Specialisation of Cells

The process by which cells specialise from progenitor cells into the enormous variety of cell types that make up the body is termed differentiation. The final mature cells may be white blood cells of the immune system; neurons of the central nervous system with dendritic 'trees' connecting to thousands of other nerve cells or with processes over a meter in length; contractile cells of skeletal muscle up to half a metre in length or of smooth muscle merely 4 millionths of a metre in length and one quarter that in diameter. Clearly, this diversity is foundational to the myriad functions carried out by the body.

The process of differentiation has been measured by a variety of means, but in the first instance differences in visual features are taken to indicate differences in function, so that when cells look different from one another or from cells at more 'primitive' stages, they are deemed to be more or less differentiated.

The zygote may be considered as the most universal cell because in the natural course of events it ultimately develops into all the cells of the body (206 different types in humans), multiplying from one to many trillions in the process. At later stages in the life of the embryo, certain visual features of cells, as well as their location and biochemistry, are taken to indicate that differentiation has taken place. But since the cells within the early embryo at 6 days of age (the blastocyst stage) appear much the same, they have been considered to be basically undifferentiated. Hence, it is not uncommon to hear the embryo at this stage described as merely a 'ball of cells', 'just a clump of cells' or 'a mass of undifferentiated cells'. Furthermore, this description has been used to support the concept that the early embryo is so unformed that it cannot be attributed any particular moral status.

There is, however, somewhat of a revolution going on in cell physiology. Recently several major findings have challenged two traditional concepts of cellular differentiation; first the idea that cells are fixed in their commitment to a certain developmental pathway from which there can be no return; second, and more recently, the notion that cells in the early embryo are unspecialised.

Cloning has overturned the first of these ideas, since a mature differentiated cell could be made to behave like a zygote. In addition, the discovery of cells within the adult body that have the capacity to give rise to a variety of other cell types indicates that the body harbours progenitor cells ready for use when required, and with appropriate manipulation, maybe even the capacity for a quite radical redirection to an even wider anthology of cell types. These cells are termed adult stem cells.

The message from these new findings is that differentiation is not simply a one-way process from uncomplicated to complicated. Furthermore, cells of many types display significant versatility and the potential for therapeutic application. This means that perhaps we should now be viewing cells as more fluid than previously.

The second idea, that cells in the early embryo are unspecialised, has been challenged by recent findings at the University of Cambridge, UK[1]. Researchers

[1] Piotrowska, K., Wianny, F., Pederson, R.A. & Zernicka-Goetz, M. Blastomeres arising from the first cleavage division have distinguishable fates in normal mouse development. *Development* **128**: 3739-3748, 2001.

separately dyed the cells of a mouse embryo at the two-cell stage, one red, the other blue, and then allowed the embryo to continue developing. They then followed the differently coloured multiplying cells to the blastocyst stage, noting that one of the cells gave rise to the embryo body and the other to the tissues that support the developing embryo. This indicates that even at this most early of stages the two cells are different from one another and are committed to a particular pathway. Another way of viewing this is that perhaps differentiation really occurs from the earliest point in time, it is just that the subtle changes are not visually recognisable.

This early specialisation may seem paradoxical in light of the known ability of very young embryos to survive partial destruction, in which case the remaining cells compensate for the loss. But more than anything this is a witness to the remarkable protective mechanisms inherent in cells for self-repair and survival.

There are a number of implications of this preliminary research.

First, there is no simple distinction between undifferentiated and differentiated. This work reinforces the idea that it is closer to the truth to acknowledge a continuum of development at least from the two-cell stage onwards, and by implication from sperm penetration onwards.

Second, the early embryo is not 'simply' a collection of cells. This should come as no surprise. Physiological systems are generally precise and efficient. Why would the developing embryo *not* specialise from the start? It would be surprising if developmental processes lingered without optimal activity directed towards a clearly defined role.

Third, the cells of the inner cell mass of the 6 day old blastocyst, typically extracted as embryonic stem cells, have been described as undifferentiated, universal cells, and maintained in culture as a cell line. While it is clear that they have the capacity to produce all the cells of the body, perhaps this is partly because of their extraction. In other words, perhaps embryonic stem cells extracted from an individual embryo are different from one another, but because of the intervention are sufficiently versatile to morph into any cell type because of the conditions to which they are subsequently subjected. Given the versatility of cells referred to earlier, this is not difficult to envisage. And perhaps being subjected to damage acts as a stimulus for cells to 'reprogramme' themselves.

The importance of early events in the life of the embryo is also supported by research by the same group. They suggested that the point at which the sperm enters the ovum is important for determining the future alignment of the embryo[2].

In summary, recent research in embryology highlights the importance of complex self-directed behaviour by the early embryo as it specialises from the very start. Other work also underscores the marked capacity of the early embryo for self-repair. However, it is also clear that extraction of embryonic stem cells stretches that capacity beyond its limits and destroys the embryo.

[2] Piotrwoska, K. & Zernicka-Goetz, M. Role of sperm in spatial patterning of the early mouse embryo. *Nature* **409**: 517-521, 2001.