Lundi 20 septembre 2010 à 10h00
Auditorium IGBMC
Séminaire Prof. Dr Francois Spitz

The role of the genome regulatory architecture in development and disease.

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Many recent findings underline the critical role of sequences located far from protein-coding genes in regulating their transcriptional activities, and illustrate that changes within regulatory elements or affecting their relative position towards their associated genes contribute to phenotypic diversity and sometimes cause diseases. However, our understanding of the mechanisms governing the range and specificity of action of such remote regulatory elements is still rather limited.

To get insight into these mechanisms and explore the regulatory organization of the genome, we have developed an *in vivo* transposition system to distribute a regulatory sensor gene and a *lox*P site throughout the mouse genome. With it, we generated and characterized about 150 mouse lines, each with an insertion of the reporter transposon at a different genomic position. Strikingly, most of these insertions - close to or several hundreds of kilobases away from genes, linked or not to developmental genes - showed highly tissue-specific expression of the reporter gene, contrasting with the rather widespread expression of most genes. This pervasive presence of regulatory potentials throughout the genome reveals its organization in distinct but overlapping regulatory domains with restricted tissue-specific activities. Importantly, each insertion can be remobilised to produce new mice with insertions around the selected starting point, as a large proportion of the new insertions lies within 1 to 2 Mb of their initial position. This property facilitates the fine mapping of the regulatory organization of specific loci, complementing other genome-wide approaches. Furthermore, combined with *in vivo* CRE-mediated recombination, this dynamic and versatile resource enables to generate series of overlapping deletions and duplications over regions of interests, notably to model human aneuploidies and copy-number/structural variants.

I will illustrate the general use of our approach and resource and discuss the new insights it provides into the regulatory organization of mammalian chromosomes. I will further present how we are combining this approach with other transgenic strategies to understand the molecular mechanisms underlying the limb malformations associated with half-megabase duplications at 10q24 in humans.

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