OVERVIEW

DNA topoisomerases have a dual relationship with the genome. They are essential to solving the topological problems inherent to all DNA transactions, but their intrinsic mechanism of action can result in the formation of DNA breaks, either accidentally during normal cellular metabolism or upon chemotherapy treatment with the so-called topoisomerase poisons. Imbalances in DNA topoisomerase activity can therefore compromise cell survival and genome integrity, entailing serious consequences for human health, such as developmental and degenerative problems and, very importantly, neoplastic transformation processes and their subsequent response to treatment.

We are interested in understanding: (i) how DNA topoisomerase activity is regulated to integrate different aspects of genome dynamics; (ii) how an imbalance in these processes can lead to the appearance of pathological DNA breaks; and (iii) how cells specifically respond to these lesions to maintain genome stability.

“We have proven a causal link between spontaneous DNA breaks induced by topoisomerase II and cancer development, especially in cancer predisposition human genetic syndromes such as Ataxia Telangiectasia.”
Work of the Group at the CNIO in these last few months since starting in September 2019 has focused on finishing data analysis to establish a link between a deficient response to topoisomerase II (TOP2)-induced DNA double strand breaks (DSBs) and spontaneous cancer predisposition. Specifically, we have worked with animal models of Ataxia Telangiectasia (AT), a human genetic syndrome that results from loss-of-function mutations in ATM.

The ATM kinase is a master regulator of the DNA damage response to DSBs and a well-established tumour suppressor. Loss-of-function mutations in the gene are not only found frequently in many types of cancer, but also constitute the underlying cause of the neurodegenerative and cancer-prone genetic syndrome Ataxia Telangiectasia. AT patients are particularly predisposed to develop lymphoid cancers, which are thought to arise from inefficient signalling and inaccurate repair of RAG-induced DSBs during V(D)J recombination, and which the Atm-/- mouse models recapitulate in the form of very aggressive T-cell malignancies.

We have unexpectedly found that specifically disturbing the repair of TOP2-induced DSBs by genetically removing the highly specialised repair enzyme TDP2 strongly increases the incidence of thymic tumours in Atm-/- mice, but without changing their molecular characteristics or underlying genomic rearrangements, including a significant association with Tcr loci. Furthermore, we found that TOP2 strongly colocalises with RAG, both in a genome-wide scale and specifically at sites undergoing V(D)J recombination, in a manner that is consistent with its involvement in solving topological problems associated to 3D genome organisation, and that results in increased chromosomal fragility of these regions. Thus, our findings demonstrate a strong causal relationship between spontaneous TOP2-induced DSBs and cancer development, confirming these lesions as major drivers of ATM-deficient lymphoid malignancies, and potentially other conditions and cancer types.

Figure 1: TDP2 deficiency increases thymic cancer predisposition of Atm-/- mice. Kaplan-Meier survival curves (A) and cumulative occurrence of thymic tumours (B) of mice with the indicated Tdp2 and Atm genotypes. Adapted from Álvarez-Quilón et al. (Nat Commun, 2020).

Figure 2: Model to explain aberrant TOP2 activity as a driver of ATM-deficient thymic tumours. TOP2 activity accidentally results in DSBs throughout the genome (top), and TOP2-DSBs arise associated to V(D)J genome rearrangements (bottom), concurred with RAG-mediated DSBs. TDP2 and ATM limit the oncogenic potential of these lesions (Álvarez-Quilón et al., Nat Commun, 2020).

Figure 2 Model to explain aberrant TOP2 activity as a driver of ATM-deficient thymic tumours. TOP2 activity accidentally results in DSBs throughout the genome (top). Additionally, TOP2-DSBs arise associated to V(D)J genome rearrangements (bottom), concurred with RAG-mediated DSBs. TDP2 and ATM limit the oncogenic potential of these lesions (Álvarez-Quilón et al., Nat Commun, 2020).

PUBLICATIONS