

## Study reveals how gene activity shapes immunity across species

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By sequencing genes from over a quarter of a million cells across six mammalian species, researchers at the Wellcome Sanger Institute, EMBL's European Bioinformatics Institute and collaborators, have shown how genes in the immune response have varied activity between cells and species.



The study, published today (24 October) in *Nature*, looked in unprecedented detail at the genes that are activated in a cell's initial response to a pathogen invasion—the innate immune response. They measured the activity of thousands of genes in over 250,000 <u>individual</u> <u>cells</u> using single cell genomics technology to chart the evolution of antiviral and antibacterial immunity.

Previous work has shown that many genes in the <u>innate immune</u> <u>response</u> have rapidly evolved in vertebrates. This is thought to be caused by the relentless pressure of attack from pathogens like bacteria and viruses. These include genes that make cytokine and chemokine molecules, which act in a variety of ways—some are inflammatory molecules that alert the body to danger; others restrict a pathogen's ability to multiply and others induce cell death. They represent a successful host strategy to counteract rapidly evolving pathogens.

The team showed that these genes which have evolved rapidly across species, also have highly variable activity in different <u>cells</u> within an individual's tissue.

In contrast, they found that genes which are conserved between species, and regulate the immune <u>response</u>, are more consistently activated across cells within a tissue. These genes may be under tighter constraints because they are involved in many different functions within cells. But, they are also targeted by viruses. These constrained genes represent an Achilles' heel, used by pathogens to subvert the immune system.

Dr. Tzachi Hagai, lead author of the research at the Wellcome Sanger Institute said: "We think that this pattern of activation—where some genes are under tight control, and others have more variable activity—has evolved as a way to fine-tune the <u>immune response</u>. It is effective, but balanced. Genes can evolve to help a cell control an attacker, and the use of those <u>genes</u> can vary between cells, so



surrounding tissues are not affected by a massive fall-out."

Dr. Sarah Teichmann, Head of Cellular Genetics at the Wellcome Sanger Institute and senior author of the research said: "The power of DNA sequencing at the resolution of single cells means this kind of study is now possible. There are an estimated 37 trillion cells in the human body, each with the same genetic code. But individual cells behave differently, they use that genetic code in a different way. By studying individual cells we can understand these fundamental building blocks of life and how they work together—including how they resist <u>pathogens</u>."

**More information:** Tzachi Hagai et al, Gene expression variability across cells and species shapes innate immunity, *Nature* (2018). <u>DOI:</u> 10.1038/s41586-018-0657-2

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