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Editorial

A Brief erition of MLL-AF4 Leukemia

Stefano Carugo*

Department of Clinical Science and Oncology, University of Milan, Milano MI, Italy

ABOUT THE STUDY

MLL-AF4 leukaemia type of acute leukaemia in children, and it has a dismal prognosis. Currently no experimental models which accurately represent human illness. Lin describes their model in this issue of Cancer Cell that recapitulates multiple key aspects of this serious illness, making future mechanistic and preclinical studies easier. MLL (KMT2A) first was identified as a gene involved in chromosome translocations that cause Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukemia (AML) on chromosome band 11q23 (AML). At least 79 MLL translocation partner genes have been identified to far, with some exhibiting distinct leukaemia phenotypic predominance [1]. The t(4;11)(q21;q23) translocation is the most common MLL translocation, and it generally leads in ALL with a pro-B/mixed-B phenotype. The MLL-AF4 (KMT2A-AFF1) fusion protein is produced as a result of this translocation that is the most frequent fusion found in infant acute leukaemia. Unlike other kinds of juvenile B-ALL, which have seen substantial improvements in cure rates, infants with MLL-rearranged leukaemia still have a poor prognosis, with 5-year event-free survival rates hovering around 35% [2]. This could be due to a variety of factors, including a short latency, involvement of the central nervous system, and high white blood cell counts. There is a clear demand for good effective treatments for this kind of leukaemia. MLL-AF4 ALL has a $CD34^{+}$ $CD19^{+}$ $CD10^{-}$ phenotypic and commonly expresses the myeloid markers CD15 and CD65, as well as the neural glial marker NG2.

In a recent study, whole-genome sequencing showed that the predominant clone in infant MLL leukemias had only 1.3 non-silent mutations on average [3]. This malignancy has one of the lowest levels of somatic mutations of any cancer sequenced to date. These results indicate that just a few, if any, cooperating mutations are needed in conjunction with MLL-AF4 to cause this aggressive, short-latency ALL. The ability to properly simulate human illness in a system that is tractable for mechanistic and preclinical studies is a critical component of research to create innovative treatment methods. With such a straightforward genetic landscape, one might think that the MLL-AF4 leukaemia would have been relatively easy to model in research labs.

Unfortunately, despite the best efforts of multiple groups throughout the world, this has not been the case. MLL-AF4 was cloned for the first gene in 1992 [4]. The first MLL leukaemia models used homologous recombination to create chimeric Mll-AF9 animals that developed AML [5], or retroviral transduction of the MLL-ENL fusion into murine bone marrow stem/progenitor cells to cause myeloid leukaemia *in vivo* [5,6]. Two approaches were used in the first reported MLL-AF4 leukaemia models. Rabbits and colleagues used invertor conditional technology to insert a floxed AF4 cDNA in the opposite orientation into the Mll breakpoint region to induce Mll-AF4 expression in either B- or T-lineage cells using different cell-type specific Cre expression drivers [7].

Mice developed B-lineage lymphomas after a long latency period and with a more mature phenotype than patient MLL-AF4 ALL, regardless of the Cre driver. Mll-AF4 knockin mice were created by Kersey and colleagues, with expression regulated by the endogenous Mll promoter [8]. After a long time of latency, these mice developed mixed lymphoid/myeloid hyperplasia and B cell lymphomas. Since then, a variety of new techniques have been used in an attempt to develop models that more closely resemble the human MLL-AF4 pro-B ALL in terms of phenotype and latency. The Armstrong lab created a conditional Mll-AF4 model that developed AML and pre-B ALL when induced by Mx1-Cre expression, whereas the Inokuchi lab produced transgenic MLL-AF4 mice that developed pro-B cell lymphoma and the Marschalek lab developed a reciprocal AF4-MLL retroviral transduction/transplantation model that induced ALL of multiple phenotypes with relatively long latency without the need for MLLAF4 [9]. Multiple different ways have been tried, but none of them have resulted in leukaemia. Lin and colleagues provide data from their freshly established MLL-Af4 leukaemia model in the current issue of Cancer Cell [10]. The researchers use a retrovirus that encodes an MLL-Af4 fusion (human amino-terminal MLL fused to carboxy-terminal murine Af4) to transduce human $CD34^{+}$ cells, which are then implanted into immunocompromised mice. The transplanted mice develop pro-

Correspondence to: Stefano Carugo, Department of Clinical Science and Oncology, University of Milan, Milano MI, Italy, E-mail: Stefanucgitl121@gmail.com

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B ALL with a short latency period and other MLL-AF4 leukaemia characteristics.

The phenotype was same whether $CD34^+$ cells form umbilical cord blood or $CD34^+$ cells of adult peripheral blood were used, and expression of the reciprocal AF4-MLL fusion was not needed. Surface marker phenotype, DNA binding as determined by ChIP-seq, and gene expression profiles were all used to confirm the model's similarity to human MLL-AF4 pro-B ALL. This model also provided other biological insights, such as evidence for the MLL fusion partner's instructional role, at least in part, through differential gene targeting and expression. Even after culturing under myeloid conditions and lack of B cell sur face-marker expression, MLL-Af4-transformed cells maintained a lymphoid gene expression profile, maintaining their plasticity and ability to produce pro-B ALL in *vivo*.

Overall, this MLL-AF4 ALL model is the most realistic representation of the human disease to date. Although the model developed in this paper is a significant step forward, it presents new problems that must be solved. For one thing, it's unclear why the identical MLL-Af4 construct produced in murine cells induces AML but pro-B ALL in human cells. MLLAF4 also generates a very low titer retrovirus for an unknown reason, leaving it incapable of providing a comparable disease phenotype. Certain DNA sequences have been reported to significantly influence retrovirus production in systems unrelated to MLL leukaemia via a variety of ways. Understanding why this happens with MLL-AF4 could have an influence on future leukaemia modelling systems.

What differences between human and murine AF4 are responsible for the fusion partner's varied instructional properties? Specific amino acid differences between Af4 and AF4 likely drive lineage-related gene expression programme by regulating critical protein-protein interactions, post-translational changes, or gene targeting in host hematopoietic cells. Although much has to be discovered mechanistically, one of the major contributions of this work is that it provides the scientific community with a very simple model that develops acute leukaemia with the correct phenotype and molecular characteristics as human MLL-AF4 ALL. This might be particularly important for the research into therapies for this common MLL fusion leukaemia with a poor prognosis.

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