Dolly's 'sisters' show cloned animals don't grow old before their time

July 27 2016, by Kevin Sinclair

Credit: University of Nottingham

It's now 20 years since the birth of Dolly the sheep, the first mammal to be cloned. This groundbreaking scientific achievement was accompanied by warnings that Dolly might age prematurely because she had been cloned from adult sheep cells, whose "biological clock" had not been reset. Fears were heightened in 2001 when Dolly was diagnosed with osteoarthritis at five years of age (she died two years later). This was heralded as evidence of premature ageing, although the condition is

actually very poorly described in sheep.

We wanted to better understand how the cloning process affected the health of the animals produced and so we've been studying a group of cloned sheep, including four of Dolly's "identical sisters". We found that most of the animals are actually in good health for their age. There was little sign of blood glucose problems, high blood pressure or osteoarthritis, all of which were highlighted as potential problems. This suggests that the cloning technique can, after all, produce perfectly normal and viable offspring that don't grow old before their time.

The technique used to produce Dolly is called somatic-cell nuclear transfer (SCNT) and involves reprogramming normal sheep cells into embryonic cells that can turn into any other specific type of cell in the body. This is done by effectively inserting the nucleus of an ordinary cell into an empty egg. The transformed eggs were then used to create embryos that were then implanted in a number of surrogate ewes, eventually leading to the birth of Dolly in July 1996.

But the Nature paper of 1997 announcing the creation of Dolly also highlighted inefficiencies with SCNT. It took 277 reconstructed embryos to produce one sheep. Analysing Dolly's DNA also suggested that her cells were biologically older than her chronological age. It's as if the cells still thought they were part of the original, older sheep from which she was cloned.

Health check

It was against this background that in 2015 we sought to formally assess the health of a group of 13 cloned sheep ranging from seven to nine years of age. Four of them were effectively clones of Dolly and shared the same DNA in the nuclei of their cells. We investigated three common age-related diseases in sheep: metabolic syndrome (problems

associated with obesity), hypertension (high blood pressure) and osteoarthritis (joint pain and stiffness).

There had been some reports of diabetes in cloned mice, and kidney defects among previously cloned lambs that didn't survive birth, which we thought could lead to increased blood pressure in adults. Dolly herself was diagnosed with osteoarthritis at the relatively young age of five.

Despite their advanced age (sheep rarely live beyond ten years), our animals had normal blood glucose levels and found to be insulin sensitive, meaning they weren't suffering metabolic syndrome. Blood pressure was also normal and, although there was radiographic evidence of mild osteoarthritis in one or two joints in most sheep, no animal was lame and none required treatment. In the 12 months that followed these assessments, our sheep have remained largely healthy. Recently, one of the now nine-year-old Dolly clones has started to show clinical signs of osteoarthritis (being a little stiff in the morning).

Our findings suggest that cloning long-lived species such as sheep by SCNT generally produces no age-related detrimental health effects in the animals that are successfully born and survive beyond the first week or two. But what about the other embryos that didn't survive? What can their health teach us about the cell reprogramming process?

During natural conception, the sperm's DNA and associated proteins are packaged in such a way that the egg can easily dismantle and reassemble it. With SCNT cloning, the egg finds it much harder to reprogram the genetic material inserted from the original animal cell and has just a few hours in which to get it right.

So perhaps it is not surprising that in the majority of cases the egg is only partially reprogrammed. Part of the success of the team behind

Dolly was in reducing the likelihood of DNA damage and abnormalities that can occur during reprogramming.

Making cloning more efficient

However, in the 20 years since Dolly's birth there have been significant advances in molecular genetics and cell biology that have greatly advanced our understanding of these early developmental processes. Professor Keith Campbell, who was part of the Dolly team, went on to improve the efficiency of SCNT so that 20% of cloned embryos developed to become live offspring, as opposed to the original 3% in the Dolly experiment. This work produced ten further Dolly clones in July 2007, seven of which lived beyond one week of age and four of which are alive today (and were part of our study).

Many embryos were still lost during pregnancy but, as with natural conception, the vast majority of these losses occurred before they were successfully implanted in the womb. Those clones that failed to survive much beyond the first week of life typically had defects in the heart, lungs or kidneys. However, these losses were of enough concern to the European Parliament that they contributed to its decision to ban farm-animal cloning for food production in September 2015.

Now that we know cloning can produce normal, healthy animals, we need to increase the survival rate of the embryos to levels similar to those of natural conception. There is reason to be optimistic that this is achievable. We now have a better understanding of the underlying molecular mechanisms involved in the remodelling of the clones' genetic material.

Scientists are attempting to do part of this reprogramming before the material is transferred to the empty egg so that it looks more like the genetic material delivered by a sperm during natural conception. If

successful, this would allow the egg to more easily complete the reprogramming process, increasing the number of embryos that survive and hopefully reducing the related animal welfare concerns.

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