mgr Sonia Maria Dębek

Discovery and Characterisation of the Epigenetic Function of PIM Kinases in Diffuse Large B-Cell Lymphoma

Abstract

The PIM kinase family consists of 3 proto-oncogenic proteins: PIM1, PIM2 and PIM3, expressed in numerous cancers, including DLBCL. PIM kinases regulate crucial processes, such as proliferation, apoptosis, metabolism, and migration, therefore their inhibition is of great interest as a potential therapeutic strategy. In fact, pan-PIM inhibitors have been studied in clinical trials, e.g. MEN1703, which currently undergoes II phase trial in AML. Although recent studies have shed new light on the biological role of PIM in lymphoid cancers, the details and mechanisms of PIM's oncogenic effects and the consequences of their inhibition in DLBCL remain insufficiently understood. Earlier studies have demonstrated a potential epigenetic role of PIM through histone H3S10 phosphorylation, however, described only at a single locus. The broad genomic role of PIM in modulating transcription in lymphoma cells remains unclear.

The effect of PIM inhibition on histone modifications and proliferation was confirmed by treatment with small molecule inhibitors and by genetic silencing of PIM kinases in DLBCL cell lines. Pan-PIM inhibitor SEL24/MEN1703 changed the global amounts of histone modifications, accompanied by lower phosphorylation of RNA polymerase II, suggesting the involvement of PIM in the elongation phase of transcription.

Local histone acetylation changes in the enhancer (H3K27ac) and promoter (H3K9ac) regions in response to treatment with the SEL24/MEN1703 inhibitor were also identified, coupled with gene expression profiling in DLBCL lines. The integrated results of epigenomic and transcriptomic analyses explain the changes in expression of genes associated with many pathways, including RNA metabolism or DNA damage. The induction of the latter was further confirmed by examining the level of DNA break marker (γH2AX) following treatment with the inhibitor. In addition, PIM inhibition decreased the expression of genes controlled by super-

enhancers (SE), i.e. wide regulatory regions responsible for the high level of expression of the most important genes for the cell, including oncogenes. The analysis also suggested novel biological processes controlled by PIM, such as the reduction of non-coding RNAs generated from SE regions.

The conducted studies document a vast epigenetic role of PIM kinases, and suggest that inhibition of PIM activity leads to potentially cytotoxic disturbances of DLBCL epigenetic patterns, and transcription. They also indicate that SEL24/MEN1703 can be a therapeutic option in DLBCL, and provide information for optimisation of PIM-targeted therapy in the clinic.