

DNA Hypermethylation and Cancer

Junior Group

Summary

Most lymphomas originate from mature B lymphocytes and are characterised by the presence of recurrent chromosome translocations. Mature B cells are unique in that they can diversify their antibody repertoire by somatic remodelling of immunoglobulin genes in germinal centres. These remodelling events are initiated by Activation Induced Deaminase (AID). While critical for the immune response, AID can also initiate chromosome translocations. We aim to study the regulation of the germinal centre reactions and their role in lymphomagenesis.

Strategic Goals

- Study the mechanisms that regulate AID activity and its role in B cell transformation
- Analyse the regulation of mature B cell function by microRNAs
- Explore the potential role of AID in the initiation of non-B cell neoplasias

Almudena R. Ramiro *Junior Group Leader*



Almudena R. Ramiro was born in Madrid in 1971 and obtained her BSc degree in Biochemistry and Molecular Biology from the *Universidad Autónoma de Madrid* in 1994, receiving her PhD with First Class Honours from the same University in 2000.

In 2001 she joined the Laboratory of M. Nussenzweig at Rockefeller University, New York, USA, as a Postdoctoral Fellow funded by the *Ministerio de Educación y Ciencia*. During this time she focused on the function of Activation Induced Deaminase in the diversification of antibodies and established the role of AID in the initiation of lymphomagenic chromosome translocations. This work has been published in leading journals and is widely recognised within the field.

Ramiro has been a *Ramón y Cajal* Investigator since 2004. She received the 2006 Biogen Idec Award for Young Investigators for her work on the role of genomic instability and p53 in AID-induced c-myc/IgH translocations published in *Nature*.

She joined the CNIO as a Junior Group Leader in 2006. In 2007 Ramiro was awarded a European Research Council Starting Grant.



Staff scientists: Maria del Pilar Delgado (since May), Virginia G. De Yébenes. **Post-doctoral fellow:** Thomas Wossning. **Graduate students:** Raúl Jiménez (until September), Pablo Pérez, Isora Vidal. **Technician:** Laura Belver.

Highlights

Estrogen activates AID transcription and function

The immunological targets of estrogen have been well documented as has estrogen's role in establishing a gender bias in autoimmunity and cancer. We have shown that the estrogen-estrogen receptor complex binds to the AID promoter, enhancing AID messenger RNA expression and leading to alterations in SHM and CSR at the Ig locus. Notably, estrogen treatment enhanced the frequency of c-myc/IgH translocations, indicating that the genotoxicity of estrogen via AID production was not limited to the Ig locus. These data suggest that estrogen-induced autoimmunity and oncogenesis may be derived through AID-dependent DNA instability.

MicroRNAs prevent the generation of autoreactive antibodies

MicroRNAs have been demonstrated to be critical for a number of aspects of immune system regulation and function. We have examined the role of microRNAs in terminal B cell differentiation by analysing CD19-Cre^{ki/+}Dicer^{fl/fl} mice. We found that in the absence of Dicer the marginal zone (MZ) B cell compartment is over-represented, and follicular (FO) B cells have an impaired response to BCR signalling. We observed that microRNAs that are differentially expressed in FO versus MZ compartments are downregulated in MZ B cells and that Btk is a potential target of one of these microRNAs. Importantly, Dicer deficient B cells have a skewed BCR

repertoire with hallmarks of autoreactivity, which correlates with high titers of autoreactive antibodies in serum and immunocomplex deposits in kidney (Figure). Together, our results reveal a crucial role of microRNAs in late B cell differentiation and in the establishment of B cell tolerance.

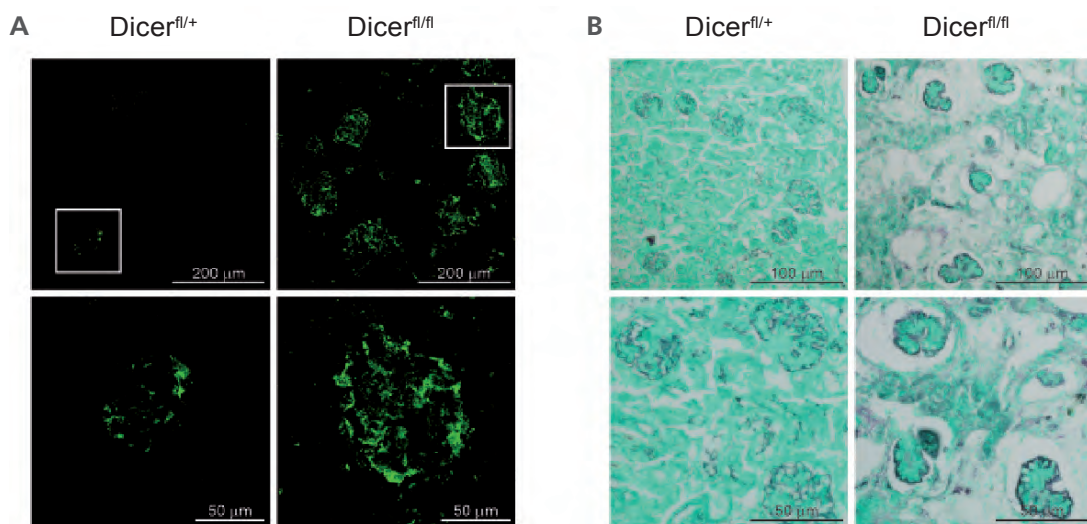


Figure: Immunocomplexes and kidney damage in CD19-Cre^{ki/+}Dicer^{fl/fl} females. Kidney sections from 40-60 week old CD19-Cre^{ki/+}Dicer^{fl/+} and CD19-Cre^{ki/+}Dicer^{fl/fl} animals were stained with anti-IgG antibodies (A) or were subjected to Silver-PAS staining (B).

Publication

Pauklin S, Sernández IV, Bachmann G, Ramiro AR, Petersen-Mahrt SK (2009). Estrogen directly activates AID transcription and function. *J Exp Med* 206, 99-111.