alliance nationale
pour les sciences de la vie et de la santé

ITMO Cancer

Mounira Amor-Guéret

Genetic Instability and Carcinogenesis

/ / Amor-Guéret Mounira

Insitut Curie / CNRS

Key Facts

- ***Team :***

  Researchers : 2
  Technicians : 2
  PhD students : 1
  Postdoc fellows : 1

- ***Translational approaches :***

  Patents : 1
  Clinical research grants : 5
  Industry partners : 0

- ***International research links :***

Keywords

- Bloom syndrome
- BLM helicase
- Cytidine deaminase
- Homologous recombination
- DNA replication
- Molecular biology
- Cellular biology

Biological resources

Our team is the only one to have shown that (1) part of the genetic instability associated with Bloom syndrome results from a strong defect in cytidine deaminase (CDA) expression and (2) CDA downregulation in wild type cells lead to genetic instability which could predispose to cancer.

Research brief

We are working on Bloom syndrome (BS), the only known human genetic disease predisposing patients to all kind of cancers commonly affecting the general population. BS displays one of the strongest known correlations between chromosomal instability and a high risk of cancer at an early age, revealing an essential role of BLM in maintenance of genetic stability and prevention of cancer.BS is caused by mutations in the BLM gene, which encodes BLM, a RecQ DNA helicase. The hallmark of BS cells is a high rate of sister chromatid exchange (SCEs). We recently found that that BLM deficiency leads to the drastic downregulation of cytidine deaminase (CDA) that results in disequilibrium in the pyrimidine pool. CDA is an enzyme of the pyrimidine salvage pathway catalyzing the hydrolytic deamination of cytidine and deoxycytidine to the corresponding uridine and deoxyuridine. The pyrimidine pool disequilibrium in BS cells causes the slowing down of the replication speed and contributes to the increase in SCE frequency associated with BS phenotype. Moreover, siRNA-mediated downregulation of CDA in BLM-expressing cells is associated with a significant slowdown of the replication speed and with a significant increase in SCE frequency, reflecting thus a genetic instability known to predispose to cancer. We are analyzing the relationship between nucleotide pool disequilibrium and genetic instability and determining whether CDA deficiency could predispose to cancer development.

Methodologies used

- -Cell culture
- -DNA molecular combing
- -Sister chromatid exchanges analysis
- -dNTP analysis
- -Real-time quantitative PCR
- -Immunofluorescence microscopy
- -FIH analysis
- -ChIP

Publications

- Rouzeau S., Cordelières F.P., Buhagiar-Labarchède G., Hurbain I., Onclercq-Delic R., Gemble S., Magnaghi-Jaulin L., Jaulin C., Amor-Guéret M. Bloom?s syndrome and PICH helicases cooperate with topoisomerase II alpha in centromere disjunction before anaphase. PLoS One, 7(4):e33905, 2012.
- Chabosseau P., Buhagiar-Labarchède G., Onclercq-Delic R., Lambert S., Debatisse M., Brison O., Amor-Gueret M. Pyrimidine pool imbalance induced by BLM helicase deficiency contributes to genetic instability in Bloom syndrome. Nat Commun, 10.1038/ncomms 1363, 2011
- Lahkim Bennani-Belhaj K., Rouzeau S., Buhagiar-Labarchède G., Chabosseau P., Onclercq-Delic R., Bayart E., Cordelières F., Couturier J., Amor-Guéret M. The Bloom syndrome protein limits the lethality associated with RAD51 deficiency. Mol Cancer Res., 8:385-94, 2010.
- -Amor-Guéret M., Dubois-d?Enghien C., Laugé A., Onclercq-Delic R., Barakat A., Chadli E., Bousfiha A.A., Benjelloun M., Flori E., Doray B., Laugel V., Lourenço M.T., Gonçalves R., Sousa S., Couturier J., & Stoppa-Lyonnet D. Three new BLM gene mutations associated with Bloom syndrome. Genetic Testing, 12:257-61, 2008.
- Temime-Smaali N., Guittat L., Wenner T., Bayart E., Douarre C., Gomez D., Giraud-Panis M.J., Londono-Vallejo A., Gilson E., Amor-Guéret M., Riou J.F. Topoisomerase III alpha is required for normal proliferation and telomere stability in alternative lengthening of telomeres. EMBO J., 27:1513-24, 2008.
- Amor-Guéret M. Bloom syndrome, genomic instability and cancer: the SOS-like hypothesis. Cancer Letters, 236:1-12, 2006.

Patents, pending/registered

Contact :
- Mounira Amor-Guéret - 01 69 86 30 53 - mounira.amor@curie.fr