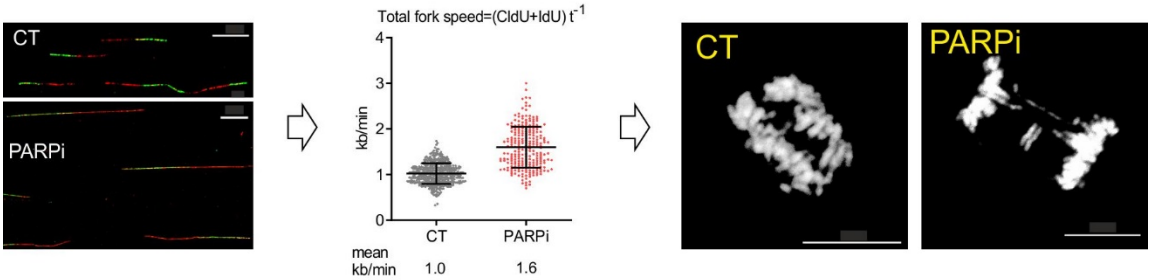
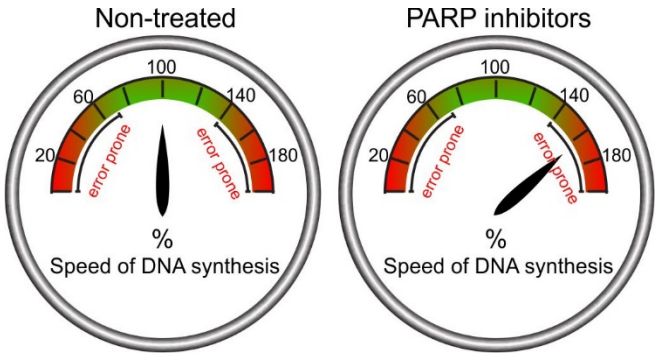
Årlige højdepunkt 1

PARylering og p21 regulerer DNA-replikationshastigheden for at bevare genomisk integritet
-Maya-Mendoza et al, *Nature* 279-284, 2018



PARP-hæmmere øger replikationshastigheden og forårsager genomisk ustabilitet (fra venstre til højre: strukket mærkede replikationsgafler, kvantificering af replikationshastighed og kromosom-abnormaliteter i mitose)

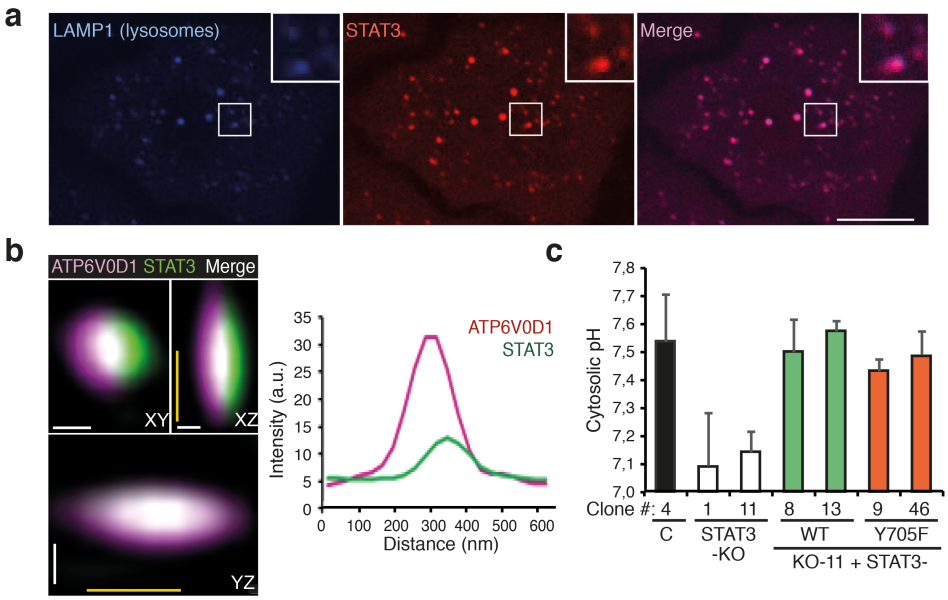
Poly(ADP-ribosyl)ering (PARylering) er en post-translationel protein modifikation som er involveret i reguleringen af DNA-reparation, genomisk stabilitet, metabolisme og autofagi. PARylering af AMPK i cellekernen er nødvendig for tilstrækkelig aktivering af autofagi under næringsmangel, og derfor påvirker hæmmere af PARylering (PARP-hæmmere) dannelsen af autofagosomer. PARylering er også nødvendig for at rekruttere reparationsfaktorer til beskadiget kromatin og reparere DNA-brud. PARP-hæmmere er godkendt til klinisk brug og er succesfuldt implementeret i behandlingen af livmoderhalskræft, prostatakræft, tripple-negativ brystkræft og bugspytkirtelkræft.
Tidligere modeller har foreslået at PARP-hæmmere virker ved at blokere progressionen af replikationsgafler og derved syntesen af DNA. Blokerede replikationsgafler vil bryde sammen og kollapse, hvilket medfører DNA-brud og celledød grundet defekt DNA-reparation. I modsætning til de tidligere foreslået modeller, opdagede vi at PARP-hæmmere øger replikationshastigheden i delende humane celler. Hvis replikationshastigheden øges med 40% over det normale niveau, medfører det akkumulering af DNA-skade og reduceret celle levedygtighed. I vores forskning har vi også karakteriseret en molekylær mekanisme der regulerer replikationshastigheden, som vi har navngivet "det replikationshastigheds-regulerende netværk". Dette netværk er afhængigt af samspillet mellem PARylering, p53 og p21 for at sikre korrekt replikationshastighed og DNA-syntese. Derfor foreslår vi at for høj replikationshastighed grundlæggende medfører replikations-stress og DNA-skade. Vores opdagelser kan dermed inspirere til nye behandlingsstrategier der fokuserer på at manipulere PAR/genbrug af metabolitter og DNA-replikationens nøjagtighed.



Annual highlight 2

Lysosomal STAT3 promotes the maintenance of alkaline cytosol in cancer cells
-Liu et al., *Cell Research* 2018

Dysregulated intracellular pH is a universal hallmark of cancer observed in malignant tumors regardless of their pathology, genetics and origin. In spite of their acidic environment and increased acid production, cancer cells maintain alkaline intracellular pH that promotes cancer progression by inhibiting apoptosis and increasing glycolysis, cell growth, invasion, immune evasion and drug resistance. Accordingly, mechanisms controlling the pH gradient reversal are emerging as promising targets for cancer therapy.
We have identified signal transducer and activator of transcription 3 (STAT3), which is best known for its cancer-promoting transcriptional activity, as a key player in the preservation of alkaline cytosol in cancer cells. A small pool of STAT3 can be found on lysosomal membranes, where it associates with the lysosomal proton pump (vacuolar H^+-ATPase) and increases its activity, thereby enhancing the flow of protons from the cytosol to the lysosomal lumen. Highlighting the essential role of STAT3 in the maintenance of alkaline cytosol, STAT3 depletion severely disrupts intracellular proton equilibrium by decreasing and increasing cytosolic and lysosomal pH, respectively. This phenotype can be reverted by reconstitution with wild type STAT3 as well as STAT3 mutants unable to activate target genes, indicating that the pH regulating function of STAT3 is independent of the transcriptional activity of STAT3. Notably, cytosolic acidification by various means further promotes the lysosomal localization and activity of STAT3 while inhibiting STAT3-dependent transcription. Taken together, these data reveal STAT3 as an essential regulator of intracellular pH, and *vice versa* intracellular pH as a potent regulator of STAT3 localization and activity. We are presently investigating this process in further detail in order to find efficient ways to target lysosomal STAT3 in future cancer treatment.



(a) Lysosomal localization of STAT3 in A549 lung cancer cells.
(b) Super resolution- structured illumination microscopy projections (*left*) and co-localization analysis (*right*) of a STAT3 and ATP6V0D1 (a subunit of vacuolar H^+-ATPase) in HeLa cells. Scale bars, 145 nm (yellow) and 200 nm (white).
(c) Cytosolic pH in control (C) and STAT3-KO HeLa clones and in STAT3-KO clones reconstituted with wild type (WT) and transcriptionally inactive (Y705F) STAT3.