First mutations in human life discovered: Archaeological traces of embryonic development seen in adult cells

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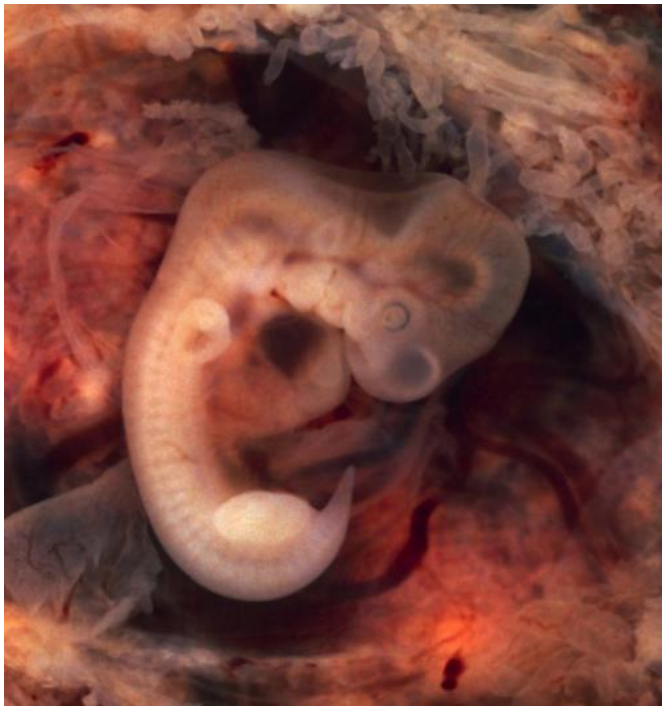

Human Embryo. Credit: Ed Uthman, MD/Wikipedia

The earliest mutations of human life have been observed by researchers at the Wellcome Trust Sanger Institute and their collaborators. Analysing genomes from adult cells, the scientists could look back in time to reveal how each embryo developed.

Published in *Nature* today, the study shows that from the two-cell stage of the human embryo, one of these cells becomes more dominant than the other and leads to a higher proportion of the adult body.

A longstanding question for researchers has been what happens in the very early human development as this has proved impossible to study directly. Now, researchers have analysed the whole genome sequences of blood samples (collected from 279 individuals with breast cancer) and discovered 163 mutations that occurred very early in the embryonic development of those people.

Once identified, the researchers used mutations from the first, second and third divisions of the fertilised egg to calculate which proportion of adult cells resulted from each of the first two cells in the embryo. They found that these first two cells contribute differently to the whole body. One cell gives rise to about 70 percent of the adult body tissues, whereas the other cell has a more minor contribution, leading to about 30 percent of the tissues. This skewed contribution continues for some cells in the second and third generation too.

Originally pinpointed in normal blood cells from cancer patients, the researchers then looked for these mutations in cancer samples that had been surgically removed from the patients during treatment. Unlike normal tissues composed of multiple somatic cell clones, a cancer develops from one mutant cell. Therefore, each proposed embryonic mutation should either be present in all of the cancer cells in a tumour, or none of them. This proved to be the case, and by using these cancer samples, the researchers were able to validate that the mutations had originated during early development.

Dr Young Seok Ju, first author from the Wellcome Trust Sanger Institute and the Korea Advanced Institute of Science and Technology (KAIST), said: "This is the first time that anyone has seen where mutations arise in the very early human development. It is like finding a needle in a haystack. There are just a handful of these mutations, compared with millions of inherited

genetic variations, and finding them allowed us to track what happened during embryogenesis."

Dr Inigo Martincorena, from the Sanger Institute, said: "Having identified the mutations, we were able to use statistical analysis to better understand cell dynamics during embryo development. We determined the relative contribution of the first embryonic cells to the adult blood cell pool and found one dominant cell - that led to 70 percent of the blood cells - and one minor cell. We also sequenced normal lymph and breast cells, and the results suggested that the dominant cell also contributes to these other tissues at a similar level. This opens an unprecedented window into the earliest stages of human development."

During this study, the researchers were also able to measure the rate of mutation in early human development for the first time, up to three generations of cell division. Previous researchers had estimated one mutation per cell division, but this study measured three mutations for each cell doubling, in every daughter cell.

Mutations during the development of the embryo occur by two processes - known as mutational signatures 1 and 5. These mutations are fairly randomly distributed through the genome, and the vast majority of them will not affect the developing embryo. However, a mutation that occurs in an important gene can lead to disease such as developmental disorders.

Prof Sir Mike Stratton, lead author on the paper and Director of the Sanger Institute, said: "This is a significant step forward in widening the range of biological insights that can be extracted using genome sequences and mutations. Essentially, the mutations are archaeological traces of embryonic development left in our adult tissues, so if we can find and interpret them, we can understand human embryology better. This is just one early insight into human development, with hopefully many more to come in the future."

More information: Young Seok Ju et al, Somatic mutations reveal asymmetric cellular dynamics in the early human embryo, *Nature* (2017). DOI: 10.1038/nature21703

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