Francis Crick Institute press release

Peer reviewed
Experimental study
Human samples, animals and cells

Age-related genetic changes in the blood associated with poor cancer prognosis

Researchers from the Francis Crick Institute, UCL, Gustave Roussy and Memorial Sloan Kettering Cancer Center (MSK), have discovered that expansion of mutant blood cells, a phenomenon linked to ageing, can be found in cancerous tumours, and this is associated with worse outcomes for patients.

Understanding the biological interface of age-related genetic changes and diseases of ageing, such as cancer and cardiovascular disease, is important to develop preventative therapies for a growing proportion of the population.

Clonal haematopoiesis of indeterminate potential (CHIP) is a condition where blood stem cells accumulate mutations over time, influenced by both ageing and external environmental factors. CHIP has already been shown to be associated with risk of age-related disorders, such as cardiovascular disease, but the impact of these genetic changes on solid cancer evolution hasn't been thoroughly investigated.

Work published today in the *New England Journal of Medicine*, is a detailed study of the link between CHIP and cancer, in over 400 patients with lung cancer as part of the Cancer Research UK funded TRACERx and PEACE studies, and 49,000 patients with different types of cancer from MSK.

CHIP and cancer prognosis

An initial examination of blood samples allowed the research team to determine which patients had CHIP mutations in their blood. When matched with clinical data, the scientists observed that these mutations were associated with patients living for a shorter period of time, regardless of their age or the stage at which the cancer was diagnosed.

The researchers then went on to study patients with CHIP in more detail and determine whether the specific mutations were also present in their lung tumours because of blood cell infiltration. This was found to be true in 42% of patients with CHIP and they called this phenomenon tumour infiltrating clonal haematopoiesis (TI-CH). The team found that it was TI-CH, not CHIP alone, that was associated with the greater risk of cancer relapse and cancer death.

This finding was supported by samples from the PEACE study, a postmortem investigation of areas where cancer has spread, the main cause of cancer death. The team found that metastatic tumours at these sites often contained TI-CH mutations.

Not all mutations are equal

To inspect the link between TI-CH and poor patient outcomes, the scientists went on to look at the composition of cells in the lung tumours. They found that patients with TI-CH had an expansion of myeloid cells, a type of immune cell. These cells are an important part of the tumour microenvironment and unlike some immune cells that are primed to recognise and fight cancer, myeloid cells have been shown to regulate inflammation and can support tumour progression and spread.

The researchers also discovered that when mutations affected a gene called *TET2*, which is an important regulator of blood cell production, across thousands of individuals, the *TET2* mutant blood cells were more likely to infiltrate the tumour. When analysing hundreds of single cells from the tumours of two patients with TI-CH, they confirmed that *TET2* mutations were mostly present in myeloid cells but not in other immune cell types.

The team then collaborated with blood cancer and CHIP experts in a Crick lab led by Dominique Bonnet, to study the impact of *TET2* mutations experimentally. Together they grew organoids, mini lung tumours, with *TET2* mutant myeloid cells. They showed that *TET2* mutant myeloid cells remodelled the tumour microenvironment and accelerated tumour organoid growth.

Looking beyond lung cancer

Finally, in collaboration with researchers at Memorial Sloan Kettering Cancer Center in the US, the team validated their findings using a much larger data set of over 49,000 patients with different types of cancer. Overall, the presence of TI-CH was an independent predictor of shorter survival. But the presence of CHIP and TI-CH varied between cancer types. Researchers found these mutations were more common in cancers known to be harder to treat like lung cancer, head and neck cancer and pancreatic cancer.

The next steps for this work will be to confirm that CHIP directly contributes to cancer outcomes and then detail the exact mechanism by which CHIP is functionally implicated in the development of aggressive cancers.

This work was led by Oriol Pich, Elsa Bernard and Maria Zagorulya.

Oriol Pich, Postdoctoral Project Research Scientist in the Crick's Cancer Evolution and Genome Instability Laboratory, said: "Our results show that blood cells carrying age-related mutations can infiltrate tumours and impact cancer evolution, leading to worse outcomes for patients.

"This is important because CHIP is a natural phenomenon of ageing that is common in patients with cancer."

Elsa Bernard, Group Leader at Gustave Roussy and co-first author of the study, explains: "Through the integrated analysis of large-scale genomic data and cellular profiling, we uncovered a previously unrecognized interaction between hematopoietic aging and tumor

evolution. These findings pave the way for new predictive approaches to assess the risk of cancer relapse or progression."

Charlie Swanton, Deputy Clinical Director at the Crick, Chief Clinician at Cancer Research UK and Chief Investigator for TRACERx, said: "This is the first time that we've been able to see at scale, the interaction of two different types of 'clonal proliferations', age-related CHIP and cancer, providing insight into how ageing might impact cancer risk.

"As we start to piece together the picture of the most important mutations which evolve during the ageing process in cells from the bone marrow, and the impact they have in disease, we hope we can start to identify opportunities for intervention and maybe even prevention of some age-related cancers."

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Notes to Editors

Reference: Pich, O. *et al*. (2025). Tumor-Infiltrating Clonal Hematopoiesis. *New England Journal of Medicine*. DOI: 10.1056/NEJMoa2413361.

The Francis Crick Institute is a biomedical discovery institute with the mission of understanding the fundamental biology underlying health and disease. Its work helps improve our understanding of why disease develops which promotes discoveries into new ways to prevent, diagnose and treat disease.

An independent organisation, its founding partners are the Medical Research Council (MRC), Cancer Research UK, Wellcome, UCL (University College London), Imperial College London and King's College London.

The Crick was formed in 2015, and in 2016 it moved into a brand new state-of-the-art building in central London which brings together 1500 scientists and support staff working collaboratively across disciplines, making it the biggest biomedical research facility under a single roof in Europe.
http://crick.ac.uk/

About Gustave Roussy
Ranked first in France, first in Europe and fourth in the world, Gustave Roussy is a centre of global expertise entirely dedicated to patients living with cancer. The Institute is a founding pillar of the Paris-Saclay Cancer Cluster. Source of therapeutic innovations and diagnostic breakthroughs, the Institute welcomes nearly 50,000 patients each year, including 3,500 children and adolescents, and develops an integrated approach combining research, care and teaching. An expert in rare cancers and complex tumours, Gustave Roussy treats all cancers at all stages of life. It offers its patients personalised care that combines innovation and

humanity, taking into account both care and the physical, psychological and social quality of life. With 4,100 employees at two sites, Villejuif and Chevilly-Larue, Gustave Roussy brings together the expertise essential for high-level cancer research; 40% of treated patients are included in clinical studies. To find out more about Gustave Roussy and follow the Institute's news: www.gustaveroussy.fr/en, X, Facebook, LinkedIn, Instagram and Bluesky.