**PhD project : Polymorphism and recombination**

**Team** : Genome Dynamics and recombination

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**Context**

Genetic polymorphism is an intrinsic component of populations. This requires that genetic mixing can make homologous but non-identical sequences recombine with each other. At the same time, there are recombination barriers that prevent genetic hybridization between "too" divergent sequences, impairing both non-allelic recombination and inter-species fetrility. The DNA mismatch repair machinery seems to play a major but still poorly characterized role in this balance between recombination or not between divergent sequences. This genome dynamics problematic highly relevant in both cancer etiology and genome evolution is the subject of this thesis work which will be based on the analysis of meiotic recombination in baker's yeast hybrids.

**Project overview**

Homologous recombination (HR) is a ubiquitous DNA repair mechanism. HR fixes DNA lesions by copying the genetic information from intact homologous donor loci and gives rise to either crossover or non-crossover recombinants (Marsolier-Kergoat et al. 2018). HR notably repairs DNA double strand breaks (DSBs) occurring accidentally during S phase involving sister chromatid exchanges. HR also repairs Spo11-induced programmed DSBs generated during meiotic prophase involving mainly exchanges between non-sister homologous chromatids. A key and efficient step in HR is homology recognition that enforces recombination between loci sharing a high degree of sequence similarity. Although the recombinase itself probes for sequence similarity, it may generate recombination intermediates that contain mismatches, and these are essential to shuffle parental genomes notably during meiosis. Mismatches are also recognized by the mismatch repair (MMR) machinery that either repairs them or promotes heteroduplex DNA rejection when divergence is too high. Heteroduplex rejection avoids mixing too diverged genomes or sequences and constitutes a speciation barrier (Hunter et al 1996; Martini et al. 2011). **Little is known about the balance between heteroduplex DNA repair and heteroduplex DNA rejection by MMR, whether it exists any quantitative or qualitative polymorphism threshold.** In order to address this issue, we will compare meiotic recombination profiles genome wide in the presence and absence of MMR during meiotic recombination in yeast hybrids. This will allow us to determine how MMR handles the myriad of natural polymorphisms existing within the *S. cerevisiae* population during meiosis (Peter et al. 2018). We expect general rules to emerge, which we may test using engineered substrates, both in meiosis and in mitosis. Indeed, the relationships between sequence polymorphism and MMR may be more stringent in mitosis where most repair occurs during S-phase between sister chromatids while meiotic recombination shuffles polymorphic parental genomes (Harfe et al. 2000). **Because most meiotic crossovers interfere with the formation of crossovers at their vicinity, it is possible that local sequence polymorphism affects distribution of crossovers at larger scale (**de los Santos et al 2003; Cooper et al.). We will test this hypothesis using engineered yeast strains containing regions with various degrees of sequence polymorphism (Muller et al. 2018). We will test, for instance, if crossovers are repressed in polymorphic regions at the expense of homozygous regions. Finally, **the relationships between sequence polymorphism, MMR and crossovers may be complex since the MMR and the meiotic crossover pathways share common players**. We will therefore explore the possible crosstalk between these two pathways using dedicated reporter systems.

Overall, this project combines yeast molecular genetics and genomics approaches, including a significant amount of bioinformatic analyses of NGS data and recombination profiles in which the lab has solid experience (Marsolier-Kergoat et al. 2018). It is expected to shed light on the poorly understood balance between heteroduplex DNA repair and heteroduplex DNA rejection. Such a balance controls both meiotic alleles shuffling, but also non-allelic mitotic and meiotic recombination that are at the root of gross chromosomal rearrangements. This project therefore holds great interest for the fields of genome evolution but also genomic instability responsible for many human diseases including cancers.

**References**

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