BIOGRAPHICAL SKETCH

Matthieu GERARD

Head of the Mammalian Epigenomics teams at the Institute for Integrative Biology of the Cell

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Strasbourg	PHD	06/1993	Basic transcription factors
University of Geneva	Postdoctoral	12/1996	Transcriptional regulation of HOX genes
National Cancer Institute (Frederick, MD)	Postdoctoral	08/1999	Genomic imprinting

A. Personal Statement

I am a team leader in genomic biology at the Institute for Integrative Biology of the Cell (I2BC), located in Gif-sur-Yvette near Paris. I have a broad background in biochemistry and molecular biology, and I am an expert in the genome-wide analysis of chromatin states and transcription mechanisms in mammalian cells. The long-term goal of my team is to understand how ATP-dependent chromatin remodeling factors (remodelers) regulate chromatin organization and transcription, and how the perturbation of these mechanisms leads to cancer. Our projects are currently focused on analyzing the BAF (BRG1/BRM-associated factors, also called SWI/SNF) complexes, which have unique functions in establishing open chromatin regions at the level of transcription cis-regulatory elements. We are exploring how key subunits of the BAF complexes, including SMARCB1, generate subnucleosomes and accessible DNA in these regions.

B. Positions

1999 – 2004 : PI position at CEA, Service de Biochimie et de Génétique Moléculaire, Gif-sur-Yvette, France.
2004 – present: Group leader at CEA, Service de Biologie Intégrative et de Génétique Moléculaire, Gif-sur-Yvette, France.
2015 – present: Head of the Mammalian Epigenomics team at the Institute for Integrative Biology of Cell (I2BC, UMR 9198 CEA, CNRS, Université Paris-Saclay), Gif-sur-Yvette, France.

C. Contributions to Science

1. Analysis of chromatin remodelers distribution and function on the genome of mouse embryonic stem cells

The human and mouse genomes contain 30 genes encoding remodelers. These factors regulate DNA access within chromatin during transcriptional regulation, DNA repair and DNA replication. Remodelers have multiple biochemical activities, including nucleosome sliding (change of position of the histone octamer in cis on the DNA), transient exposure of nucleosomal DNA, nucleosome assembly and disassembly. These activities can affect transcription at several levels: i) by facilitating the access of transcription factors to their binding sites within nucleosomes, ii) by generating nucleosome-free DNA areas and iii) by changing the chromatin composition through the incorporation of histone variants. To understand how remodelers bind to the mammalian genome and regulate transcription, we performed a genome-wide binding study of 15 chromatin remodelers in mouse embryonic stem (ES) cells. We also analyzed how each remodeler's depletion perturbs ES cells' transcriptome. One of the most exciting concepts unravelled by this work is that the remodelers cooperate to control the activation of a large set of genes required to maintain ES cell pluripotency and self-renewal. The same remodelers also cooperate to repress genes with bivalent promoters, which are silenced in ES cells but activated after the onset of differentiation.

Reference: de Dieuleveult, M., Yen, K., Hmitou, I., Depaux, A., Boussouar, F., Dargham, D.B., Jounier, S., Humbertclaude, H., Ribierre, F., Baulard, C., et al. (2016). Genome-wide nucleosome specificity and function of chromatin remodellers in ES cells. Nature *530*, 113–116. 10.1038/nature16505.

2. Regulation of the chromatin organization and function of cis-regulatory elements by BAF (SWI/SNF) complexes

Large-scale genome sequencing of human tumour cells revealed that the remodelers of the BAF (BRG1/BRM-associated factors, also called SWI/SNF) family have tumour suppressor properties. BAF complexes belong to three subfamilies, defined by subunit composition: canonical (cBAF), polybromo-associated (PBAF), and non-canonical (ncBAF). Loss-of-function mutations in the genes encoding subunits of these three complexes are associated with a large variety of cancers.

While the initiating genetic events of tumour formation are generally well characterized, we do not yet understand the mechanisms that convert the mutant cells into cancer cells. A first step to understanding these complex transformation events is to determine the functions of each BAF subcomplex in chromatin remodeling and the regulation of cis-regulatory element activity. For this purpose, we generated a series of cell lines in which the genes encoding selected subunits of each BAF complex are fused to the plant auxin inducible-degron (AID) sequence. These cell lines are being used in loss-of-function studies to define how cBAF, PBAF and ncBAF regulate the activities of cis-acting DNA regulatory elements controlling transcription and initiation of DNA replication.

In the first part of this project, we identified a new chromatin remodeling activity controlled by BRG1, one of the two possible catalytic subunits of BAF complexes. We showed that BRG1 targets fragile nucleosomes at enhancers and converts them into subnucleosomal particles composed of the four core histones associated with a 50-80 bp-long DNA fragment. In ES cells, these subnucleosomal particles interact with the master transcription factor OCT4 independently of a DNA binding motif, suggesting interactions with the histone component of the subnucleosomes. We provide evidence that this new class of subnuclesomal particles allows the OCT4 binding interval to expand at enhancers, resulting in the projection of OCT4 regulatory function beyond the boundaries of its binding sites on the DNA.

Reference : Nocente, M.C., Karamitsos, A.M., Drouineau, E., Albawardi, W., Dulary, C., Ribierre, F., Picaud, H., Alibert, O., Aude, J.-C., Gilbert, N., et al. (2022). Oct4 interacts with subnucleosomal particles generated by Brg1 at enhancers. bioRxiv doi.org/10.1101/2022.09.15.507958