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The evolutionary history of colorectal cancers

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In this presentation, I describe insights provided by multi-region exome and genome sequencing into evolutionary trajectories of colorectal tumours, including “classical” carcinomas, “lypermutator” carcinomas with defective mismatch repair and benign precursor lesions (adenomas). We find that adenomas are more genetically diverse than carcinomas, as assessed by total somatic mutation burden. The driver mutation complements of carcinomas and adenomas are also extremely similar. Adenomas, but not carcinomas, are also frequently polyclonal for major driver mutations. No individual driver mutation is specific to carcinomas. Carcinomas do, however, differ from adenomas in their copy number alteration burdens, which timing analysis shows to be often acquired close together in time, probably as a result of genome doubling. The evolutionary dynamics of hypermutator colorectal cancers are unexpectedly similar to those of classical cancers. Sub-clones in all lesions appear to be spatially discrete and geographic distance between samples correlates with genetic distance. Overall, our data add to the classical model of colorectal tumorigenesis, and provide some challenges to more recent models.