Anatomy of a decision—mapping early development

July 6 2016

In the first genome-scale experiment of its kind, researchers have gained new insights into how a mouse embryo first begins to transform from a ball of unfocussed cells into a small, structured entity. Published in *Nature*, the single-cell genomics study was led by the European Bioinformatics Institute (EMBL-EBI) and the Wellcome Trust-MRC Cambridge Stem Cell Institute.

Gastrulation is the point when an animal's whole body plan is set, just before individual organs start to develop. Understanding this point in very early development is vital to understanding how animals develop and how things go wrong. One of the biggest challenges in studying gastrulation is the very small number of cells that make up an embryo at this stage.

"If we want to better understand the natural world around us, one of the fundamental questions is, how do animals develop?" says Bertie Gottgens, Research Group Leader at the Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute. "How do you turn from an egg into an animal, with all sorts of tissues? Many of the things that go wrong, like birth defects, are caused by problems in early development. We need to have an atlas of normal development for comparison when things go wrong."

Today, thanks to advances in single-cell sequencing, the team was able to analyse over 1000 individual cells of gastrulating mouse embryos. The result is an atlas of gene expression during very early, healthy

mammalian development.

"Single-cell technologies are a major change over what we've used before - we can now make direct observations to see what's going on during the earliest stages of development," says John Marioni, Research Group Leader at EMBL-EBI, the Wellcome Trust Sanger Institute and the University of Cambridge. "We can look at individual cells and see the whole set of genes that are active at stages of development, which until now have been very difficult to access. Once we have that, we can take cells from embryos in which some genetic factors are not working properly at a specific developmental stage, and map them to the healthy atlas to better understand what might be happening."

To illustrate the usefulness of the atlas, the team studied what happened when a genetic factor essential for the formation of blood cells was removed.

"It wasn't what we expected at all. We found that cells which in healthy embryos would commit to becoming blood cells would actually become confused in the embryos lacking the key gene, effectively getting stuck," says John. "What is so exciting about this is that it demonstrates how we can now look at the very small number of cells that are actually making the decision at the precise time point when the decision is being made. It gives us a completely different perspective on development."

"What is really exciting for me is that we can look at things that we know are important but were never able to see before - perhaps like people felt when they got hold of a microscope for the first time, suddenly seeing worlds they'd never thought of," says Bertie. "This is just the beginning of how single cell genomics will transform our understanding of early development."

More information: Antonio Scialdone et al, Resolving early

mesoderm diversification through single-cell expression profiling, *Nature* (2016). DOI: 10.1038/nature18633