**How to survive a viral apocalypse: a rabbit’s tale**

*In 1950, a novel virus was used as a biological weapon to control the invasive rabbit populations in Australia, killing millions of animals on the first impact. But then, evolution kicked in and rabbits evolved genetic resistance to the disease. This is the story of how it all happened.*

In 1859, an English settler named Thomas Austin decided to import 24 rabbits from England to Australia so he could hunt on his property. He could have not been more successful, and by 1910, hundreds of millions of rabbits covered the entire continent. Thomas’ success, besides frustrating the farmers whose crops were being obliterated by a pest of biblical dimensions, was causing an ecological disaster for the native flora and fauna. With the inefficiency of conventional methods to stop the spread of the rabbits the problem seemed to be intractable. However, an unexpected discovery on the other side of the ocean changed the course of history. In 1896, Guiseppe Sanarelli, a bacteriologist working in Uruguay, noticed a novel and lethal disease in domestic rabbits where infected animals exhibited a characteristic swelling of the ears and eyes and mucous lumps on the skin. These symptoms led Sanarelli to name the disease myxomatosis, from the Greek muxa (mucus) and oma (tumour). Three decades later, Brazilian researcher Henrique Aragão identified the myxoma virus as the cause of myxomatosis. A solution to the rabbit infestation problem appeared to be found.

In 1950, the virus was finally released into mainland Australia and in less than three months, it spread thousands of kilometres, killing 99% of the infected animals on its destructive path. Two years later, Armand Delille, a French physician, acquired the virus and released it illegally on his estate near Paris, where rabbits were a pest. From here, it spread across Europe reaching England in 1953. With almost no exception the introduction of myxoma virus caused an identical outcome: the death of millions of rabbits. However, a few years after the introduction, rabbit mortality rates started to decrease and when researchers went to the field, they found that both host and pathogen had changed. The most lethal strains of the virus had killed the rabbits before they had time to pass the disease on, so the virus had evolved to become more benign. By keeping the rabbit alive for longer there was more time for the virus to be transmitted. Alongside this, only the most disease-resistant rabbits had survived the pandemic, so the species had evolved to become more resistant to myxomatosis. The importance of these studies went far beyond rabbits and they continue to shape our understanding of disease to this day.

Fascinated by this extraordinary example of co-evolution we set out to identify the genes that confer resistance to the virus. First, we visited museums worldwide and sampled rabbit skins or bones that were collected before 1950 in Europe and Australia. These rabbits pre-dated the virus release and therefore were still very susceptible to myxomatosis. Then we went to the same locations and collected samples from modern populations that evolved resistance to the virus. With the help of the museums and collaborators, we were able to collect samples and extract DNA from hundreds of rabbits going as far back as 1865. We then sequenced the genetic code of nearly 20,000 genes to pinpoint the genetic changes that had occurred in rabbits over the course of more than 60 years coevolution with the myxoma virus.

By comparing the DNA sequences of rabbit populations before and after the virus release, we have found that exactly the same genes have changed in the populations of Europe and Australia and that many of these genes played a key role in the immune system of rabbits, defending them against infection. This shows that evolution was repeatable with the occurrence of parallel changes in rabbit populations worldwide as a response to the same selective pressure, the myxoma virus. Moreover, we found that this appears to result from the combined effect of many different genes instead of a few genes that have large effects which is likely the case for many cases of adaptive evolution. One of the genes we found in particular, produces a protein called interferon that triggers an immune system alarm upon pathogens detection. By testing the two different forms of interferon in rabbit cell lines, the one found in 1950s rabbits and the form most commonly found today we found that the latter is more potent against the virus. Ultimately this study allowed us to understand how genetic variation present in populations before a pandemic of a new pathogen enabled the host to rapidly evolve resistance. It is likely that similar processes will happen in other species that face threats from new infectious diseases, providing hope that they too may adapt to these new threats.

Almost 150 years have passed since Thomas Austin imported rabbits to Australia. Unbeknown to him, this ultimately caused a cascade of events leading to what is considered by many as one of the greatest natural biological experiments of the 20th century. With rabbits and viruses still coexisting in the wild, the experiment is still ongoing.