

A causal mechanism for childhood acute lymphoblastic leukaemia

Mel Greaves

<https://doi.org/10.1038/s41568-018-0015-6>

Corrected: Author Correction

fusion (red/green, yellow). Remaining (non-fused) *ETV6* allele, green spot. Remaining (non-fused) *RUNX1* allele, large red spot. Residual portion of rearranged *RUNX1* allele, small red spot. 10^{-4} : frequency of CD19⁺ cells scored positive for fusion in cord blood by M-FISH.

Modified with permission from reference ⁵.

Supplementary Box 2. Infections and ALL: experiments of nature

Further validation of the infection hypothesis might be forthcoming if it were possible to conduct a very large, prospective cohort study on the impact of day care or school attendance on risk. This would be logistically difficult but two ‘experiments of nature’ may have done just that.

After the reunification of Germany in 1989, incidence rates of childhood ALL in the old East Germany increased by 25% in a short period of six years ⁶. This compares with an estimated 1% per year increase in Europe over the same period and was considered unlikely to be ascribable to better diagnostic ascertainment post-1989. No such increase was observed for AML or paediatric solid cancers. The authors of this report drew attention to the fact that a major change in day care attendance took place abruptly in 1989. Prior to this date, effectively all infants, starting at age three months, attended state run care centres, cohabiting with large numbers of older children in order for their mothers to return to work. This ceased in 1989. A prediction, at that time, would have been that a significant increase in ALL should occur by the time infants in that cohort reached 3-5 years of age, as was indeed observed.

Following the onset of the SARS epidemic in Hong Kong in 2003, the local government introduced extraordinary measures to reduce the likelihood of spread of infection. All schools were closed for two months and for the following six months, very strict steps were taken to optimise sanitation in schools. A striking impact of these measures was a drop in infectious, communicable disease in 2003 compared with the preceding four years and following two years. This included chickenpox, measles and scarlet fever. There was also a significant ($p = 0.01$) drop in the incidence of ALL, but not other childhood cancers, during this same period ⁷.

These observational studies do not provide evidence for causal associations but they accord with predictions of the delayed infection hypothesis.

Supplementary Box 3. Determinants of microbial exposure in infancy

The pattern, degree and impact of infection peri-natally and during infancy will be collectively influenced by many factors including family structure, other social exposures, maternal infection history and variables that may influence acquisition of the microbiota, which occurs soon after birth ⁸, including breastfeeding, diet and mode of delivery at birth. We do not currently have an algorithm that enables us to compute net exposure. The cellular architecture and functional competence of newborn innate and adaptive immune systems has been mapped ⁹ and twin studies have identified specific and generalised patterns of gut microbiota during the first two years of life ¹⁰. Against this background, some quantitative measure of changes in the key components of the immune network in blood (regulatory T cells and cytokines) during the first year of life could be very informative. Intriguingly, low

levels of the key immuno-regulatory cytokine IL-10¹¹ at birth were found to be associated with increased risk of BCP-ALL¹².

Supplementary Box 4. Other cancer risks and health consequences of unmodulated immunity in infants

Gutensohn and Cole¹³ have suggested that Hodgkin lymphoma in young adults could also be a consequence of altered patterns of infectious exposure in modern societies. Analysis of risk factors for Hodgkin lymphoma in young adults has highlighted the same early life circumstances as in childhood ALL including lowered risk associated with high birth order, day care attendance and the protective effect of some early microbial exposures¹⁴. A parallel was drawn between Hodgkin lymphoma epidemiology and the differential responses to polio virus. Polio virus infection early in life is considerably more common in poorer and less sanitary communities. But, paradoxically polio, as a pathological response, is considerably more common in more affluent settings¹⁵. Similar observations apply to Epstein-Barr virus (EBV) infections and infectious mononucleosis¹³.

The ‘hygiene’ hypothesis proposed for allergies in 1989 and later applied to type 1 diabetes is similar to the delayed infection hypothesis for BCP-ALL. And the epidemiological data on allergies and some auto-immune diseases in the young - type 1 diabetes and multiple sclerosis, are similar to BCP-ALL with respect to socio-economic development, the impact of day care attendance, birth order and socio-economic features of communities¹⁶. Common infections can both trigger or promote autoimmunity and protect dependent upon timing and, possibly, type of infection¹⁷.

Childhood ALL, allergies and type 1 diabetes do not occur at increased rates together in families, indeed risk of allergies and ALL are reciprocal¹⁸ and their genetic susceptibility variants are different. They do, however, track together ecologically with higher incidence in the most affluent countries¹⁹.

References

1. Breatnach, F., Chessells, J.M. & Greaves, M.F. The aplastic presentation of childhood leukaemia: a feature of common-ALL. *Br J Haematol* **49**, 387-393 (1981).
2. Horsley, S.W. et al. Genetic lesions in a preleukemic aplasia phase in a child with acute lymphoblastic leukemia. *Genes Chromosomes Cancer* **47**, 333-340 (2008).
3. Anderson, K. et al. Genetic variegation of clonal architecture and propagating cells in leukaemia. *Nature* **469**, 356-361 (2011).
4. Zimmermannova, O. et al. Acute lymphoblastic leukemia with aleukemic prodrome: preleukemic dynamics and possible mechanisms of immunosurveillance. *Haematologica* **102**, e225-e228 (2017).
5. Mori, H. et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. *Proc Natl Acad Sci USA* **99**, 8242-8247 (2002).
6. Spix, C., Eletr, D., Blettner, M. & Kaatsch, P. Temporal trends in the incidence rate of childhood cancer in Germany 1987-2004. *Int J Cancer* **122**, 1859-1867 (2008).
7. Li, C.K. et al. Impact of SARS on development of childhood acute lymphoblastic leukaemia. *Leukemia* **21**, 1353-1356 (2007).
8. Lim, E.S. et al. Early life dynamics of the human gut virome and bacterial microbiome in infants. *Nat Med* **21**, 1228-34 (2015).

9. Fragiadakis, G.K. et al. Mapping the Fetomaternal Peripheral Immune System at Term Pregnancy. *J Immunol* **197**, 4482-4492 (2016).
10. Planer, J.D. et al. Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice. *Nature* **534**, 263-6 (2016).
11. Wills-Karp, M., Santeliz, J. & Karp, C.L. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* **1**, 69-75 (2001).
12. Chang, J.S. et al. Profound deficit of IL10 at birth in children who develop childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev* **20**, 1736-40 (2011).
13. Gutensohn, N. & Cole, P. Childhood social environment and Hodgkin's disease. *N Engl J Med* **304**, 135-140 (1981).
14. Cozen, W. et al. A protective role for early oral exposures in the etiology of young adult Hodgkin lymphoma. *Blood* **114**, 4014-20 (2009).
15. Backett, E.M. Social patterns of antibody to poliovirus. *Lancet* **i**, 778-783 (1957).
16. Rook, G.A.W. (ed.) The hygiene hypothesis and Darwinian medicine (Birkhäuser, Basel, 2009).
17. Zacccone, P. & Cooke, A. Infectious triggers protect from autoimmunity. *Semin Immunol* **23**, 122-9 (2011).
18. Linabery, A.M., Jurek, A.M., Duval, S. & Ross, J.A. The association between atopy and childhood/adolescent leukemia: a meta-analysis. *Am J Epidemiol* **171**, 749-64 (2010).
19. Feltbower, R.G., McKinney, P.A., Greaves, M.F., Parslow, R.C. & Bodansky, H.J. International parallels in leukaemia and diabetes epidemiology. *Arch Dis Child* **89**, 54-56 (2004).