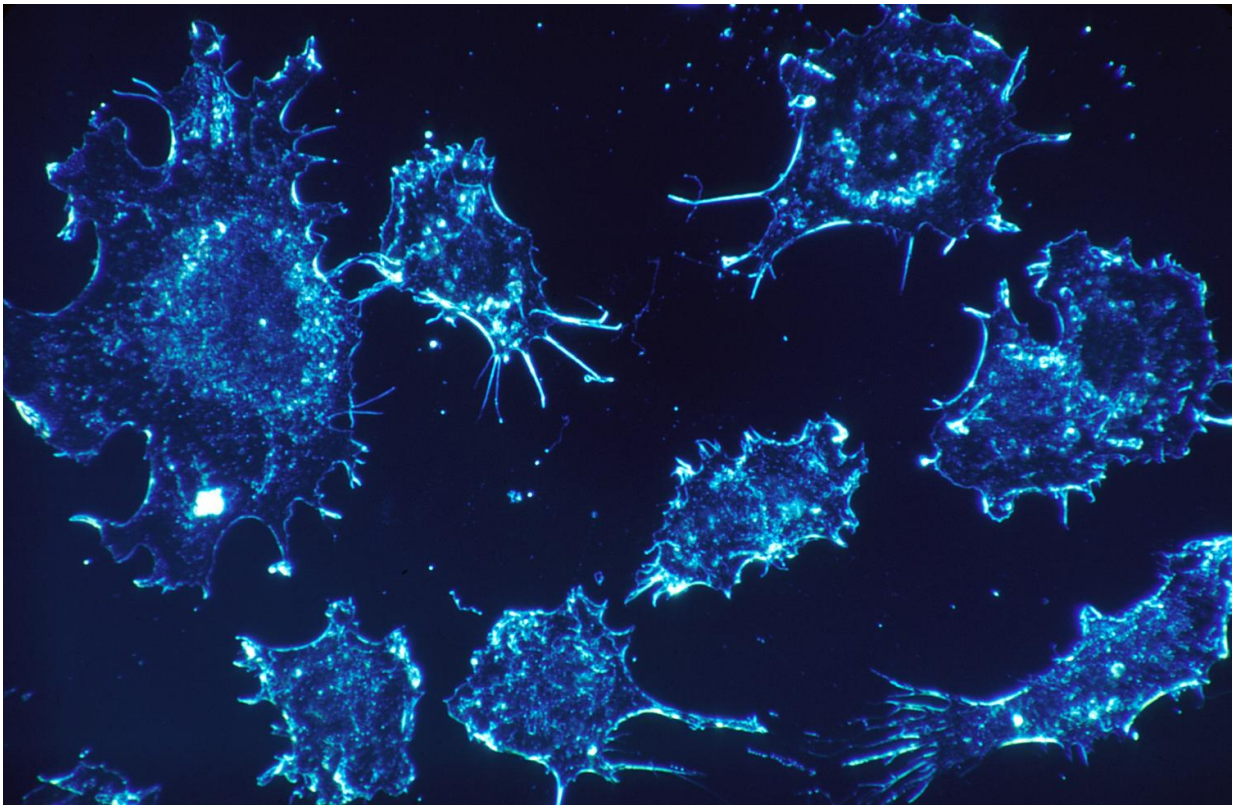
MedicalXpress

Cancer genes' age and function strongly influence their mutational status

February 26 2019



Credit: CC0 Public Domain

Researchers have provided new insight on why some genes that formed during the evolution of the earliest animals on earth are particularly impaired (or dysregulated) by specific mechanisms during cancer development.

Their study, published today in *eLife*, suggests investigating the implications of this dysregulation for the entire function of cancer cells may provide useful insights for the development of potential new therapies.

Cancer is a complex disease characterised by cellular mutations that are unique to each patient. But all cancers have a similar set of biological characteristics known as hallmarks, which include the dysregulation of cell replication and loss of a process called differentiation—where cells change from one cell type into a more specialised type as needed by the body.

Previous research has suggested these hallmarks can be interpreted as dysregulated multicellularity in cancer. 'Multicellularity' refers to the coordination of multiple cells that allows complex tissues and organs to form, and which led to the evolution of multicellular organisms, such as humans, from our single-celled ancestors.

"Our previous work pointed to widespread dysregulation in cancer between cellular processes that emerged in single-celled organisms and those that evolved in multicellular species," says lead author Anna Trigos, postdoctoral researcher at Peter MacCallum Cancer Centre, Victoria, Australia. "In our current study, we wanted to investigate the role of mutations in this dysregulation of multicellularity in cancer."

Using computational analyses, Trigos and the team explored how the mutational status of genes across cancers was associated both with the point in evolutionary time when the genes appeared, and with their role and position in the human gene regulation network. Their aim was to provide a clearer picture of how the diversity of mutational landscapes in cancers across individual patients aligns with specific hallmarks.

Their studies revealed that mutations in 30 different solid tumour types

in over 9,000 patient samples disrupt the regulation between genes that evolved in ancient unicellular species, and more recently acquired genes that evolved at the onset of multicellularity. They also found that this disruption occurs through different mechanisms.

"Key genes in the human regulatory network that link genes from single-cell ancestors and those unique to multicellular species had more mutations affecting a single nucleotide (a structural component of DNA or RNA) in key positions of the gene, possibly resulting in a cascade effect of widespread downstream dysregulation," Trigos explains.

On the other hand, she adds, mutational processes that lead to a gain or loss of the copies of a gene did not affect these regulatory genes, but rather activated or deactivated specific sets of genes of unicellular or multicellularity ancestry, respectively.

"Together, these results provide comprehensive evidence that both the frequency and types of mutations in cancer genes are strongly influenced by a given gene's evolutionary age and its regulatory functions," concludes David Goode, senior author and Group Leader, Junior Faculty, at Peter MacCallum Cancer Centre. "Our method could be used to identify which mutations in a particular tumour are most important, creating a novel framework that with further advances in genomics will become increasingly informative for future cancer research."

More information: Anna S Trigos et al, Somatic mutations in early metazoan genes disrupt regulatory links between unicellular and multicellular genes in cancer, *eLife* (2019). DOI: 10.7554/eLife.40947

Provided by eLife