Metabolic control of DNA replication and DNA repair in the Somyajit Group

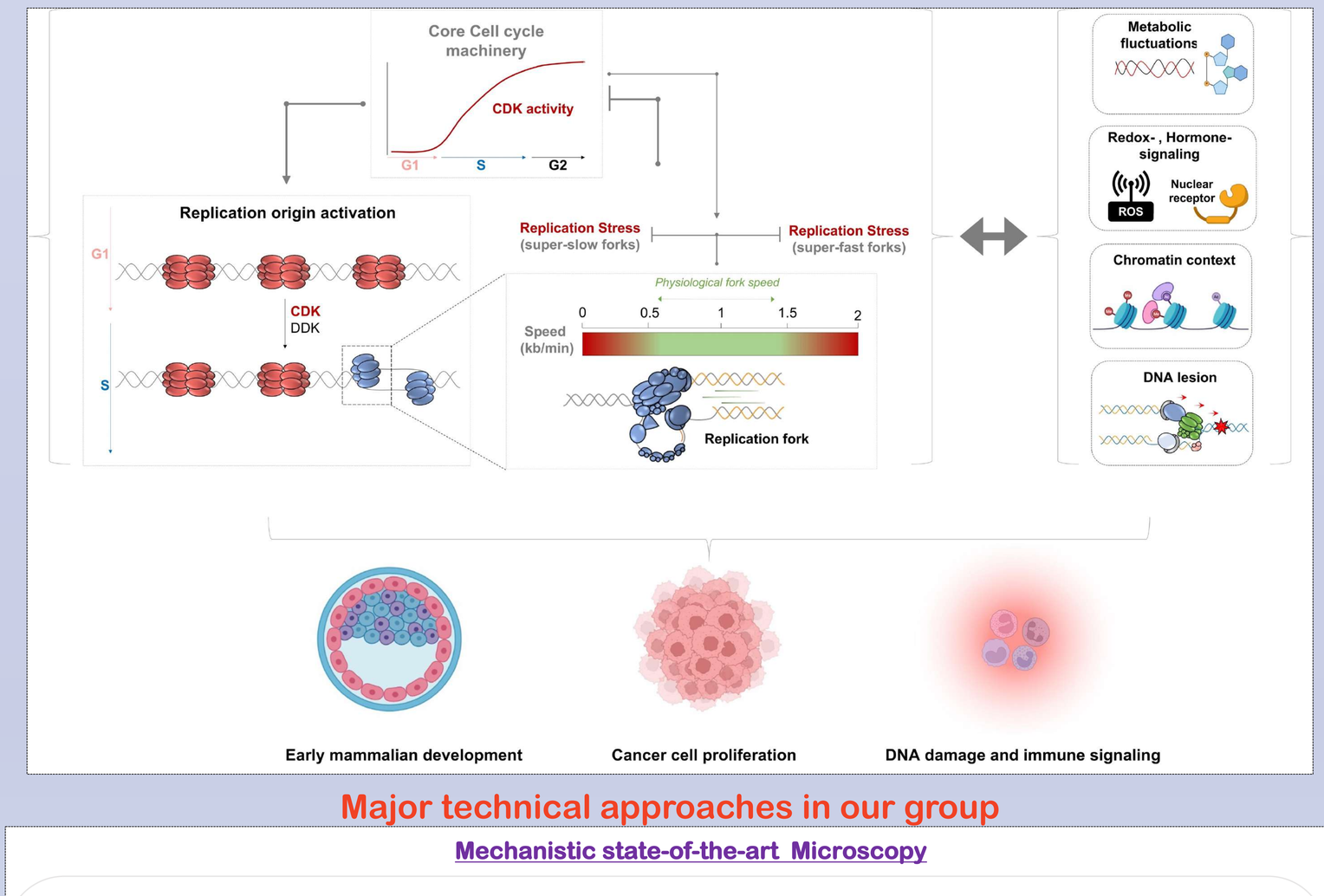
Our group has a deep interest in understanding how mammalian cells adjust major activities of DNA replication, cell cycle, and DNA repair in response to various forms of cell-intrinsic stress

Research in Nutshell:

Accurate and timely propagation of genetic information across multiple generations of dividing cells is an essential process initiated by DNA replication and completed by segregation of intact and duplicated copies of the genome. The process of DNA replication relies on the precisely coordinated action of numerous proteins with complementary enzymatic activities of the 'replisome', a powerful molecular machine responsible for unwinding the parental DNA template and synthesizing nascent DNA. However, plethora of endogenous and exogenous threats challenge accurate genome duplication, with perturbation of DNA replication dynamics frequent in cancer cells and underline the cause of accelerated ageing, inflammatory response, range of developmental disorders. To counteract such 'replication stress, defined as the pausing/stalling of individual replication fork progression, cells mount replisome-based genome surveillance that orchestrates replication speed modulations, replication fork stability, cell cycle progression, replication initiation, and DNA repair.

In our recently established lab, we are interested in exploring the molecular mechanisms that allow mammalian cells to fully and faithfully replicate their DNA content, repair their broken DNA, and align physiological cell cycle states to continuously varying cell metabolic conditions. To this end, we combine classical cell biology, biochemistry, genetics and quantitative mass spectrometry with state-of-the-art light imaging methodologies such as automated high-content microscopy and AI-assisted image analysis at single-cell resolution. Our research is performed employing mammalian cell culture models of early development and cancer, where we induce physiological metabolic stress, chromatin perturbations, and replication stress, together with genetic manipulations (siRNA and CRISPR) to identify previously concealed genome safeguard mechanisms and cellular responses to genotoxic stress.

Genome surveillance during DNA replication in human health and disease



Current Project Directions:

- Fundamental principles of replication fork velocity and replisome integrity
- Metabolic coupling of cell cycle during early development and oncegene-induction
- Role of homology-directed repair (BRCA-RAD51 pathway) and 53BP1-Sheildin complex during hormone-induced cell proliferation and tissue tropism in cancer

Contact us:

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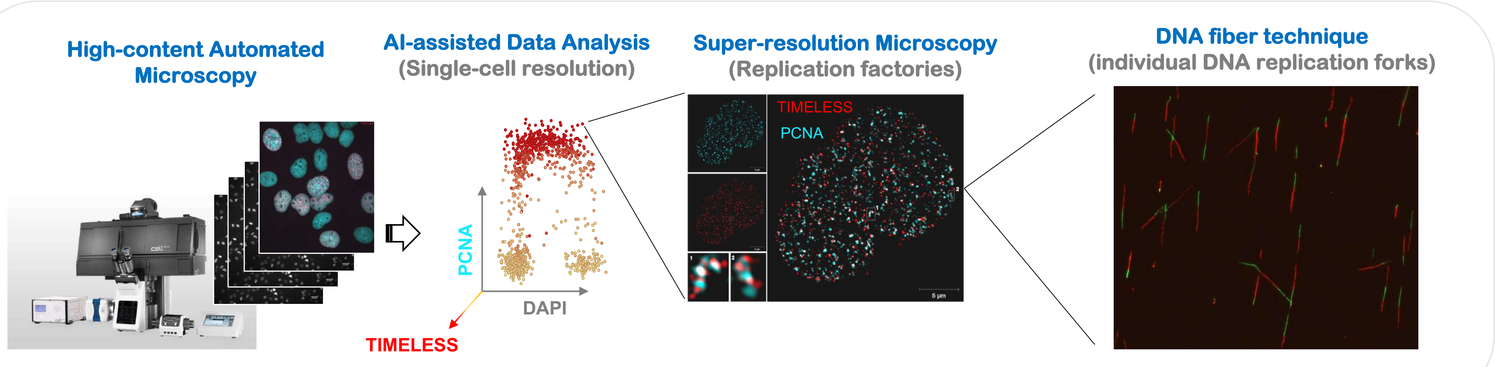
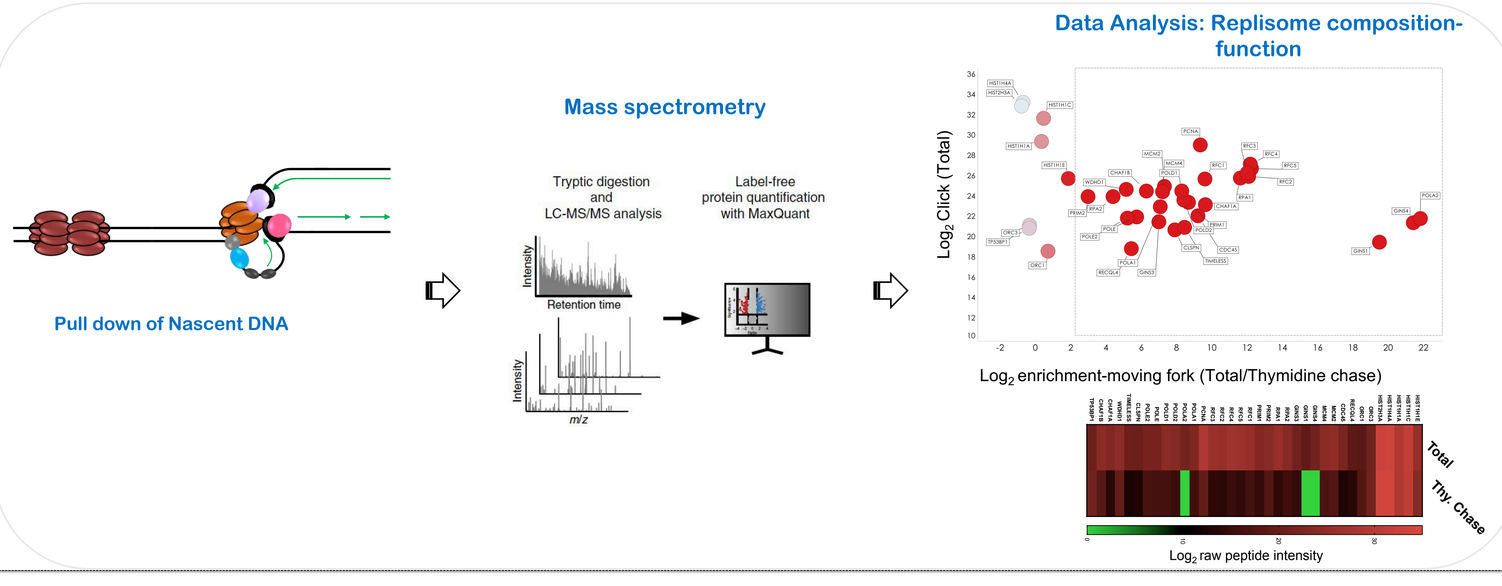
Major technical approaches in our group

Mechanistic state-of-the-art Microscopy



In-depth Replisome/DNA repair Biochemistry



Further Reading:

- Homology-directed repair protects the replicating genome from metabolic assaults. **Somyajit K#***, Spies J#, Coscia F, Kirik U, Rask MB, Lee JH, Neelsen KJ, Mund A, Jensen LJ., Paull. TT, Mann M, Lukas J*. ***Dev Cell.*** 2021 Feb 22;56(4):461-477. #- contributed equally *- Corresponding authors.
- Redox-sensitive alteration of replisome architecture safeguards genome integrity. **Somyajit K**, Gupta R, Sedlackova H, Neelsen KJ, Ochs F, Rask MB, Choudhary C, Lukas J. ***Science.*** 2017 Nov 10;358(6364):797-802.
- The equilibrium of nascent and parental MCMs safeguards replicating genomes. Sedlackova H, Rask MB, Gupta R, Choudhary C, **Somyajit K***, Lukas J*. ***Nature*** 20 Nov;587(7833):297-302. *- Corresponding authors
- DNA Repair Network Analysis Reveals Shieldin as a Key Regulator of NHEJ and PARP Inhibitor Sensitivity. Gupta R, **Somyajit K**, Narita T, Maskey E, Stanlie A, Kremer M, Typas D, Lammers M, Mailand N, Nussenzweig A, Lukas J, Choudhary C. ***Cell.*** 2018 May 3;173(4):972-988.e23.