PRESS RELEASE

IMB Scientists Discover a Novel Role for Topoisomerases

September, 2013. *Scientists at the Institute of Molecular Biology (IMB) in Mainz have identified a novel role for topoisomerase proteins in gene regulation during development. Previously thought to only function in relieving torsional stress to DNA, these findings represent a leap forward in our understanding of how genetic stability, epigenetic states and gene regulation are interlinked. The findings have far-reaching implications for both basic and translational research and were published in the high-impact multidisciplinary journal* Nature Communications*.*

DNA topoisomerases are among the most highly conserved proteins known. They have key functions in resolving superhelical strains caused to DNA during processes such as replication, recombination and chromosomal segregation. However, a role in gene regulation, especially in the context of cell-fate specification during development, had so far not been described.

Says IMB Group Leader Vijay Tiwari, "*we were puzzled why nature has evolved two type II topoisomerases—topoisomerase II α (TOP2α) and β (TOP2β)—that are very similar in structure and enzymatic properties*". He continues, "*this was until we discovered that the differential expression of these isoforms defines distinct cellular states and shows a clear division of labour during organismal development*".

Research carried out in the laboratory of Dr Tiwari now shows that both Topoisomerase II isoforms preferentially bind gene promoters that show an active chromatin state and are largely expressed. While the common targets of both Topo II isoforms are housekeeping genes, the unique targets of Top2α and Top2β are involved in proliferation/pluripotency and differentiation respectively (Fig. 1). Interestingly, Top2α also prepares a number of developmental genes in an accessible state in embryonic stem cells for their subsequent occupancy by Top2β and transcriptional activation upon differentiation.

The scientists also provide the mechanism of how these enzymes contribute to gene regulation. They show that the absence of topoisomerase activity results in DNA damage as well as changes in histone modifications at target genes. These aberrations further accompanied an altered function of the transcription machinery and consequently, misregulated gene expression.

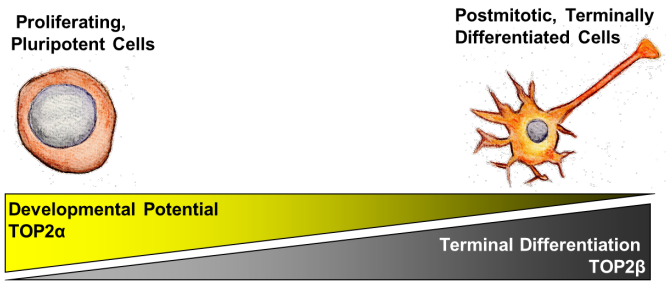

Figure 1. Functional cooperation between topoisomerase II isoforms during development. By contributing to genetic and epigenetic stability as well as gene regulation, Top2α and Top2β define the identity of proliferating, pluripotent and postmitotic, terminally differentiated cells, respectively.

The findings of Dr Tiwari's group provide an unexpected insight into the function of topoisomerase isoforms during development and the regulation of genomic integrity and chromatin stability. "*These findings provide a great advancement in our knowledge of how genetic stability is interlinked with epigenetic states and ultimately gene regulation during cellular differentiation*" says Dr Tiwari.

Original reference: Sudhir Thakurela*, Angela Garding*, Johannes Jung, Dirk Schübeler, Lukas Burger and Vijay K. Tiwari (2013). Gene regulation and priming by topoisomerase IIα in embryonic stem cells. Nat. Commun. 4:2478 doi: 10.1038/ncomms3478 (*=equal contribution)

Webpage of Dr Tiwari's Research Group at IMB: www.imb-mainz.de/Tiwari

Institute for Molecular Biology gGmbH (IMB)

The Institute of Molecular Biology gGmbH (IMB) is a centre of excellence in the life sciences which was established in March 2011. Research at IMB concentrates on three cutting-edge areas: epigenetics, developmental biology and DNA repair. The institute is a prime example of a successful collaboration between public authorities and a private foundation. The Boehringer Ingelheim Foundation has dedicated 100 million euro for a period of 10 years to cover the operating costs for research at IMB, while the state of Rhineland-Palatinate provided approximately 50 million euro for the construction of a state-of-the-art building. For more information about IMB please visit: www.imb.de.

Boehringer Ingelheim Foundation

The Boehringer Ingelheim Foundation is an independent, non-profit organisation committed to the promotion of the medical, biological, chemical and pharmaceutical sciences. It was established in 1977 by Hubertus Liebrecht (1931-1991), a member of the shareholder family of the company Boehringer Ingelheim. With the "PLUS 3" Perspectives Programme and the Exploration Grants, the foundation supports independent group leaders, it endows the internationally renowned Heinrich Wieland Prize as well as awards for up-and-coming scientists. In addition, the foundation has endowed 100 million euro over a period of ten years to finance the scientific running of the Institute of Molecular Biology (IMB) at the University of Mainz.

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