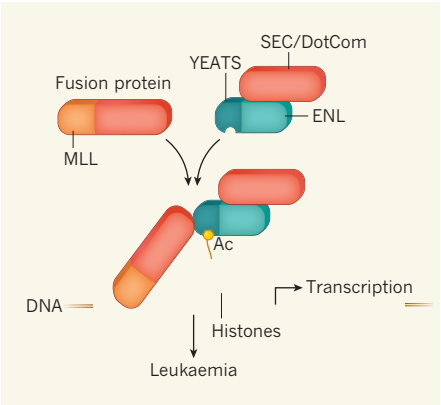

Figure 1 | The protein ENL is crucial for MLL-rearranged leukaemia. Some leukaemias involve abnormal hybrid proteins formed by the fusion of part of the protein mixed lineage leukaemia (MLL) with a portion of a second protein. This second protein is often part of the super elongation complex (SEC) or the DOT1L-containing complex (DotCom), both of which modulate gene-transcription programs in MLL-rearranged leukaemias (whole and fused SEC/DotCom indicated in red). The protein ENL associates with both complexes, and, in cells in which one copy of the complex is fused to MLL, interacts with both the fused and non-fused complexes. ENL contains a YEATS domain that binds to specific acetyl groups (Ac) on the protein histone H3 — part of a histone complex around which DNA is packaged. Erb *et al.*[2] and Wan *et al.*[3] show that the ENL YEATS domain helps to stabilize the association of SEC and DotCom with DNA, promoting leukaemia-driving programs of gene expression.

of MLL-r cells. H3K79 methylation has long been associated, circumstantially, with genes actively undergoing transcription[14], and as the regulatory mechanisms that govern DOT1L activity come into sharper focus, a major unanswered question is how the signals encoded by this histone modification could directly influence transcription.

Methyl–lysine signals are typically connected to downstream processes by mechanisms analogous to those involved in the YEATS domain's reading of acetyl–lysine signals. Reader domains have been identified[15] for all major histone methylation sites apart from H3K79. Furthermore, methylated lysines can be dynamically regulated by demethylase enzymes, but a demethylase that removes methyl groups at H3K79 is yet to be identified[14]. Erb *et al.* and Wan *et al.* provide further motivation to find readers and demethylases for H3K79 methylation, which would be predicted to intersect with ENL-mediated signalling under both physiological and pathological conditions.

There is an emerging appreciation that epigenetic regulators can have fundamental roles in disease. This awareness has ushered in focused efforts to develop inhibitors that target these mechanisms to treat cancer. A DOT1L inhibitor has been evaluated in a clinical trial for MLL-r leukaemias (see go.nature.com/2lquysj for details). Intriguingly, Erb *et al.* showed that treating cells with a DOT1L inhibitor in conjunction with an ENL mutant that cannot recognize acetylated lysine suppressed the leukaemia-promoting gene-expression program more effectively than disruption of either protein alone, suggesting synergistic cooperation between these interventions.

Wan *et al.* also investigated the potential of combinatorial therapy to treat MLL-r leukaemia, targeting acetyl–lysine binding by both the ENL YEATS domain and another reader of lysine acetylation — the bromodomain of BET family proteins. BET proteins normally interact with SEC and promote transcriptional elongation[16–18]. Drugs called BET inhibitors disrupt the binding of BET proteins to acetyl–lysine moieties, and there are currently about 20 clinical trials testing the efficacy of these drugs as cancer treatments. Wan and colleagues found that perturbation of the ENL YEATS domain combined with treatment with the BET inhibitor JQ1 was highly toxic to MLL-r leukaemic cells.

The effects of these combinatorial interventions highlight how the integration of multiple modified histone signals is instrumental in establishing the distinct epigenetic state of MLL-r leukaemia. As such, these cancers may be susceptible to a multi-pronged targeting approach that could increase therapeutic efficacy while mitigating the emergence of drug resistance, which is a risk with single-drug approaches.

Historically, drug hunters have focused on targeting enzymatic activities rather than protein–protein interactions. However, there is growing excitement — in part owing to the success of BET inhibitors — about therapies that target diverse reader domains. The binding pocket of the YEATS domain is attractive for drug development, because it is deep and amenable to the accommodation of acetyl–lysine along with larger analogous modifications[19]. Thus, the discovery that MLL-r leukaemias are reliant on ENL not only provides fundamental insight into how cells integrate signals relating to transcription, but also has provocative implications for the treatment of a complex human disease. ■

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50 Years Ago

The solution of the ribonuclease structure at a resolution of 2 Å … is clearly an event of unique importance and interest … The schematic illustration of the chain outline shown in the article gives only a small portion of the information which is expected shortly to emerge, but some interesting conclusions may already be drawn, particularly in connexion with predictions based on chemical evidence … The appearance of the ribonuclease structure necessarily represents, among other more important consequences, a day of reckoning for those bold enough to have offered three-dimensional structures based only on indirect evidence. Such structures do not appear to have fared well … At the present stage it therefore appears that the indirect approach to the construction of three-dimensional protein structures is of dubious value. The appearance of more complete structural data will … now be awaited with the greatest interest.
From *Nature* 11 March 1967

100 Years Ago

The main thesis of the authors of this book is that much of the fatigue occurring among industrial workers is unnecessary, and is caused by the carrying out of the work under conditions which involve excessive and avoidable expenditure of energy. The methods suggested for the elimination of unnecessary fatigue consist for the most part of various mechanical devices. One of these consists in the provision of high chairs so that the workers can sit to their work instead of having to stand. Another suggestion is the use of chairs with springs which exclude vibration from the floors … application of these methods produces a striking improvement.
From *Nature* 8 March 1917

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