TEMS

TLL External Monthly Seminar

TEMASEK LIFESCIENCES LABORATORY

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*Scan for address

22 March 2024 (Friday), 3pm
The Auditorium (Level 1)

Hosted by: Dr Zhang Dan

Genome damage by mechanical stress



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Prof Foiani is a professor at the *National University of Singapore* (NUS) and principal investigator at the *Cancer Science Institute* (CSI) of Singapore. Prof Foiani has been studying the pathways and mechanisms controlling nuclear and genome integrity and more recently the connections between cell metabolism and genome integrity pathways and between chromosome dynamics and mechano-transduction circuits controlling cell plasticity.

Confined migration hampers genome integrity and activates the ATR and ATM mechano-transduction pathways. Using live cell imaging, micro-fluidic approaches and scRNA-seq we found that tumor cells dividing across constrictions exhibit altered spindle pole organization, chromosome mis-segregations and micronuclei formation, despite functional ATR, ATM and Spindle Assembly Checkpoint (SAC) pathways. Migration across constrictions generates chromosome fragility, high gene copy number variations, massive transcriptional de-regulation and up-regulation of c-MYC oncogenic transcriptional signature via c-MYC locus amplifications. *In vivo* tumor settings, show that malignant cells populating metastatic foci or infiltrating the interstitial stroma give rise to cells expressing high levels of c-MYC.

Altogether our data suggest that mechanical stress during metastatic migration boosts genotoxic and oncogenic events. Our finding that confined migration is a source of aberrant chromosome segregation may explain why cancer cells are largely aneuploid while SAC genes are rarely mutated.

Recent Publications:

1. Bastianello G, Porcella G, Beznoussenko GV, Kidiyoor G, Ascione F, Li Q, Cattaneo A, Matafora V, Disanza A, Quarto M, Mironov AA, Oldani A, Barozzi S, Bachi A, Costanzo V, Scita G, Foiani M. Cell stretching activates an ATM mechano-transduction pathway that remodels cytoskeleton and chromatin. Cell Rep. 2023 Dec 26;42(12):113555. doi: 10.1016/j.celrep.2023.113555. Epub 2023 Dec 11. PMID: 38088930
2. Ajazi A, Bruhn C, Shubassi G, Lucca C, Ferrari E, Cattaneo A, Bachi A, Manfrini N, Biffo S, Martini E, Minucci S, Vernieri C, Foiani M. Endosomal trafficking and DNA damage checkpoint kinases dictate survival to replication stress by regulating amino acid uptake and protein synthesis. Dev Cell. 2021 Sep 27;56(18):2607-2622.e6.
3. Achar YJ, Adhil M, Choudhary R, Gilbert N, Foiani M., Negative supercoil at gene boundaries modulates gene topology., Nature. 2020 Jan;577(7792):701-705. Epub 2020 Jan 22., PMID: 31969709. ATR is essential for preservation of cell mechanics and nuclear integrity during interstitial migration, Nature 2020 Jan;577(7792):701-705.