Master project 2021-2022

Personal Information

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Project

Computational genomics

Project Title:

Deciphering the role and regulation of spatial-temporal genome architecture in B cells and diffuse large B cell lymphomas

Keywords:

B lymphocytes, lymphoma, DLBCL, spatio-temporal genome architecture, transcriptional regulation

Summary:

During differentiation, B cells diversify - through mutation and translocations - their immunoglobulins loci to efficiently recognize a specific pathogenic insult, facilitating its neutralization and destruction. Additionally, alterations of B cell differentiation and immunoglobulins diversification cause the development of cancer, immunodeficiency, allergy and autoimmunity. For instance, off-target mutations and translocations during immunoglobulins diversification is a major cause of diffuse large B cell lymphoma. Despite of the clinical relevance of all these processes, we still do not have a complete understanding of the underlying molecular mechanisms that regulate them. To fill this gap of knowledge, I propose a multidisciplinary approach combining state-of-the-art omics strategies, computational biology, genome engineering and mouse experimentation to provide fundamental insights about B cells and their malignant transformation from the spatio-temporal genome architecture perspective. First, I will shed light on the regulatory factors and their underlying molecular mechanisms that spatially organize the B cell chromatin. Second, I will evaluate whether the spatio-temporal genome organization transcriptionally controls B cell differentiation and function, and whether it can protect the genome from collateral oncogenic damage during immunoglobulins diversification. This will require the development and implementation of a novel, low-input, genome-wide method for studying the gene promoter-centered genome architecture. Finally, I will clinically translate the mechanistic and functional insights to improve our understanding about diffuse large B cell lymphoma and its clinical manage. Collectively, we will provide unprecedented mechanistic insights into our understanding of how B cells function and protect their genome from intrinsic oncogenic damage, with clinical impact on regenerative medicine, immunotherapy, autoimmunity, allergy, immunodeficiencies and cancer.

References:

Javierre B.M. et al. Lineage-Specific Genome Architecture Links Enhancers and Non-coding Disease Variants to Target Gene Promoters. Cell 167, 1369-1384.e19 (2016).

Expected skills::

• A high level of motivation and interest. • Proficiency in at least one scripting or programming language. • Proficiency in scripting environments for statistics and data analysis. • Competitive CV. • High level of collaborative and communicative skills. • Good level of English speaking and writing skills. • International mobility will be considered a major plus.

Possibility of funding::

To be discussed

Possible continuity with PhD: :

Yes