Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition.

In most colorectal cancer (CRC) patients, outcome cannot be predicted because tumors with similar clinicopathological features can have differences in disease progression and treatment response. Therefore, a better understanding of the CRC biology is required to identify those patients who will benefit from chemotherapy and to find a more tailored therapy plan for other patients. Based on unsupervised classification of whole genome data from 188 stages I-IV CRC patients, a molecular classification was developed that consist of at least three major intrinsic subtypes (A-, B- and C-type). The subtypes were validated in 543 stages II and III patients and were associated with prognosis and benefit from chemotherapy. The heterogeneity of the intrinsic subtypes is largely based on three biological hallmarks of the tumor: epithelial-to-mesenchymal transition, deficiency in mismatch repair genes that result in high mutation frequency associated with microsatellite instability and cellular proliferation. A-type tumors, observed in 22% of the patients, have the best prognosis, have frequent BRAF mutations and a deficient DNA mismatch repair system. C-type
patients (16%) have the worst outcome, a mesenchymal gene expression phenotype and show no benefit from adjuvant chemotherapy treatment. Both A-type and B-type tumors have a more proliferative and epithelial phenotype and B-types benefit from adjuvant chemotherapy. B-type tumors (62%) show a low overall mutation frequency consistent with the absence of DNA mismatch repair deficiency. Classification based on molecular subtypes made it possible to expand and improve CRC classification beyond standard molecular and immunohistochemical assessment and might help in the future to guide treatment in CRC patients.