The war on leukaemia: how the battle for cell production could be decisive

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A key step in understanding the nature of the fight for superiority between mutated genes and normal genes could lead to new therapies to combat leukaemia, say researchers from the University of Birmingham and Newcastle University.

The study, published in *Cell Reports*, investigated Acute Myeloid Leukaemia to understand why leukemic cells are not able to develop normally into mature blood cells.

Stem cells in the bone marrow generate billions of different blood cells each day. The process resembles a production line with genes acting as regulators to control each step of the blood formation.

Leukaemia arises when the DNA encoding regulators in the stem cells is changed by a mutation. When a mutation occurs in the relevant regulator genes, the finely balanced order of the production line is disrupted with drastic consequences.

A chain reaction occurs, with the function of other regulators in the process being altered. The new cells no longer develop into normal blood cells, but leukemic cells that multiply and begin to take over the body.

Professor Constanze Bonifer (/staff/profiles/cancer/bonifer-constanze.aspx), of the University of Birmingham, explained, “This particular leukaemia is characterised by a mutation in a gene that produces a rogue regulator. That is, one that is not normally made and behaves in a different way. The knock-on effect of that one mutation is huge.”

The team showed that this aberrant regulator switches off hundreds of other genes, many of them regulators themselves, by using state of the art technology that looks at the activity of all genes within a cell. As a consequence of the drastically altered production line, normal blood formation cannot happen, and leukemic cells are formed.

Professor Bonifer added, “Understanding how these rogue regulators operate is essential. Because all cells contain two copies of each gene, one from the mother and one from the father, these leukemic cells have one mutated gene and one unchanged one that would make the normal regulator.”

“What happens in the leukemic cell is fundamentally a battle for supremacy between the two regulators, and the mutated one wins much of the time. This is compounded by the normal regulator which tries to compensate for defeat, and in doing so changes the output of genes that would be otherwise unaffected by the abnormal regulator. Quite simply, the result is a real mess. The cells are confused and can’t develop into mature blood cells.”

Crucially, the team identified that removing the mutated regulator allowed the cells to resume their normal behaviour and the production line returns to the regular process.

Professor Olaf Heidenreich, of Newcastle University, said, “This one aberrant regulator reprograms thousands of genes. If targeting it can reverse the changes it is making to the cellular production line then it would ultimately point towards new avenues for a more precise treatment of leukaemia.”

“Knowing that the production line can be restored to normal function gives us real hope. Of course, that is much easier to do in the lab that it is in the human body. But now we know how this works we can look to deliver inhibitors to those mutated regulators. Creating one that works is the next step we have to overcome.”

Professor Heidenreich is leading on turning this breakthrough discovery into therapies that could provide new ways of combatting leukaemia.

The project was funded by **Leukaemia and Lymphoma Research (http://leukaemialymphomaresearch.org.uk/)**, **Cancer Research UK (http://www.cancerresearchuk.org/)**, and the **Medical Research Council (http://www.mrc.ac.uk/)**.

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Notes to editors

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Read the full paper (PDF - 4.4Mb) (http://www.cell.com/cell-reports/pdf/S2211-1247(14)00687-1.pdf): ‘Identification of a dynamic core transcriptional network in t(8;21) AML regulating differentiation block and self-renewal’ *Cell Reports* 2014.

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