Embryos, stem cells and moral status: a response to George and Lee

In an earlier essay, we argued that those who grant a special moral status to human embryos cannot consistently refuse to grant a similar moral status to other entities, such as stem cells, that also have the potential to develop into adult humans (Sagan & Singer, 2007). To do so, however, would have absurd implications. In a recent issue of *EMBO reports*, Robert George and Patrick Lee defended their attribution of special moral status to the human embryo against our argument (George & Lee, 2009). But their defence fails.

In making the case that a stem cell is an entity with the potential to become an adult human, we suggested that when a cell is transferred to an enucleated egg, we should regard the cytoplasm of the egg as the environment in which the cell develops. In rejecting our contention that the stem cell is such an entity, George and Lee deny that the cytoplasm is merely the environment in which the cell develops. They wrote: "something that qualifies as 'merely environmental' does not enter into an organism and modify its internal parts resulting in an entity with a new developmental trajectory." This statement appears to overlook the fact that, at least from implantation onwards, there is a constant acquisition of substances from the outside that modify the embryo's internal parts, including its gene expression (Waterland & Jirtle, 2003).

In our article, we speculated that further advances in science might help to resolve what is crucial for development into an adult organism. Indeed, researchers recently created mice from reprogrammed cells (Zhao *et al*, 2009; Kang *et al*, 2009). No egg cytoplasm was used. This clearly demonstrates that even somatic cells alone have the potential to become an adult human being.

George and Lee might reply that when reprogramming cells, the new being comes

into existence only after the reprogramming is complete. But such a response would miss the point that the potential was there before the cells were reprogrammed. If we are concerned about moral status, then it is hard to see why the embryo should have a moral status that is markedly superior to that of the reprogrammable cell, just because it is one step further along the path towards becoming, if everything goes well, a mature human being.

REFERENCES

- George RP, Lee P (2009) Embryonic human persons. *EMBO Rep* **10**: 301–306
Kang L, Wang J, Zhang Y, Kou Z, Gao S (2009) iPS cells can support full-term development of

tetraploid blastocyst-complemented embryos. *Cell Stem Cell* **5**: 135–138

Sagan A, Singer P (2007) The moral status of stem cells. *Metaphilosophy* **38**: 264–284
Waterland RA, Jirtle RL (2003) Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* **23**: 5293–5300

Zhao X *et al* (2009) iPS cells produce viable mice through tetraploid complementation. *Nature* **461**: 86–90

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Response to Sagan and Singer

Agata Sagan and Peter Singer strive heroically to salvage their claim that a stem cell, no less than an embryo, is an entity with the potential to become an adult. Their salvage operation fails, but not without advancing the discussion on an important point.

They note that factors that alter gene expression in a cell are in many cases environmental, as opposed to intrinsic factors and changes that generate a new type of cell or organism. This is evident, for example, in diseases arising from altered gene expression caused by poor nutrition in a developing embryo. But this is beside the point. In the process described by Sagan and Singer, whereby a stem cell is joined to an enucleated ovum and a developing embryo is produced, the epigenetic constitution of the stem cell nucleus is dramatically changed from one that orients it to functioning as a part of a larger organism, to one that programmes it to develop itself into the mature stage of the organism as a whole. This shows that the cell produced by that process—just like a zygote produced in natural fertilization—is a new, whole organism.

The epigenetic state of a nucleus is not sufficient to define an entity as an embryo. If a zygotic nucleus formed by fertilization

were transplanted to an enucleated muscle or skin cell, the reconstituted cell would not be an embryo, and would not develop into an adult under any circumstances. When a stem cell is joined to an enucleated ovum the stem cell nucleus similarly becomes part of a newly constituted cell, with fundamental properties that are distinct from the original stem cell.

We need a criterion to distinguish between a mere alteration of a cell or organism that persists after the change on the one hand, and a process that results in the production of a new organism on the other hand. In pressing the issue, Sagan and Singer advance the discussion by showing the need for such a criterion. When an isolated cell A interacts with B, does A survive as a distinct whole and merely become modified by its relation to B, or does this process generate a new entity, C, composed of the constituents previously in A and B? In the first case, B can be viewed as an environment for A. In the second case, A does not survive as a distinct whole but becomes part of a larger entity, and B is more than merely environmental. The criterion for how to answer this question for different cases could be expressed as follows: if A and B become stably joined, and a

fundamentally new developmental pathway belonging to this composite is produced, then A has become part of a larger organism, rather than a persisting entity merely modified by its relation to B. If that does not occur, then A may remain a distinct entity, not a part of a larger organism, and it might also generate new cells or exhibit new properties, within a certain range, as a result of its interaction with B.

In the process that Sagan and Singer describe in their article, the components—a stem cell and factors in the cytoplasm from the ovum—combine to form a stable entity and then act together to initiate an internally ordered and entirely new developmental pathway toward a mature organism of the same species as the original stem cell. It is false to say that the stem cell “persists” following fusion to the ovum, just as it is false to say that a sperm cell persists after fertilization. In both cases, a cell with unique properties is formed (a zygote) and a radically new developmental trajectory is initiated. So *pace* Sagan and Singer, the process they describe generates a new organism; it does not merely release the inherent developmental potential of a stem cell.

Things are much the same in the case of tetraploid complementation. Although relatively undifferentiated, a stem cell is still a specialized cell—it has a special role in the life of the organism of which it is a part, namely to generate more specialized cells in

response to cues from neighbouring cells. If it is removed from the organism, it retains that constitution even though it is no longer actually part of that whole; it is then analogous to a heart removed from a donor before transplantation into a recipient. When the stem cell is implanted into another organism or joined to other cells to form a new organism, it does not survive as a distinct entity. Thus, if a stem cell is joined to other cells, it—or its constituents—become an actual part of either an existing organism or of a new one. The status of tetraploid ‘embryos’, which can show some degree of normal development on their own, is not entirely clear. However, it is clear that when a stem cell is combined with a tetraploid entity—whether or not the tetraploid entity is properly regarded as an embryo—the stem cell once again exhibits a substantial change in its cellular behaviour and developmental trajectory and becomes part of a larger organism.

The difference between the behaviour of the zygote (in natural reproduction) and that of the stem cell is decisive evidence that the first is an organism while the second is only a part. The stem cell does not internally direct its own ordered growth by cell division toward a more mature and complex stage of development. Such ordered development only occurs when stem cells are combined with other entities—either an enucleated egg or a tetraploid embryo—after which there is a substantial

change in the behaviour of the stem cell. By contrast, it is obvious that the regular, complex and ordered development of the embryo from the zygote to the blastula stage—which includes ordered gene expression, differentiation into inner cell mass and trophoblast, and many other precisely timed events that prepare the embryo for implantation and for processes that will occur only after implantation—is internally coordinated, because during the first six days, travelling down the uterine tube, the developing embryo is not attached to the mother and is only receiving nutrients from her.

Likewise, Sagan and Singer are mistaken when they claim that tetraploid complementation of reprogrammed cells “demonstrates that even somatic cells alone have the potential to become an adult”: this process shows only that these cells have the potential to be manipulated to produce, together with other factors, a new organism.

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