Immune and molecular landscape in colorectal cancer

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While large-scale cancer genomic projects are comprehensively characterizing the mutational spectrum of various cancers, so far little attention has been devoted to either define the antigenicity of these mutations or to characterize the immune responses they elicit. A number of molecular subtypes of colorectal cancer (CRC) have been identified based on microsatellite instability, hypermutation, CpG island methylator phenotype, and somatic copy number aberrations. Based on different gene expression signatures there are also recent efforts to define consensus molecular subtypes[1], which might associate with driver mutations (KRAS, BRAF, APC, TP53).

Here we present a strategy[2] to characterize the immunophenotypes and the antigenome in CRC which delineates a step toward the development of personalized cancer immune-therapies. Further microRNA expression signatures as well as their target landscape was studied which add a molecular layer in discerning cellular and molecular phenotypes in CRC and provide potential molecular markers for diagnosis and therapy.

We apply our strategy to a large colorectal cancer cohort (n>500) from The Cancer Genome Atlas (TCGA) and show that subpopulations of tumor-infiltrating lymphocytes are associated with distinct molecular phenotypes. The characterization of the antigenome shows that a large number of cancer-germline antigens are expressed in all patients. Neo-antigens, in contrast, are rarely shared between patients. Analysis of the genetic basis of the tumors reveals distinct tumor escape mechanisms for the patient subgroups. Hypermutated tumors are depleted of immunosuppressive cells and show upregulation of immunoinhibitory molecules. Non-hypermutated tumors are enriched with immunosuppressive cells, and the expression of immunoinhibitors and MHC molecules is downregulated. Reconstruction of the interaction network of tumor-infiltrating lymphocytes and immunomodulatory molecules and identifies BCMA as a novel druggable target. Linear regression modeling identifies major determinants of tumor immunogenicity including CCR8 as novel candidate. Analysis of RNAseq data from microRNAs and mRNAs and their (predicted) target interaction enabled us to identify microRNAs which are differentially regulated between tumor vs normal tissue, to identify signatures that discern previous defined molecular subtypes and also to stratify patients in two prognostic subtypes (including let-7f, miR-106a, miR-210). Regularized regression and network analysis showed also that miR-93 might be an

interesting candidate for cancer-stem like cellular subtype. Finally, for functional association of found microRNAs and to construct a target landscape a module score analysis were performed. In summary, many known microRNAs involved in the carcinogenesis of CRC could be identified (e.g. miR-135b, miR-17~92 cluster) but also a number of novel follow-up candidates and their targets could be suggested.
We are currently expanding these approaches to a pan-cancer analysis of 20 different cancer types.

[1]Guinney et al. The consensus molecular subtypes of colorectal cancer. Nature Med. 2015. 10.1038/nm.3967
[2]Angelova et al. Characterization of the immunophenotypes and antigenomes of colorectal cancers reveals distinct tumor escape mechanisms and novel targets for immunotherapy. Genome Biol. 2015. 16:64