Profile N° (à remplir par VAS) **FUNDING Planned** ARED

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Sheet abstract of thesis 2017 **Disciplinary Fields** **Biologie fondamentale et Santé**

Thesis Title : (1-2 lines)
Role of TET proteins in DNA double-strand break repair and activation of transcription

3 keywords : (1 line) **ACRONYME** TIDDR
TET/ DNA repair / Transcription

Unit/Team of supervising : (1-2 lines)
UMR6290 CNRS, Team SPARTE

Name of the scientific director and co-director : (1 line)

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Socio-economic and scientific context : (10 lines)

Genomic instability is a hallmark of cancer and is partly due to deficiencies in proteins involved in the repair of DNA double-strand breaks (DSBs). In cells, DNA associates with histones to form the chromatin fiber, a structure allowing the deposition of epigenetic marks which are essential to the spatial organization of the genome and the organization of domains functional for transcription, DNA replication and DNA repair. In this project, we will analyze the impact of 5-methylcytosine oxidation in 5-hydroxymethylcytosine by the TET proteins on DNA repair processes. 5hmC has recently been shown to accumulate at sites of double-strand breaks induced by irradiation and we will characterize, by means of live cell imaging and genomics/epigenomics studies, the function of this modified base in the regulation of DNA repair, both in terms of efficiency and type of mechanism involved (homologous recombination of non-homologous end joining).

Assumptions and questions (8 lines)
The recent literature indicates that 5mC oxydation could play a role in the regulation of DSB repair. In this context, it is becoming esssential to study the relation between TET proteins, DNA breaks occurence and repair together with transcription processes which also favor DNA breaks. We propose a research programme which has been elaborated to answer the following questions:
- what is the dynamics of TET recruitment at DNA breaks?
- Is the activity of TETs influencing the dynamics of DNA repair factor at DSBs?
- Is 5hmC playing a role in the selection of the repair mechanism (HR vs NHEJ)?

The main steps of the thesis and demarche (10-12 lines)
Our project has two main objectives. First, we will analyze the role of 5mC oxydation by TETs in the processes of DNA repair targeting damages unrelated to transcription. In particular, we will study the influence of the 5mC/5hmC balance on chromatin remodeling events which are supposed to help DNA repair. The second objective is to study the putative role of 5hmC in the induction and repair of DSBs linked to active transcription. We will particularly focus on the processes which allow DNA repair both in the context of breaks induced by either laser irradiation or restriction enzymes, and in the context of "natural" breaks associated to transcription in gene bodies and regulatory regions.

Methodological and technical approaches considered (4-6 lines)
The implementation of this research programme will require live cell imaging techniques which will allow to localize and follow DNA repair proteins and TETs labelled with a fluorescent tag, in cells subjected to laser irradiation or controlled nuclear translocation of a restriction enzyme. Chromatin immunoprecipitation and techniques to localize 5hmC genome-wide will also be used to analyze the engagement of DNA repair factors and its relation with TET activity in transcription regulatory regions.

Scientific and technical skills required by the candidate (2 lines)
The candidate will have skills in cell culture, molecular biology and microscopy.