acetylation can be reversed by various histone deacetylases, there are no known histone demethylases. Therefore, once a genomic region is methylated, modified nucleosomes must be replaced rather than altered to remove this epigenetic mark. Further work will be required to understand the mechanisms responsible for the spread of local histone

modifications and the impact of these modifications on chromatin structure and transcriptional regulation.

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Src kinases in Ph⁺ lymphoblastic leukemia

Michael Deininger

Philadelphia chromosome–positive leukemia may present as chronic myeloid leukemia or B-cell acute lymphoblastic leukemia. A new study shows that certain Src kinases are necessary for the induction of B-cell acute lymphoblastic leukemia but not chronic myeloid leukemia.

What is the basis of the tissue specificity of certain oncogenes? Are there differences in the frequency of certain mutations, perhaps related to differences in DNA repair, or is tissue specificity a question of the target cell having the right signaling network in place to allow for transformation by a specific oncogene? In the latter case, are the essential components of this network identical, regardless of the cell type? In Philadelphia chromosome–positive (Ph⁺) leukemia, caused by the *BCR-ABL1* translocation, this has been a longstanding question, as Ph⁺ disease may present as one of two distinct entities, chronic myeloid leukemia (CML) or B-cell acute lymphoblastic leukemia (B-ALL). Clinical observations, mutational studies of *BCR-ABL1* and mouse leukemia models present a complex picture, and it has been difficult to identify differences in the use of downstream signaling pathways by Bcr-Abl. On page 453 of this issue, Yiguo Hu and colleagues¹ show that certain Src kinases are essential to the ability of Bcr-Abl to induce B-ALL but not CML. Their results shed new light on an old discussion and provide a rationale for the use of Src kinase inhibitors to treat Ph⁺ B-ALL.

CML and Ph⁺ B-ALL

The Philadelphia chromosome was initially thought to be specific for CML², a disease characterized by excessive proliferation of myeloid cells with mostly normal differentiation. The picture blurred when individuals

Figure 1 Induction of B-ALL versus CML by Bcr-Abl. p190, the shorter form, is practically restricted to B-ALL, whereas p210 is found in both conditions. As shown by Hu *et al.*¹, certain Src kinases are required for induction of B-ALL, whereas several structural motifs in p210 *BCR-ABL1* are required for or favor the induction of CML. It is not clear if multilineage B-ALL and lymphoid blast crisis are different presentations of the same entity or different diseases.

were reported with Ph⁺ myeloproliferative disorders other than CML or acute leukemias, including ALL, a rapidly fatal disease of undifferentiated lymphoid cells³. Then it was determined that the blastic phase of CML could include lymphoid differentiation. Conversely, CML was diagnosed in some individuals after successful treatment of Ph⁺ ALL. This suggested the existence of ‘genuine’ Ph⁺ B-ALL as opposed to multilineage disease, perhaps representing CML diagnosed in lymphoid blast crisis⁴ (Fig. 1).

Is the phenotype of Ph⁺ leukemia determined by features of Bcr-Abl, by the cell type that acquires the oncogene or by both? Clinically, the two common Bcr-Abl variants differ greatly in their capacity to induce CML

but not B-ALL. The larger p210 Bcr-Abl variant is found in almost all individuals with CML and also in one-third of those with Ph⁺ B-ALL. In contrast, the p190 variant of Bcr-Abl is present in two-thirds of those with Ph⁺ B-ALL and only rarely in CML⁵. Explanations include the weaker tyrosine kinase activity of p210 Bcr-Abl, which may consistently induce CML but only occasionally induce B-ALL. Alternatively, the GTP exchange and Rac GTPase functions present in p210 Bcr-Abl but not in p190 Bcr-Abl may be crucial for induction of CML but not B-ALL. In mice transplanted with bone marrow infected with *BCR-ABL1* retroviruses, motifs in the first 210 amino acids of Bcr (specifically, the coiled-coil domain and Tyr177) promote CML but not B-ALL⁶. Despite these hints, no signaling pathways specific for either type of disease had been definitively identified.

A role for Src kinases

Hu *et al.*¹ show that the Src family kinases Lyn, Hck and Fgr are activated by Bcr-Abl in primary mouse B-lymphoblasts. They show that disease latency and survival were greatly extended in wild-type mice transplanted with *BCR-ABL1*-infected marrow obtained from mice with homozygous deletions of at least two of these three Src kinases. In contrast, the induction of CML was not affected. CGP76030, a Src kinase inhibitor, significantly prolonged the survival of mice with B-ALL but not CML. Taken together, this is strong evidence that Lyn, Hck and Fgr are crucial to induction of B-ALL by Bcr-Abl but dispensable for induction of CML. Lack of one kinase alone had no effect, suggesting that there is considerable redundancy.

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The first hint that Src kinases may have a role in the pathogenesis of Bcr-Abl-driven leukemia came from the observation that Lyn and Hck are activated in a complex with Bcr-Abl in myeloid cells^{7,8}. Hck complexed with Bcr-Abl directly phosphorylates STAT5 (ref. 9) and Tyr177 of Bcr-Abl⁸, a residue crucial for the induction of myeloid leukemia in mice. In view of these data, Src kinases seemed to be more important for myeloid than lymphoid transformation, and the results of Hu *et al.*¹ caution against placing too much weight on data from cell lines. But we might not yet have the full story with respect to CML. Although Lyn, Hck and Fgr are dispensable, a role for other Src kinases cannot be ruled out, as this would require proof that CGP76030 completely blocks all Src kinases in the CML mice.

Regardless, the authors' work may have important implications for the treatment of BCR-ABL1-positive leukemias. Many individuals with Ph⁺ ALL develop resistance to the Abl kinase inhibitor, imatinib, as a result of mutations in the BCR-ABL1 kinase domain. Given that Src kinases are downstream of Bcr-Abl, these individuals should still be responsive to Src inhibitors. In addition, activation of Src kinases has been seen in some resistant

individuals without BCR-ABL1 mutations¹⁰; shutting this 'back door' from the beginning may help prevent this type of resistance.

Exploring B-cell development

A consistent feature of mouse and human BCR-ABL1-positive B-ALL is their pre-B-phenotype, with immunoglobulin heavy but not light chains rearranged¹¹. In contrast, the Philadelphia chromosome is rare in pre-pre-B-ALL or in more mature B-cell malignancies. Thus, it is conceivable that only pre-B-cells have all the 'wiring' in place to be transformed by Bcr-Abl, and that the three Src kinases are required for differentiation to the pre-B stage. Although no B-cell defect has been observed in the triply deficient mice used by Hu *et al.*¹, their results may justify a detailed study. Defective B-cell development with arrest at the pro-B stage was reported in *Lyn^{-/-} Blk^{-/-} Fyn^{-/-}* mice¹². These mice might also be resistant to induction of B-ALL by Bcr-Abl. Alternatively, Bcr-Abl may require Src kinases to arrest B-cells at the pre-B stage.

Another question relates to lymphoid transformation of CML. Analysis of proviral integration sites in mice with both CML and ALL is consistent with independent clones¹³, whereas lymphoid blast crisis arises from the

same clone that produced the chronic phase of disease. In chronic-phase CML, a considerable proportion of B-cell progenitors and peripheral blood B-cells are Bcr-Abl-positive¹⁴ but do not expand. It would be interesting to see if there are also Ph⁺ pre-B-cells. If so, this would argue that an additional genetic event is required to start proliferation, perhaps in contrast to genuine Ph⁺ B-ALL. As the work of Hu *et al.*¹ shows, further defining cell type-specific signaling pathways may allow us to develop rational therapies to exploit them.

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The rat comes clean

Caroline A Wallace & Timothy J Aitman

The rat genome sequence, the third mammalian genome sequence to be generated, was recently reported in *Nature*. The sequence provides new insights into mammalian genome evolution and the opportunity to translate decades of descriptive phenotyping to an understanding of the molecular mechanisms that underlie these phenotypes.

The importance of being *Rattus*

The rat has an important place in our social and demographic history (Fig. 1). Through its contributions to famine and the spread of fatal diseases, and its place in everyday language as a term of abuse, the rat has become synonymous with fear and loathing. Even in the scientific community, the value of the rat, as compared with the mouse, has been hotly debated, both in terms of its suitability as a model organism and its contribution to the bank of genome sequences now available. The

Rat Genome Sequencing Project Consortium (RGSPC) has now published a high-quality draft sequence covering over 90% of the rat genome¹. The rat genome sequence will yield new insights when it is laid alongside those of mice and humans and also promises to advance diverse areas of biology explored during 50 years of research in rat genetics, toxicology, pharmacology and physiology².

Drawing on experience from sequencing the human, mouse and other genomes, the RGSPC adopted a combined BAC sequencing and whole-genome shotgun (WGS) strategy. From the outset, the intention was not to provide finished sequence, although at an estimated 1.32 errors per 10 kb, the sequence quality is close to that accepted for finished sequence. The 2.75 Gb draft sequence has 7× coverage generated from 36 million high-

quality sequence reads, 60% of which originated from WGS and 40% from BACs. To combine the BAC and WGS sequence reads, the RGSPC developed the Atlas software package³, which they also used to give users immediate access to BAC assemblies as each BAC was processed.

The completion of the draft sequence raises the questions of whether finished sequence should be generated for the rat and whether new sequence from other strains should be pursued. The rat community must also decide how the available sequence will be curated and error-checked in the future.

Three's company

The availability of a third mammalian genome sequence presents new opportunities for comparative genome analysis. In a three-way

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