CMS subtype characterized by high TMB shows immunosuppressive microenvironment that implies resistance to immunotherapy

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BACKGROUND
Tumor mutational burden (TMB) is emerging as an important biomarker for immune checkpoint therapy (ICT) response. Yet, even in the context of high TMB, ICT may be ineffective in an immunosuppressed microenvironment. Here we demonstrate that a well-characterized subtype of CRC, CMS2, associated with Wnt pathway activation, is immunosuppressive despite high TMB.

METHODS
- Tumor-normal paired DNAseq (WGS or WES) and deep RNAseq (~200x10^6 reads per tumor) was performed on 464 GI tumors from a commercial database.
- TMB was calculated by observing all somatic specific non-synonymous exonic mutations as previously established (Rizvi et al., 2015).
- Each sample was assigned to one of the colorectal Consensus Molecular subtypes (CMS) based on RNA classification.
- A curated panel of 129 genes that discriminate between 22 immune subsets was identified. A database containing 1467 unselected tumors was used to define a distribution of expression for each signature.
- Somatic-specific pathogenic/likely pathogenic mutations were identified using ClinVar annotations.
- Significant enrichment was analyzed between immune subsets, CMS types, TMB status, and somatic mutational status.

RESULTS
Figure 1: TMB and CMS have significantly associated TMB.

Figure 2: CMS1 and CMS2 have significantly associated TMB.

Figure 3: CMS2 has high checkpoint expression.

Figure 4: CMS2 is significantly associated with being pathogenic Wnt/β-catenin mutations.

Figure 5: CMS2 is significantly associated with lower inherent immune infiltrate activity, implying an effector immune cell.

Figure 6: Immune activity can modulate immune response through gene type updates.

Figure 7: The most common subtype of CRC, CMS2 (~37% in unselected populations), is highly immunosuppressive despite high TMB. ICT is only effective in an immunologically active microenvironment. TMB alone as a biomarker likely is insufficient to indicate the effectiveness of immunotherapy.

KEY FINDINGS
- CMS1 & CMS2 have significantly higher TMB.
- CMS1 (MSI-enriched) expresses selected TME markers more than other subtypes.
- Perplexingly, CMS2 had significantly lower expression of 6 targetable checkpoint markers.
- As expected, CMS2 tumors were significantly lower expression of 6 targetable checkpoint markers.
- Immune-deconvolution indicated substantial exclusion of Tem cells from CMS2 tumors, line with Wnt/β-catenin blockade of Tcm→ Tem maturation for immunoreactivity.

CONCLUSIONS:
The most common subtype of CRC, CMS2 (~37% in unselected populations), is highly immunosuppressive despite high TMB. ICT is only effective in an immunologically active microenvironment. TMB alone as a biomarker likely is insufficient to indicate the effectiveness of immunotherapy.

REFERENCES