Stem Cell Discussions at the Royal Society Summer Exhibition
Tuesday 2 and Wednesday 3 July 2013.

by A.C.Sturt

This year there was a discussion of stem cells led by Dr Kevin Chalut of Cambridge University at the Café Scientifique. The University of Nottingham also had an exhibit of stem cells. This note collects some of my thoughts which arose from them. My interest stems from the papers that I have written on The Co-evolution of Species and Human Evolution as a Continuous Process, which propose new paradigms based on analysis of the particle dynamics. Stem cells are in effect the fundamental particles of a biological entity.

Background

The following definitions were presented in hand-outs by in the discussion by Dr Chalut. Stem cells comprise a population of cells which are self-renewing and dividing, and whose function is to maintain healthy tissue. The matrix is the connective tissue between cells which determines structure and chemical and mechanical signals to cells. Tissue homeostasis is when old cells are shed and replaced from the stem cell population without diminishing the stem cell population (in effect steady state). The inner cell mass of an embryo is the tissue from which the cell arises (mammalian). Pluripotency is the property of some cells within the inner cell mass that defines the ability to give rise to the foetus (i.e. differentiated into arms, legs etc). Embryonic stem cells are the *in vitro* analogue of the pluripotent inner cell mass (i.e. they can go off in any direction potentially). Mechanochemical signalling is a hypothesis that mechanical and chemical signalling can cooperate to maintain stem cell function. Microfluidics is the engineering of polymers to mimic cell environments. Biomimetic substrates are engineered to mimic the environments of cells.

I asked Dr Chalut questions (quite a lot!) at his presentation and grilled a number of exhibitors from the University of Nottingham on their demonstrations of stem cells. It emerged that stem cells are defined by what they do; they are indistinguishable from other cells in tissue. They are much longer lived than non-stem cells i.e. resistant to senescence. They make other cells. There are ‘non-committed’ stem cells which can go off to form any organ. These are found in the embryo. When differentiation begins, stem cells become ‘committed’, which means that they make cells only within the scope of their particular organ. When ordinary cells die e.g. within a month for skin cells, they are replaced by the action of the appropriate stem cells. ‘Committed’ cells are distributed e.g. muscle stem cells are found in muscle, though some ‘committed’ stem cells may collect in specific locations. When the numbers of cells becomes excessive because cells are being made faster than they are dying, this may lead to problems, perhaps cancers. When stem cells are grown in the laboratory, the nature of the plate on which they are grown affects the type of ‘commitment’ which they develop. This effect has been linked to the tensile properties of the substrate.

Comments

If this is a reasonably accurate summary, I would like to make a few comments which may be helpful in researching what is an important and difficult emerging area. If you have to define a system by what it does, it is a sure sign that there is something more fundamental to be discovered. This is not a criticism of biochemistry, because physicists have defined light and gravity in just this way in order to make any progress until the underlying process is discovered. Thus light has been treated as particles or waves, and gravity as Higgs bosons or who knows what?

For stem cells, it seems to be established that the nature of surfaces is extremely important in determining the function to which they become 'committed'. In that case if surfaces are a controlling factor in growing stem cells on a plate, this must also apply to stem cells in the embryo, where the only surfaces are the inside of the embryo membrane and the outside of the other stem cells. The corollary would be that stem cells from the embryo may operate differently from stem cells embedded in tissue. The corollary is, if you want to grow 'uncommitted' stem cells, use the lining of an embryo or the equivalent biomimetic film as a substrate. It also seems likely that the influence of the substrate may depend on the particular wall of the stem cell with which it interacts through contact. If you turned over the cell to a different face, you might get a different result. If you carried out the growth in suspension or a stirred medium to avoid contact with surfaces, you might get a different result again.

It is difficult to see why stem cells should live much longer than other cells when they appear to be identical in tissue. If stem cells became 'committed' at the differentiation stage of the embryo, they could be interpreted as meaning that they acquire an additional factor, say a coating, which carries the essence of a stem cell. If this transferred from cell to cell to carry out its 'committed' function, it would always be associated with a young cell. The cell from which the coating was taken would function and die at the usual rate, but the population of stem cells would not diminish, and they would have an apparently longer life. In such a scheme stem cells which are extracted from organs would always be 'committed'. This assumes that the generation, living and death of cells are parts of a different process, which carries on without the stem cell coating. It is also possible that stem cells become 'committed' by contact with the surface of tissue cells which are already differentiated.

Homeostasis is the state in which differentiated dead cells are replaced by the action of stem cells i.e. the number dying equals the number being made. Presumably growth would occur when more were made than died. This implies some sort of process which has a diminishing effect on the difference between numbers being formed and dying when the entity is approaching full size.

The left and right problem

All this starts with the cells in the embryo. Somewhere in the process, differentiation begins for unknown reasons. Cells learn one end of a structure from the other, and how to tell left from right of the final mammal. This must be settled at the very beginning, because these are the configurations which are transmitted throughout the growth process to the adult entity. As far as the ends of a structure of cells are concerned a mechanism can be formulated which depends on the anisotropy of the

cell walls i.e. different walls of different sizes with different properties, being assembled back to back. They will always finish up with different ends, which become apparent when the baby separates from its mother.

However, it is more difficult to envisage what sort of mechanism could fix the left and right side of a foetus which is twisting and turning throughout its construction. How do our heart cells know that they should form the organ on the left hand side of the body, at least for almost all people, and how do cells know that they should be at the front of the body or the back?

For this I draw on my paper on cosmology that proposes a model in which the stuff of the entire Universe is constructed from an infinite cloud of particles of a single species, which I have called the ε-particle. The paper may be found on www.churingapublishing.com/newpartchwebsite.pdf on my personal website. In this model all ε-particles are spheres which have the same size as an electron but without the charge, and all spin on their axes at the same immutable rate. They are attracted to or repelled from each other by their spins, but that does not concern us here. What is relevant is that the axes of individual ε-particles in the cloud are randomly oriented. There is no preferential direction in the cloud itself, because the Universe can have no bias. However, as soon as an observer is introduced, then in whichever direction you look, half of the particles always seem to be rotating to the left and half to the right. This would still be true if the observer was in a different place; it is just that it would be a different half. It is the observer who determines which direction of spin is which, or in engineering terms provides the degree of freedom against which everything else can be aligned. It is the spin of the ε-particles which determines what is left and what is right for the observer.

Far-fetched as it may seem, and I can see no alternative phenomenon which would encompass the whole animal world on Earth, the only phenomenon which can provide a left and right irrespective of the observer is the direction of the Earth's rotation. The axis of rotation provides a direction, but this is not unique because it has both north and south. If the axis were the determinant, you might expect the population to be divided into 'north' and 'south'. However, the unique direction which every living entity on Earth has is the east, the direction of rotation which is illuminated by the Sun. The biological model would be that particles of genetic material in the embryonic sac were suspended in a liquid without the constraints of walls to give a degree of freedom, but as genetic strings they took on in some way an alignment parallel to the direction of rotation of the Earth's surface. The west of all living entities would be what they had left behind, and their east would be where they were going. This is not unlike the flow of air on the Earth's surface. As soon as the first structure began to be formed by the embryo's development, this would supply it with a degree of freedom which was fixed, whatever the subsequent orientation of the growing embryo. Everything anisotropic built on this basis would contain the directions of the left or right of the structure i.e. the foetus.

By contrast his would be a mechanism which did not apply to plants, because these are isotropic; they do not know left from right, but only gravity i.e. up and down, and the direction of the Sun, which might mean that they have no equivalent of the embryo stage.

It was said at the exhibition that bonds between the elements which give plants their structure are all ionic, rather than covalent, but what about animals? I cannot help feeling that our skin must also have covalent bonds between chains to achieve its resilience, or perhaps hydrogen bonds to provide crosslinks. In their absence the long molecules would eventually slide over each other under stress. I might add that a well informed exhibitor vehemently denied that ionic bonds would mean that we tended to liquefy in solvents!

Flaws on the skin of mammals sometimes occur as mirror images on the creature's left and right. This is hardly likely to be coincidence. Either the opposing blemishes must have remarkably accurate of the passage of time since conception, or more likely the two sides were in communication in some way, probably at the beginning. This looks like electromagnetic induction with matching outputs generated at a distance, and/or stem cells again.

This is all very speculative of course, but it seemed to me that this area, apart from being interesting in its own right, might find a little speculation from outside the discipline stimulating and even helpful. It follows on from my previous letter on Cell Walls – the Limits to Growth.

A.C. Sturt

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