# New insights into blood cancer that develops before birth

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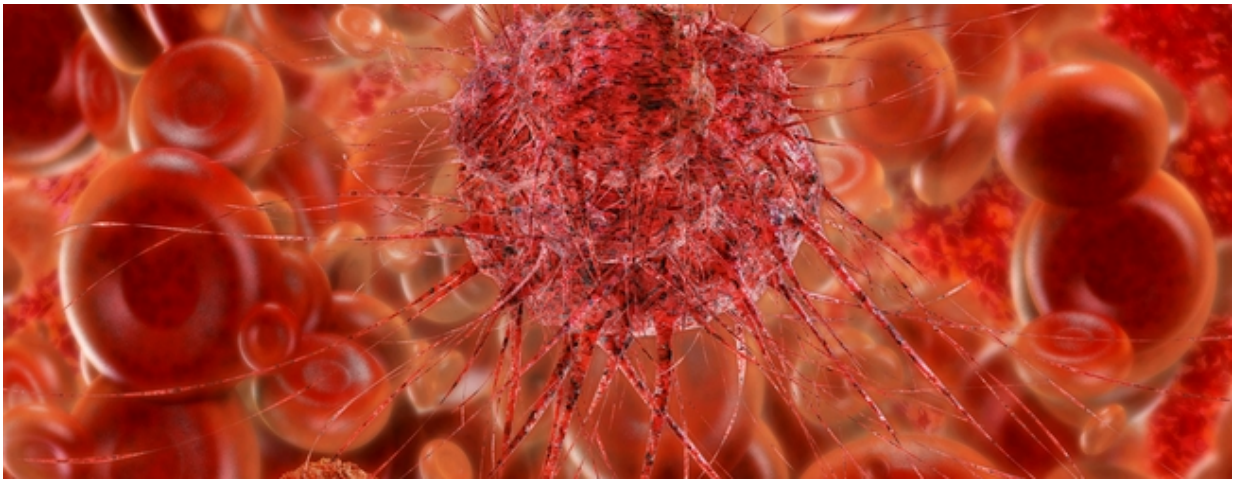

Researchers from the Medical Research Council (MRC) Centre for Regenerative Medicine at the University of Edinburgh have identified the cells responsible for a form of leukaemia that can develop while a baby is in the womb. The research, published in *Cell Reports*, adds to our knowledge of how this aggressive type of cancer advances and will help identify future therapies.

One form of leukaemia is caused by a type of DNA damage called 'chromosomal translocation'. This is where parts of two different chromosomes fuse together. The resultant fusion gene – in this instance

MLL-AF4 – acts in a very different way from when the two genes are separate.

The expression of the MLL4-AF4 fusion gene can occur at very early stages of the embryo's development while in the womb and can result in infants being born with a very aggressive form of leukaemia. The earlier the onset of this form of blood cancer, the worse the prognosis.

Survival rates for the most common form of childhood leukaemia, acute lymphoblastic leukaemia (ALL) have improved dramatically, with around nine in 10 children surviving for longer than five years. Infant ALL, which develops when the child is under 12 months of age, accounts for less than five percent of cases of childhood ALL and is a biologically distinct cancer – often involving just a few genetic faults. It has a much poorer outlook, with only around half of patients surviving for longer than five years. A MLL gene fault is involved in 80% of cases of infant acute lymphoblastic leukaemia.

Because this cancer begins to develop "in utero" and prior studies have studied the effect of MLL-AF4 in blood cells of adult mice only, the key question of how MLL-AF4 might affect an unborn baby's unique blood cells remained unanswered. This is the first study to investigate how MLL-AF4 effects developing blood forming cells in mouse embryos in a bid to understand how this aggressive leukaemia emerges.

To investigate the disease process, scientists bred mice where one parent carries an inactive form of the fusion gene and the other parent expresses a gene for an enzyme that activates the fusion gene. The embryos from this pairing were found to have a development window where a pre-leukaemic state took hold with increased production of pro-B cells – precursor to a type of white blood cell.

Lead researcher, Dr Katrin Ottersbach, said of the results: "One of the

most common and aggressive types of infant blood cancer is associated with the MLL-AF4 fusion gene, which arises during pregnancy. One of the main impediments to improving the survival rates in infants is the lack of knowledge on where and when during development this mutation arises and how it affects the developing blood system of the baby.

"Our findings reveal the first changes that take place in blood development caused by the MLL-AF4 mutation during a pre-cancerous state. This has increased our knowledge on how this aggressive disease develops and will help identify early signs of disease and points for therapeutic intervention."

Dr Alasdair Rankin, Director of Research at blood cancer charity Bloodwise, which funded the study along with the MRC and the Wellcome Trust, said "Long term survival rates for childhood leukaemia have improved significantly overall, but the outlook for infants who develop leukaemia soon after birth remains comparatively poor. The intensive chemotherapy used can itself be fatal for babies and many survivors will develop health problems in later life. This more detailed understanding of how a key genetic fault drives the majority of infant leukaemia cases could lead to more effective and kinder treatments in the future."

Provided by Medical Research Council