Ectopic tissue-specific gene activations and cancer

Dr. Sophie Rousseaux
Research Director

An unexplored consequence of epigenetic alterations associated with cancer is the ectopic expression of tissue-restricted genes. A systematic strategy was applied to search for these "off-context" gene activations, which consisted first, in identifying a large number of tissue-specific genes epigenetically silenced in normal somatic cells and second, in detecting their expression in cancer. Using this approach we demonstrate that ectopic activations not only occur in any cancer, revealing a large source of universal biomarkers, but also could be used as a strong and independent predictor of poor prognosis in lung tumors, as shown in our series of 300 patients, as well as in an external population of 443 patients. This strategy enabled us to isolate a homogenous group of metastatic-prone highly aggressive lung tumors, whose specific gene expression profile revealed the activation of a germline and embryonic stem (ES) proliferation program coregulated with *ATAD2*, a gene encoding for a AAA-ATPase bromodomain containing factor. Finally we show that ATAD2 specifically controls the expression of a large set of genes, involved in ES cell proliferative capacity as well as in tumor growth, suggesting that it represents an excellent candidate for new targeted therapeutic strategies against highly aggressive tumors.

Molecular basis of post-meiotic male genome programming

Dr. Saadi Khochbin
First Class Research Director at CNRS
Head of Department N°1, INSERM Research Unit 823
Institut Albert Bonniot, France

In mammals, post-meiotic male genome reorganization and compaction could be considered as conceptually related to sporulation in lower eukaryotes or pollen formation in plants all involving the preparation of the genome to confront the hostile exterior environment. All involve genome compaction mechanisms of completely unclear nature. In mammals, the current knowledge implies a post-meiotic stepwise replacement of histones by transition proteins and protamines to finally pack the genome into the mature spermatozoid. Our investigations have already highlighted the existence of another level of organization involving new testis-specific histone variants, which are specifically incorporated when canonical histones are removed. We suggest that these histones are the actors of a general post-meiotic reprogramming process that directs the packaging of specific genomic regions in differentiated structures and mark their identity in the fully packed genome of mature spermatozoa. Furthermore, we propose that the wave of genome-wide histone acetylation that occurs at the beginning of the spermatid elongation triggers the subsequent post-meiotic reprogramming process leading to histone replacement and regional differentiation of various genomic regions. An essential factor mediating these histone acetylation-dependent events has been identified in our laboratory and the molecular basis of its action has been dissected. All together our investigations now allow to describe the first general traits of the mechanisms underlying the structural transitions taking place during the post-meiotic reorganization and epigenetic reprogramming of the male genome.