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.
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 2020

(2020 Aug 26)
**Identification and Analysis of Different Types of UFBs**

*A decrease in NAMPT activity impairs basal PARP-1 activity in cytidine deaminase deficient-cells, independently of NAD*⁺
*Scientific Reports* : 10 : 13907 : DOI : [10.1038/s41598-020-70874-6]

Simon Gemble, Géraldine Buhagiar-Labarchède, Rosine Onclercq-Delic, Gaëlle Fontaine, Sarah Lambert, Mounira Amor-Guéret (2020 May 14)
**Topoisomerase IIα prevents ultrafine anaphase bridges by two mechanisms.**
*Open biology* : 190259 : DOI : [10.1098/rsob.190259]

Year of publication 2017

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]

**Cytidine deaminase deficiency impairs sister chromatid disjunction by decreasing PARP-1 activity.**
*Cell cycle (Georgetown, Tex.)* : 1-8 : DOI : [10.1080/15384101.2017.1317413]

**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