

POSTER PRESENTATION

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

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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.

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