell migration.

Results in "mosaic" development: cells cannot change fate if a blastomere is lost.

CONDITIONAL SPECIFICATION

Predominates in vertebrates and a few invertebrates.

Specification by interactions among cells. Positions of cells relative to each other are key.

Variable cleavages, no invariant fate assignment to cells.

Massive cell rearrangements and migrations precede or accompany specification.

Capacity for "regulative" development allows cells to acquire different functions as a result of interactions with neighboring cells.

SYNCYTIAL SPECIFICATION

Predominates in most insect classes.

Specification of body regions by interactions between cytoplasmic regions prior to cellularization of the blastoderm.

Variable cleavage produces no rigid cell fates for particular nuclei.

After cellularization, both autonomous and conditional specification are seen.

Source: After Davidson 1991.

The Brainbow system triggers the expression of different combinations and amounts of distinct fluorescent proteins (green, red, blue, etc.; see Weissman and Pan 2015). The resulting stochastic distribution of fluorescent protein combinations gives each cell a distinct color that is stably inherited by all its progeny. How is that achieved? The answer is that genes for each fluorescent protein are engineered into the genome of the organism being studied in such a way that they are initially inactive; upon exposure to Cre-recombinase (an enzyme that catalyzes recombination events at specific sites in the DNA), however, a random combination of fluorescent genes can become active (Figure 1a). Different cells are then distinguishable based on the hue of fluorescence created by the different combinations of fluorescent proteins active in each cell.

Brainbow enables researchers to study the morphology of cells and their interactions in any tissue at any age and allows us to chart the developmental lineage of an individual cell from the early embryo through its progeny to their final destinations. For instance, Kevin Eggan's research team has used the Rainbow system to label cells of the early cleavage stages of the mouse embryo to address the following question (Tabansky et al. 2013): Is the first lineage choice of becoming an embryonic cell or an extraembryonic cell a random or a regulated process? They discovered that it is nonrandom (Figure 1B). This example illustrates how powerful this innovative technology is at providing new insights into the life history of individual cells within a community of cells within a whole embryo.

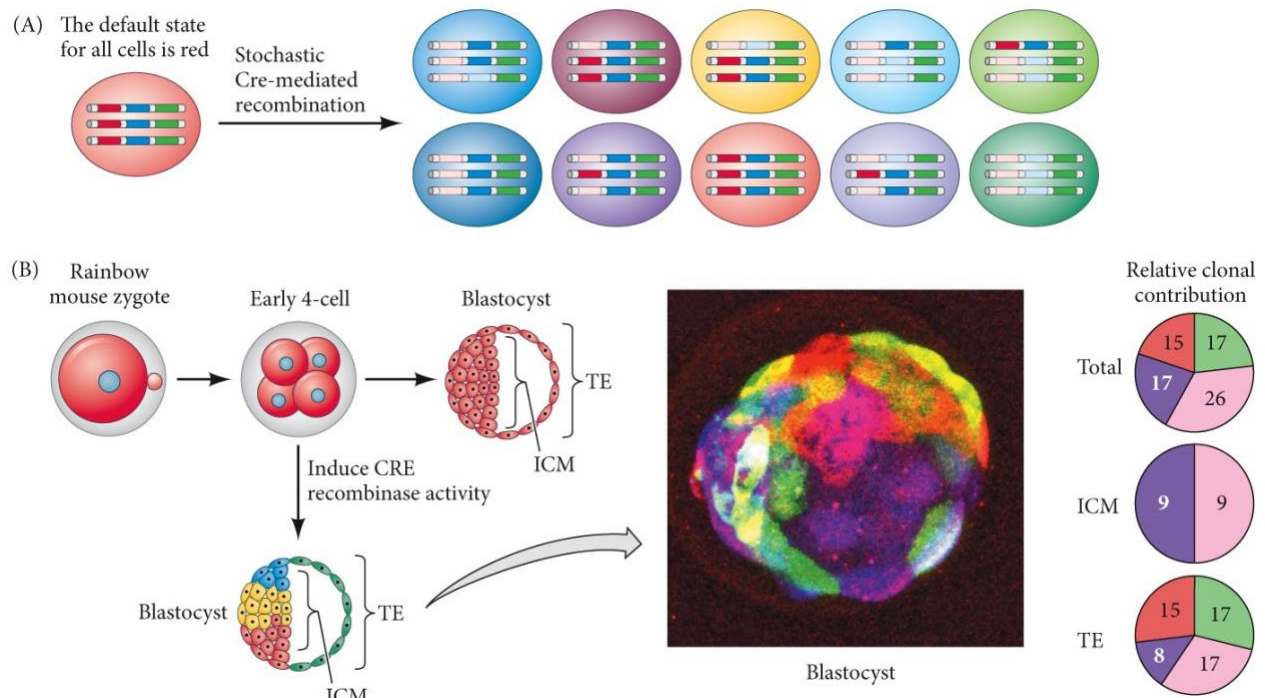


Figure 1 The Brainbow lineage tracing system. (A) The Brainbow genetic system is used to randomly fix cells with a distinct fluorescent color or hue and is accomplished by inserting multiple copies of different fluorescent genes into the organism's genome. Through Cre-recombinase activity, different combinations of these fluorescent genes can be activated to produce an array of different colors. In the example here, each cell will, by default, express red fluorescent protein; upon Cre-mediated recombination, however, cyan, yellow, or green fluorescent proteins begin to be expressed in a stochastic manner (in this example, 10 differently colored cells are labeled). (B) The Rainbow mouse system is a version of Brainbow and works similarly. In this experiment, recombination was initiated during early mouse blastocyst development to permanently mark different cells within the trophectoderm (TE) and inner cell mass (ICM) with unique colors. Those colors were then followed over time and the populations quantified (pie charts), which revealed a statistically significant distribution demonstrating clonal origins from the earlier labeled cells. (A after Weissman and Pan 2015; B after Tabansky et al. 2013.)

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