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The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints

Nicolas L Losa[1*], Michael Cruise[2], Ada Tam[1], Elizabeth Wick[1], Elizabeth Hechenbleikner[1], Janis M Taube[1], Richard Blosser[3], Hongni Fan[4], Hao Wang[4], Brandon Luber[4], Ming Zhang[4], Nickolas Papadopoulos[4], Kenneth Kinzler[4], Bert Vogelstein[4], Cynthia Sears[4], Robert A Anders[1], Drew Pardoll[1], Franck Housseau[4], Nicholas Siegel[4]

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We examined the immune microenvironment of primary colorectal cancer (CRC) using immunohistochemistry, laser capture microdissection/qRT-PCR, flow cytometry and functional analysis of tumor infiltrating lymphocytes. A subset of CRC displayed high infiltration with activated CD8+ CTL as well as activated Th1 cells characterized by IFN-gamma production and the Th1 transcription factor Tbet. Parallel analysis of tumor genotypes revealed that virtually all of the tumors with this active Th1/CTL microenvironment had defects in mismatch repair, as evidenced by microsatellite instability (MSI). Counterbalancing this active Th1/CTL microenvironment, MSI tumors selectively demonstrated highly up-regulated expression of multiple immune checkpoints, including five - PD-1, PD-L1, CTLA-4, LAG-3 and IDO - currently being targeted clinically with inhibitors. These findings link tumor genotype with the immune microenvironment, and explain why MSI tumors are not naturally eliminated despite a hostile Th1/CTL microenvironment. They further suggest that blockade of specific checkpoints may be selectively efficacious in the MSI subset of CRC. Our findings are the first to demonstrate a link between a genetically defined subtype of cancer and its corresponding expression of immune checkpoints in the tumor microenvironment. The mismatch repair defective subset of CRC selectively up-regulates at least 5 checkpoint molecules that are targets of inhibitors currently being clinically tested. Furthermore, our results were clinically validated in a Phase II study at Hopkins which showed mismatch-repair status as a predictor of clinical benefit to immune checkpoint blockade with pembrolizumab.

Authors' details
[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA. [2]Cleveland Clinic, Cleveland, OH, USA. [3]Johns Hopkins University: School of Medicine, Baltimore, MD, USA. [4]Johns Hopkins Hospital, Baltimore, MD, USA.

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[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA
Full list of author information is available at the end of the article