Unravelling the side-dependent chemotherapy response of colorectal cancer using a patient-derived organoid model

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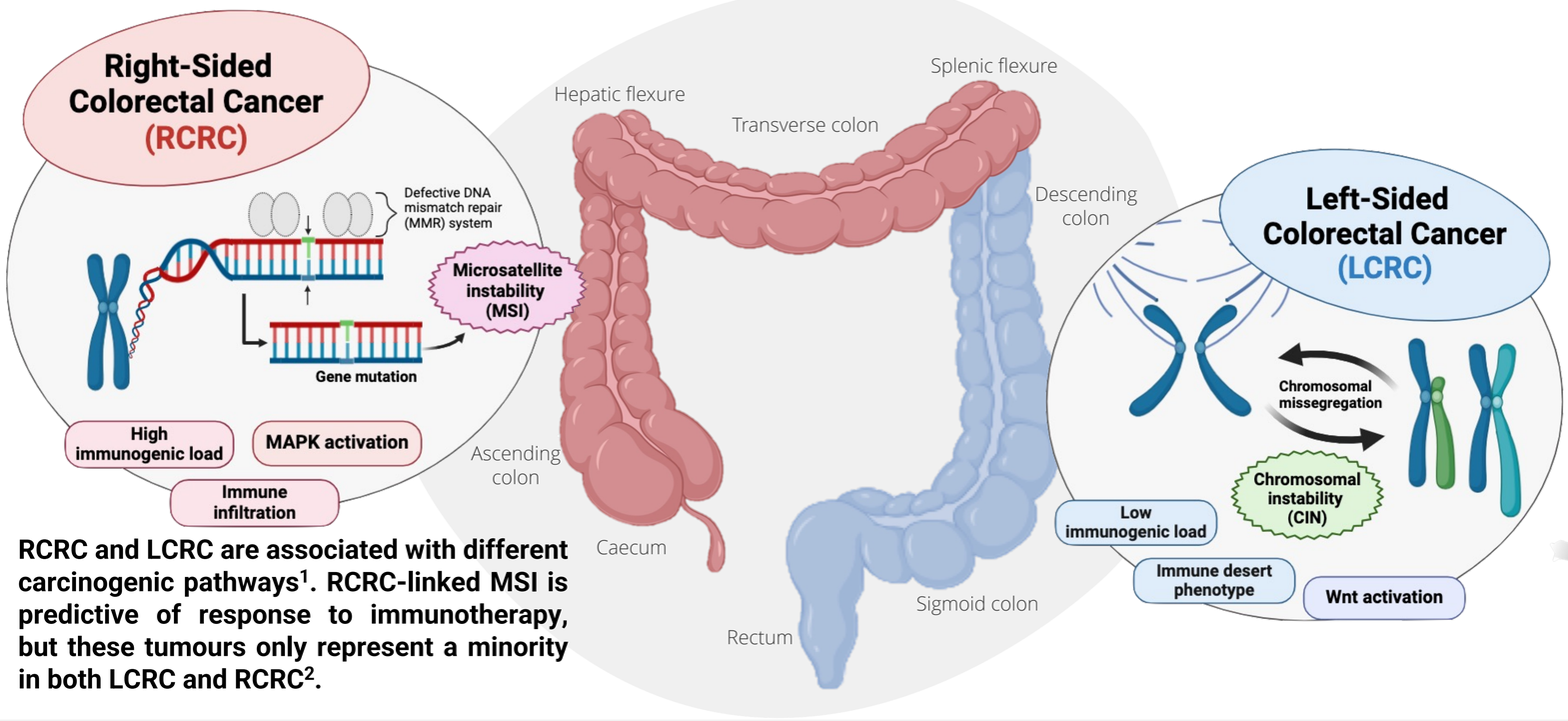
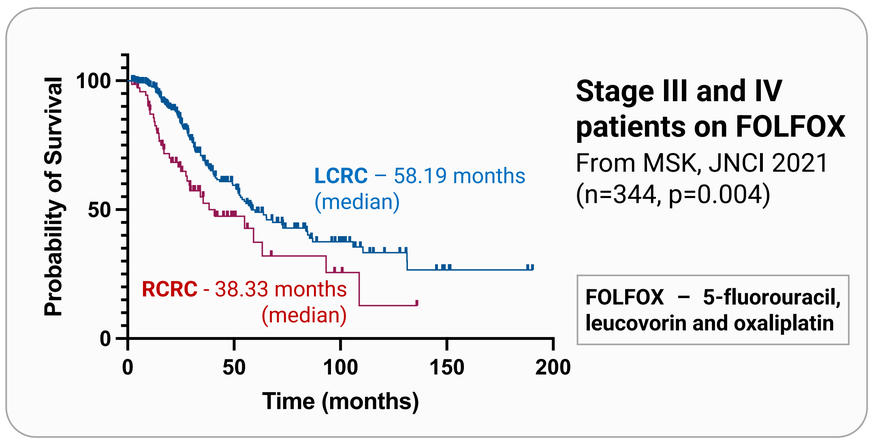
Background



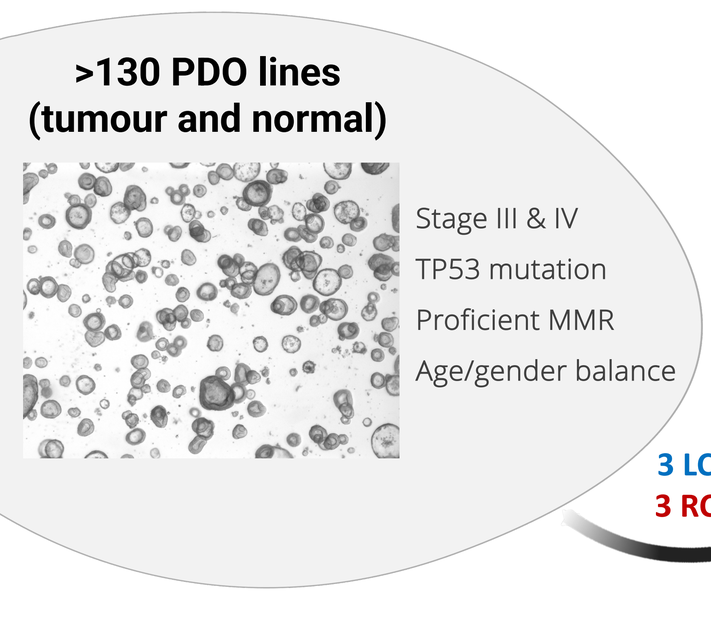
RCRC and LCRC are associated with different carcinogenic pathways[1]. RCRC-linked MSI is predictive of response to immunotherapy, but these tumours only represent a minority in both LCRC and RCRC[2].



FOLFOX chemotherapy

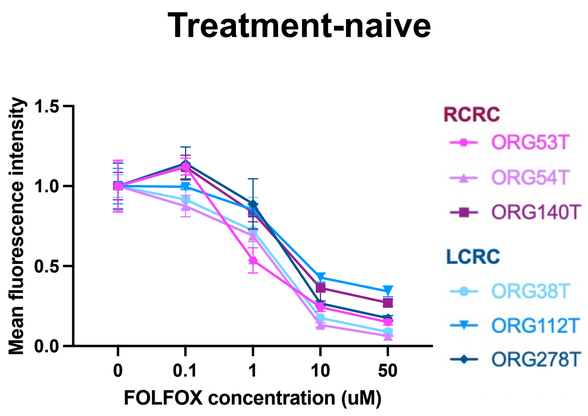
Chemotherapy remains the standard of care for late-stage CRC, with the FOLFOX regimen the most common[3]. RCRC patients have significantly poorer outcomes, but the mechanisms are unknown. We hypothesise that chemotherapy exacerbates the metabolic, transcriptomic and microenvironmental differences of RCRC and LCRC and impacts disease progression and recurrence.

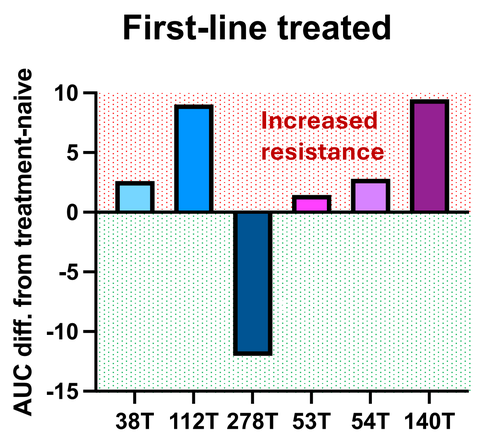
Methodology

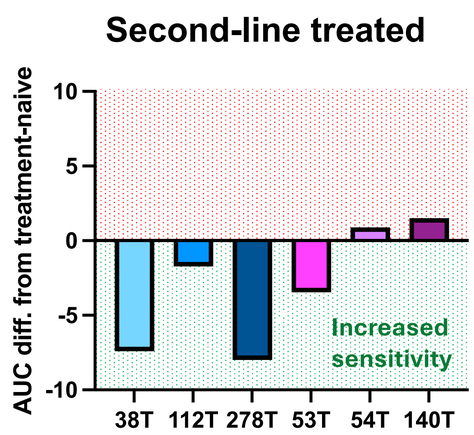


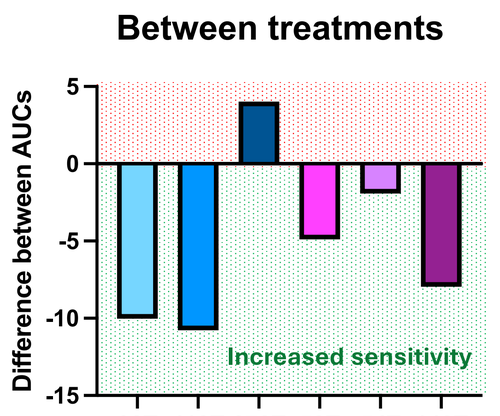
We have developed a bioresource of over 130 CRC patient-derived organoid (PDO) lines. Extensive characterisation of these PDOs has enabled us to select patients broadly representative of late-stage RCRC and LCRC. Through sequential cycles of FOLFOX administration and recovery, we have been able to observe long-term cellular adaptations to chemotherapy across our PDO cohort.

Results









Each of our PDOs demonstrated sensitivity to FOLFOX chemotherapy

After a single FOLFOX administration, PDOs generally demonstrated greater FOLFOX resistance

After a second FOLFOX administration, PDOs demonstrated increased FOLFOX sensitivity, with this most pronounced in LCRC PDOs

The apparent increased sensitivity of PDOs to FOLFOX may be suggestive of a drug-tolerant persister (DTP) phenotype[4]

Conclusion and Future Direction

- The efficacy of cytotoxic FOLFOX chemotherapy differs between tumours on the right and left sides of the colon, with right-sided tumours associated with poorer overall and progression-free survival.
- We demonstrate that CRC PDOs can be utilised to model sequential FOLFOX treatments and demonstrate differences in drug sensitivity.
- Future transcriptional profiling will reveal the molecular differences underlying drug sensitivity and whether this is influenced by tumour sidedness. This has the potential to identify novel targets for treatment of late-stage CRC.

References

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3. Xie et al. *Sig Transduct Target Ther*. 2020; 5(1):22.
4. Rehman et al. *Cell*. 2021; 184(1):226-242.e21.

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