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We are currently working on the relationship between genetic instability and carcinogenesis through the model of Bloom syndrome (BS), which displays one of the strongest known correlations between chromosomal instability and a high risk of cancer at an early age.

This suggests that early initial events occurring in BS cells lead to genetic instability, which probably underlies the diversity of independent cancers developed by BS patients. Such early events may also be involved in the initiation of carcinogenesis in the general population and may be common to several kinds of cancers. BS is caused by mutations in the *BLM* gene, which encodes BLM, a RecQ 3’-5’ DNA helicase. The specific functions of BLM remain unclear, but it is widely thought that it is involved in restarting blocked replication forks. In the absence of BLM, cells display a high rate of sister chromatid exchanges (SCEs) (Fig. 1), pathognomonic for BS, mitotic abnormalities and high levels of oxidative stress.

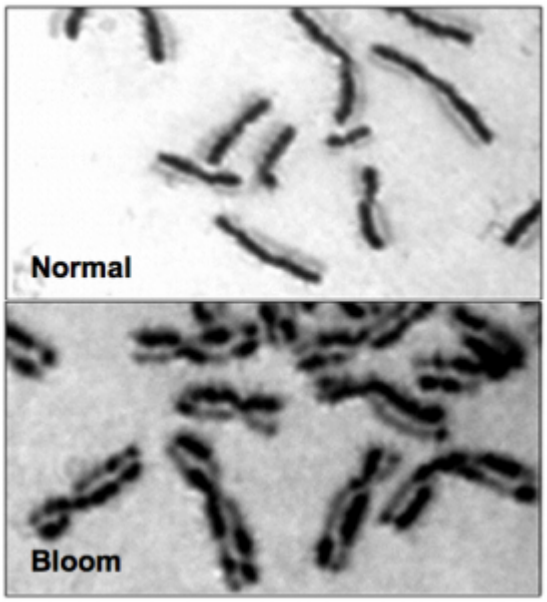

Figure 1: Increased sister chromatid exchange in BS cells. The sister chromatids in the images are differentially labelled so that regions of chromatid exchange can be seen as regions of light and dark staining. Little chromatid exchange is seen in normal cell metaphase (top panel), whereas most of the chromosomes in a Bloom syndrome cell metaphase (bottom panel) show chromatid exchange.

BS cells also display a slowing of replication fork progression associated with endogenous activation of the ATM-Chk2-γH2AX pathway. This pathway is activated in precancerous lesions and is thought to be a part of an anti-tumorigenesis barrier. BS cells may therefore be in a precancerous state. Our working hypothesis is that BLM deficiency results in a global “SOS-like” cellular response facilitating progression through the anti-tumorigenesis barrier potentially involved in carcinogenesis in the general population. We have shown that BLM deficiency leads to a cytidine deaminase (CDA) defect, causing a pyrimidine pool imbalance, known to result in genetic instability and oncogenic transformation. CDA is an enzyme of the pyrimidine salvage pathway catalyzing the hydrolytic deamination of cytidine and deoxycytidine to uridine and deoxyuridine, respectively. The pyrimidine pool imbalance in BS cells causes a slowing down of replication speed, but not the accumulation of blocked replication forks; it also contributes to the increase in SCE frequency. Moreover, CDA downregulation in BLM-expressing cells is associated with a slow down of the replication speed and with a significant increase in SCE frequency, reflecting thus a genetic instability, which is known to confer a predisposition to cancer.

Our research activities also focus on the specific role of BLM during G2 phase and mitosis. We showed that BLM is recruited at centromeres from G2 to mitosis, where it cooperates with PICH to recruit topoisomerase IIa, likely to facilitate correct centromere disjunction and to prevent the formation of supernumerary ultrafine anaphase bridges. We recently showed that a CDA defect in BS cells was fully responsible for the increase in ultrafine anaphase bridges frequency (Gemble *et al*., submitted).

Our projects aim to improve our understanding of (a) how cells tolerate endogenous replication stress and the DNA damage associated with BLM and/or CDA deficiencies, (b) the consequences of CDA deficiency for DNA damage responses in BS and non-BS conditions, (c) the link between CDA deficiency and carcinogenesis in the general population.

Key publications

Year of publication 2019

Matthieu Gratia, Mathieu P Rodero, Cécile Conrad, Elias Bou Samra, Mathieu Maurin, Gillian I Rice, Darragh Duffy, Patrick Revy, Florence Petit, Russell C Dale, Yanick J Crow, Mounira Amor-Gueret, Nicolas Manel (2019 Apr 1)
Bloom syndrome protein restrains innate immune sensing of micronuclei by cGAS.
The Journal of experimental medicine : DOI : jem.20181329

Year of publication 2017

Alexis Fouquin, Josée Guirouilh-Barbat, Bernard Lopez, Janet Hall, Mounira Amor-Guéret, Vincent Pennaneach (2017 Dec 1)
PARP2 controls double-strand break repair pathway choice by limiting 53BP1 accumulation at DNA damage sites and promoting end-resection.
Nucleic acids research : DOI : 10.1093/nar/gkx881

Elias Bou Samra, Géraldine Buhagiar-Labarchède, Christelle Machon, Jérôme Guitton, Rosine Onclercq-Delic, Michael R Green, Olivier Alibert, Claude Gazin, Xavier Veaute, Mounira Amor-Guéret (2017 Sep 25)
A role for Tau protein in maintaining ribosomal DNA stability and cytidine deaminase-deficient cell survival.
Nature communications : 693 : DOI : 10.1038/s41467-017-00633-1

Simon Gemble, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Christian Jaulin, Mounira Amor-Guéret (2017 Jun 3)
Cytidine deaminase deficiency impairs sister chromatid disjunction by decreasing PARP-1 activity.
Cell cycle (Georgetown, Tex.) : 1-8 : DOI : 10.1080/15384101.2017.1317413

Hamza Mameri, Ivan Bieche, Dider Meseure, Elisabetta Marangoni, Géraldine Buhagiar-Labarchède, Andre Nicolas, Sophie Vacher, Rosine Onclercq-Delic, Vinodh Rajapakse, Sudhir Varma, William C Reinhold, Yves Pommier, Mounira Amor-Guéret (2017 Apr 15)
Cytidine deaminase deficiency reveals new therapeutic opportunities against cancer.
Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : 10.1158/1078-0432.CCR-16-0626

Year of publication 2016

Simon Gemble, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Denis Biard, Sarah Lambert, Mounira Amor-Guéret (2016 Aug 15)

A balanced pyrimidine pool is required for optimal Chk1 activation to prevent ultrafine anaphase bridge formation.

Journal of cell science : 3167-77 : DOI : 10.1242/jcs.187781