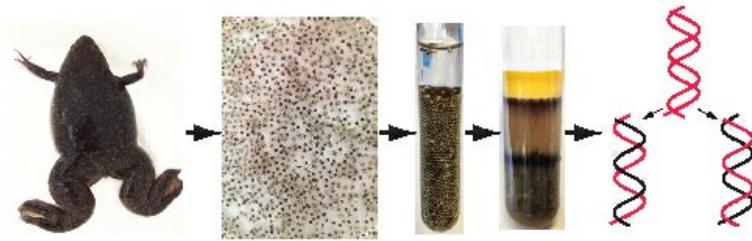


Chromosomal replication



Group leader: [Dr Aga Gambus \(/staff/profiles/cancer/gambus-aga.aspx\)](/staff/profiles/cancer/gambus-aga.aspx)

Overview

Problems during DNA duplication (DNA replication) are thought to be a major cause of mutations that are observed in cancer. Our research focuses, therefore, on understanding the organization of protein machinery involved in DNA replication and its regulation especially through modification by small modifiers: ubiquitin and SUMO.

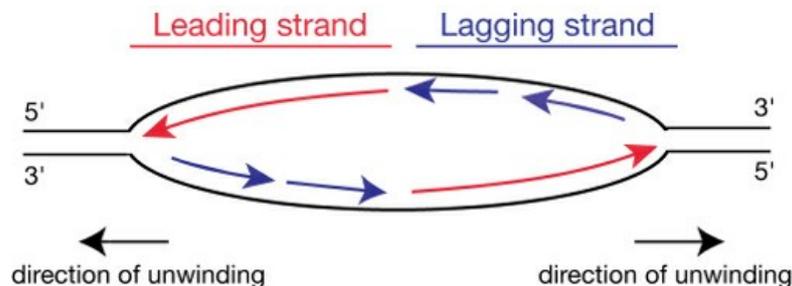
Our research group

Our cells contain about 2 meters of DNA that needs to be faultlessly duplicated before every cell division to produce two identical daughter cells. Amazingly, most of the time our cells manage to achieve this task, but sometimes mistakes do happen and, if not repaired efficiently, they can lead to mutations and genomic instabilities. DNA replication therefore plays a major role in the development of cancer, genetic diseases and aging. Yet, despite years of intense study we still have much to learn about this essential process.

DNA replication is one of the most fundamental processes in life and thus is very highly conserved throughout evolution. This fact facilitates meaningful studies of the DNA replication process in model systems. In our laboratory we use *Xenopus laevis* egg extract system which is the only higher eukaryotic cell-free system capable of efficient replication of template DNA in vitro and thus provides an invaluable model system for biochemical studies of DNA replication and cell cycle processes.

We use this system to study the organization and regulation of the DNA replication machinery. In particular we are interested in understanding how modification of replication factors by attachment of small protein modifiers (ubiquitin and SUMO) regulates this process.

Below: DNA replication bubble. Two DNA replication forks start from the origin of replication and move in the opposite directions replicating DNA.



Current projects

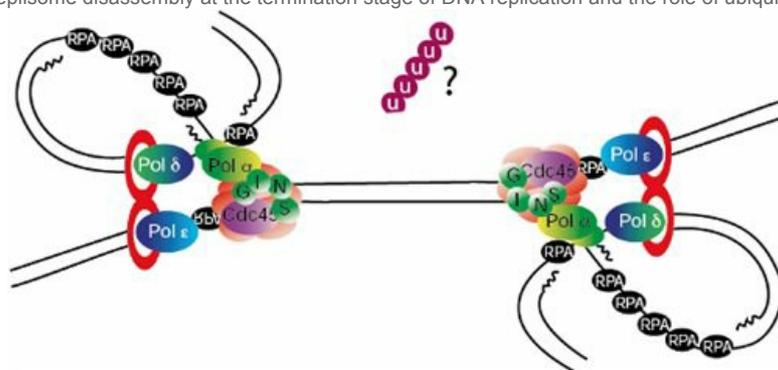
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Ubiquitylation and sumoylation are essential tools for modulating the function of proteins involved in the response to DNA damage. A series of specialised enzymes: E1, E2 and E3 covalently attach single or multiple ubiquitin or SUMO moieties to target proteins most often via lysine residues. All of the seven lysine residues of ubiquitin can be used for further ubiquitylation resulting in the formation of ubiquitin chains. In addition, there are three forms of SUMO (1,2 and 3). All these create a wide scope for the functional complexity of ubiquitin and SUMO signalling.

The role of ubiquitylation in regulation of chromosomal replication – especially the termination stage of replication

To ensure faultless duplication of the whole genome, DNA replication initiates from thousands of origins of replication. An origin fires when the replicative helicase is activated and starts to unwind double stranded DNA creating two DNA replication forks. The progressing replication fork moves through the chromatin until it encounters a fork from the neighbouring origin. When the forks converge (the termination of replication forks) the replisomes disassemble by an unknown mechanism and topoisomerase II resolves the daughter DNA molecules. If not resolved properly, the terminating forks are at high risk of stalling and fork reversal, leading to DNA damage and genomic instabilities.

We are investigating the mechanism of replisome disassembly at the termination stage of DNA replication and the role of ubiquitylation in this process. (Model)



The role of SUMO in regulation of chromosomal replication

The process of sumoylation resembles closely this of ubiquitylation, but the role of SUMO modification during DNA replication and damage are much less understood. We aim therefore to identify replication factors modified by SUMO during the process of replication and characterise the function of these modifications.

Selected publications

- Moreno SP, Bailey R, Campion N, Herron S, **Gambus A**. **Polyubiquitylation drives replisome disassembly at the termination of DNA replication** (<http://www.ncbi.nlm.nih.gov/pubmed/25342805>). *Science*. 2014 Oct 24;346(6208):477-81. doi: 10.1126/science.1253585.
 - Abstract** (<http://www.sciencemag.org/cgi/content/abstract/346/6208/477?ijkey=bgdl23CCdRDz6&keytype=ref&siteid=sci>) - available at Science
 - Reprint** (<http://www.sciencemag.org/cgi/rapidpdf/346/6208/477?ijkey=bgdl23CCdRDz6&keytype=ref&siteid=sci>) - available at Science
 - Full Text** (<http://www.sciencemag.org/cgi/content/full/346/6208/477?ijkey=bgdl23CCdRDz6&keytype=ref&siteid=sci>) - available at Science
- Gambus A**, Blow JJ. Mcm8 and Mcm9 form a dimeric complex in *Xenopus laevis* egg extract that is not essential for DNA replication initiation. *Cell Cycle*.2013 Mar 21;12(8).
- Park J, Long DT, Lee KY, Abbas T, Shibata E, Negishi M, Luo Y, Schimenti JC, **Gambus A**, Walter JC, Dutta A. The MCM8-MCM9 Complex Promotes RAD51 Recruitment at DNA Damage Sites To Facilitate Homologous Recombination. *Mol Cell Biol*.2013 Apr;33(8):1632-44. doi: 10.1128/MCB.01503-12.
- Gillespie PJ*, **Gambus A***, Blow JJ. Preparation and use of *Xenopus* egg extracts to study DNA replication and chromatin associated proteins. *Methods*,2012 Apr 19. PMID: 22521908
- Gambus A**, Khoudoli GA, Jones RC, Blow JJ. Mcm2-7 Form Double Hexamers At Licensed Origins In *Xenopus* Egg Extract. *J Biol Chem*.2011 Apr 1;286(13):11855-64. Epub 2011 Jan 31. PMID: 21282109
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Staff

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Past members

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Tereza Krsjakova (ERASMUS exchange student)



Public engagement

We greatly enjoy sharing our enthusiasm for science with members of the public. We believe that it is possible to get across very complex ideas of cell biology – sometimes this involves simplifying the terminology, building models and drawing on analogies: anything that allows people to access these concepts and to share our excitement for discoveries.

Apart from opening our lab to members of the public we also take part in fundraising activities and university community days.



Above left: DNA repair race game. Birmingham University Community Day 2012. **Above right:** Cancer therapy game. Birmingham University Community Day 2013.





Above: Frog cake for the Great Science Cake Off competition 2013: to explain our science through the art of baking! **Above right:** Helping the fundraising. CRUK Relay for life 2013.

Below left: Scale model of a nucleus created for Cancer Showcase It has 200km of thread inside it. **Below right:** Model of DNA replication fork made of winegumms – educational and yummy. Made for Cancer Showcase 2013.

