CANCER RESEARCH

Clinical Research (Excluding Clinical Trials)

Abstract 479: *BRAF* and *KRAS* mutation define distinct subtypes of the CpG island methylator phenotype in colorectal cancers

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Abstract

BACKGROUND AND AIMS: Colorectal cancer is an epigenetically heterogeneous disease, however the extent and spectrum of the CpG Island Methylator Phenotype (CIMP) is not clear.METHODS: Genome scale methylation and transcript expression were measured using the Illumina HM450 DNA methylation and HT12 V3 expression microarrays in 216 unselected colorectal cancers. Mutations in epigenetic regulators were assessed using CIMP-classified Cancer Genome Atlas exomes.RESULTS: CIMP-High cancers dichotomised into CIMP-H1 and CIMP-H2 based on methylation profile, which was supported by over-representation of *BRAF* (74%, P<0.0001) or *KRAS* (55%, P<0.0001) mutation. Congruent with increasing methylation, there was a stepwise increase in patient age from 62 years in the CIMP-Negative subgroup to 75 years in the CIMP-H1 subgroup (P<0.0001). CIMP-H1 were predominantly comprised of consensus molecular subtype 1 (CMS1) cancers (70%) whilst CMS3 was over-represented in the CIMP-H2 subgroup (55%). PRC2-marked loci were subjected to significant gene body methylation in CIMP cancers ($P<1.6x10^{-78}$). We identified oncogenes susceptible to gene body methylation and Wnt pathway antagonists resistant to gene body methylation. CIMP cluster specific mutations were observed for in chromatin remodeling genes, such as in the SWI/SNF and NuRD complexes, suggesting synthetic lethality.CONCLUSION: There are five clinically and molecularly distinct subgroups of colorectal cancer. We show a striking association between CIMP and age, gender and tumor location and identify an unidentified role for gene body methylation in progression of serrated neoplasia. These data support

our recent findings that CIMP is uncommon in young patients and that BRAF mutant polyps in young patients may have limited potential for malignant progression.

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