Mexican salamander helps uncover mysteries of stem cells and evolution

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Dr Andrew Johnson is speaking today at the UK National Stem Cell Network annual conference. He and his team from the University of Nottingham have been using a Mexican aquatic salamander called an axolotl to study the evolution and genetics of stem cells - research that supports the development of regenerative medicine to treat the consequences of disease and injury using stem cell therapies. This team has found that there are extraordinary similarities in the development of axolotls and mammals that provide unique opportunities to study the properties of embryonic stem cells and germ cells. These findings are underpinned by a novel theory of evolution that unifies the diversity of mechanisms in animal developmental into a single conceptual framework.

Dr Johnson said "We've produced evidence that pluripotency - the ability of an embryonic stem cell to become absolutely any kind of cell - is actually very ancient in evolutionary terms. Even though received wisdom is that it evolved with mammals, our research suggests that it was there all along, just not in many of the species that people use in the lab. In fact, pluripotent cells probably exist in the embryos of the simple animals from which amphibians evolved.

"Axolotls, unlike many of the frogs, fish, flies and worms that are used in the lab, have pluripotent cells in their embryos that are the equivalent to those found in embryos from mammals, in that they can produce germ cells, in addition to somatic cells, a property known as ground-state pluripotency. And from a practical perspective, axolotl embryos will provide a very useful tool for understanding how to manipulate embryonic stem cells for modern regenerative medicine."

Axolotls are salamanders that retained primitive characteristics of the first amphibians, the animals descended from fish that moved onto land about 385 million years ago. These early amphibians were the ancestors of every land dwelling vertebrate, including humans. This places axolotls in a perfect position to understand how vertebrates evolved on land.

Dr Johnson continued "We've found that the genetic mechanisms controlling the development of salamander embryos were not changed as amphibian embryos evolved into those of reptiles and then, later, mammals. This explains why newts (salamanders) look so much like lizards (reptiles), and since mammals evolved directly from reptiles it makes sense that the genetic mechanisms controlling embryo development remain largely unchanged from axolotls to humans. Axolotl embryos are therefore far more similar to those of humans than the more commonly studied embryos of frogs and fish that most development researchers use.

"We recently found out that pluripotency in axolotls and mammals depends on a gene called Nanog, which frogs do not have. Therefore we think that the Nanog gene was lost from the frog genome after frogs and salamanders evolved separately from their common amphibian ancestor. This is contrary to a long-held opinion that ground-state pluripotency evolved with mammals and suggests that pluripotency could actually be one of the most ancient features of embryos. But since evolution depends on generating advantageous changes, and pluripotency seems to be a good thing - we had to ask ourselves why would frogs have lost the Nanog gene, and with it pluripotency?""

Through work to explore why frogs might have lost pluripotency Dr Johnson and colleagues developed a new theory of evolution in 2003.

This theory says that a key driver of vertebrate evolution is the relationship of the germ cells, which become sperm and egg, and the rest of the body, called the soma.

Dr Johnson said "The reason that losing pluripotency would have been an advantage to frogs, for example, is that it has actually made it possible for them to diverge into numerous closely related species - it is possible for them to make far more frequent fairly subtle changes in the evolution of their body shape and physiology. In axolotls and humans it has been necessary to keep a far more rigid arrangement of the soma and therefore they have not diverged into multiple closely related species. And the reason for this is that there are two quite different ways of producing germ cells."

The embryos of most lab animals, including frogs but not mice, contain material called germ plasm, and germ plasm has the role of instructing cells to become the primordial germ cells which go on to become sperm and egg. But axolotls are different; Dr Johnson's team found that their embryos actually don't contain germ plasm and instead they use a system very similar to mice and humans. Axolotls produce their primordial germs cells from pluripotent cells - similar to embryonic stem cells - by a process called induction.

Dr Johnson said "Within our new theory of evolution pluripotency came first and so germ plasm would have to have evolved independently several times in species within the branches of the tree, for example in frogs and many fish. This is a process called convergent evolution - where a common advantage leads to several species developing features that make them appear more similar, rather than less.

"What is the advantage of germ plasm such that it would have evolved several times? We had to resolve the argument that germ plasm wasn't necessary because pluripotency did the job just fine. We knew that with germ plasm pluripotency is not necessary, because the embryos contain primordial germ cells anyway. This explains why the Nanog gene became dispensable, and was lost from the DNA but it doesn't explain what is the advantage to having germ plasm."

Dr. Johnson and his colleagues suggest that the evolution of germ plasm liberates the soma of an organism to evolve more rapidly, simply because the embryo doesn't need to induce germ cells - they are already there because of germ plasm. As a result of this, the genetic mechanisms that control the soma are free to evolve, because they are no longer occupied with producing the signals that induce primordial germ cells from pluripotent embryonic cells.

Dr Johnson concluded "Organisms with germ plasm evolve more rapidly, and produce more species than those without it because there is a great deal more genetic flexibility. So, in the case of frogs, the selective advantage to having lost pluripotency in favour of germ plasm is the freedom to evolve many more species of frogs, which can inhabit many different environments. The down side is that once frogs evolved they never gave rise to anything but other frogs. On the other hand, because salamander embryos contain pluripotent cells they had the raw material to evolve completely new structures such as extraembryonic membranes, which are fundamental to the development of reptiles and mammals.

"We think that ultimately, the germ line-soma relationship is likely to be a major contributor to the astonishing diversity of species that inhabit the earth."

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