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DISSERTATION TITLE:	*A novel pioneer function of the transcription factor c-Myb*

All the cells in the human body contain the same DNA and the same set of genes. The various cells are different and have distinct functions because specific genes are turned on or off in different cell types. Regulation of gene expression is a highly complex process that is controlled by a group of proteins named transcription factors. Disruption of these regulatory mechanisms can have severe consequences, resulting in developmental failures and cancer. The transcription factor c-Myb is involved in regulating the development of blood cells, known as haematopoiesis, and high protein levels of c-Myb has been observed in several types of human leukaemias.

In this study, the PhD candidate and colleagues have explored the role of c-Myb as a pioneer transcription factor. In order to regulate the expression of genes, c-Myb binds to DNA as well as to the proteins that DNA is wrapped around in the cell nucleus, named histones. The complex of DNA and histones is known as chromatin and can be found in an open state associated with active gene expression, as well as a closed and more compact state where genes are turned off. Pioneer factors are the first transcription factors to access a silent gene and initiate its expression by increasing the accessibility of DNA. Bettina Maria Fuglerud has investigated the pioneer factor functions of c-Myb by studying a mutated version of c-Myb where one amino acid in the protein has been substituted by another. This mutant is known as c-Myb D152V and has previously been shown by others to cause haematopoietic defects in mice. By the use of binding assays and whole-genome approaches, the study discovered that the interaction with histones is weakened in c-Myb D152V, which impairs c-Myb's ability to open up closed chromatin while keeping DNA binding intact. This defect was found to specifically alter the expression of genes associated with haematopoiesis and disrupts normal differentiation of blood cells in culture. Thus, the D152V mutation seems to knock out the pioneer factor function of c-Myb and is thereby the first pioneer-defect mutant of any transcription factor identified so far. The mutant was further used as a tool to get insight into the mechanisms underlying c-Myb-dependent gene regulation, which revealed that the pioneer factor activity of c-Myb may involve induction of histone modifications followed by dissociation from chromatin.

Taken together, the results from this work has revealed a novel function of c-Myb as a pioneer transcription factor in haematopoiesis, clarifying roles of c-Myb in haematopoietic development which may also be relevant for its functions in human disease.