Abstract ID: B10

Prognostic impact of different mRNA immune-signatures in mismatch repair deficient (dMMR) colorectal cancers (CRCs).

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Background

Alterations in mismatch repair system lead to accumulation of gene mutations and microsatellite instability in CRC. The high mutational burden of dMMR CRCs induces an increase of neoantigens and elicits a remarkable endogenous anti-tumor immune response, counterbalanced by the strong expression of immunosuppressive ligands and signals.

We aimed at describing the immune-profile of dMMR CRCs and its potential prognostic value through mRNA expression analysis.

Methods

Treatment-naïve primary tumors of both metastatic and non-metastatic (defined by a minimum follow-up duration of 3 years) dMMR CRC patients were analyzed by means of NanoString nCounter® PanCancer Immune Profiling Panel (Seattle, WA, USA), including 730 immune-related genes.

Clustering analysis was performed through the functional categories of immune-related gene expression revealed by the PanCancer Immune Profiling Advanced Analysis, obtaining four main functional clusters.

Samples classification was achieved through the quartile clustering technique that assigned to each cluster a discrete value ranged from -1 to +1. For each sample a "deregulation" score (DS) was calculated by the algebraic sum of the discrete values of the four functional clusters.

Based on DS values, two groups of tumors samples were obtained: COLD and NOT COLD. The COLD group had a strong immune system down-regulation (DS ≤ -3), while the NOT COLD group had an incomplete down-regulation or at least a partial up-regulation (DS ≥ -2) of immune system.

Overall survival curves for both groups were determined according to the Kaplan-Meier method and compared using the log-rank test.

Results

Eighty-nine patients with dMMR CRC admitted to two Italian Oncology Units were included.

Several immune-related genes were differently expressed in dMMR CRCs. Based on the classification described above, two tumor subgroups can be identified according to the mRNA expression immune-profile: 28 tumor samples were classified as COLD and 61 as NOT COLD.

There are no statistically significant differences between the two groups regarding clinical, pathological and molecular features, but there is a trend in favor of the COLD group for advanced disease at diagnosis (stage III and IV) (57% vs 34%, p= 0.07) and for the left side of the primary tumor (40% vs 18%, p= 0.06) (Table 1).

Characteristics	COLD N=28 N (%)	NOT COLD N=61 N (%)	p value
Disease Volume			
Not metastatic	14 (50)	38 (62)	p*= 0.39
Metastatic	14 (50)	23 (38)	
Stage at diagnosis			
I-II	12 (43)	40 (66)	***p*= 0.07***
III-IV	16 (57)	21 (34)	
Genotype			
RAS + *BRAF* mutation	6+12 (72)	19+26 (80)	p*= 0.40
Wild Type	7 (28)	11 (20)	
NA	3	5	
Primary tumor side			
Right	17 (60)	50 (82)	***p*= 0.06***
Left	11 (40)	11 (18)	
NA	1	3	

Table 1. Patient characteristics
(N=number; NA= not available; p*= Fisher's exact test or χ2 test, when appropriate)

NOT COLD tumors, when compared with the COLD group, show significant up-regulation in a wide range of genes functionally related to the immune system as HLA-DPA1, HLA-DPB1, HLA-DMB, HLA-DRB3, CXCL9, IDO1, GZMA (Figure 1).

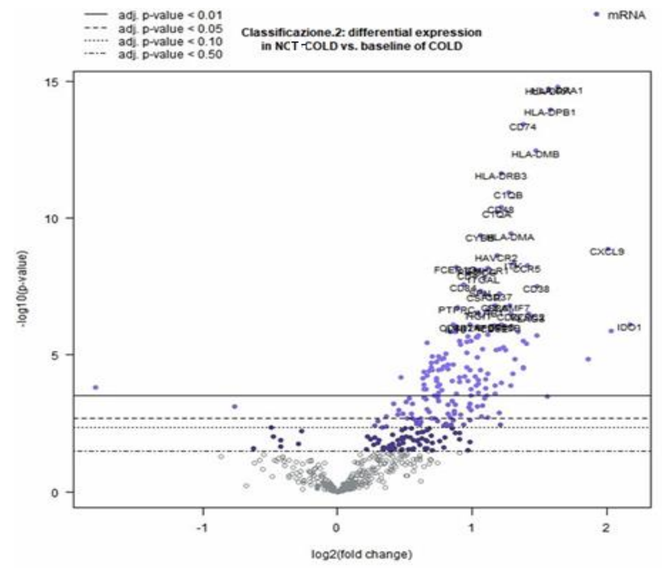

Figure 1. Gene expression in the NOT COLD group respect to the COLD one

The Tumor Infiltrating Lymphocyte score (TILs) was higher in the NOT COLD group than in the COLD one (Figure 2).

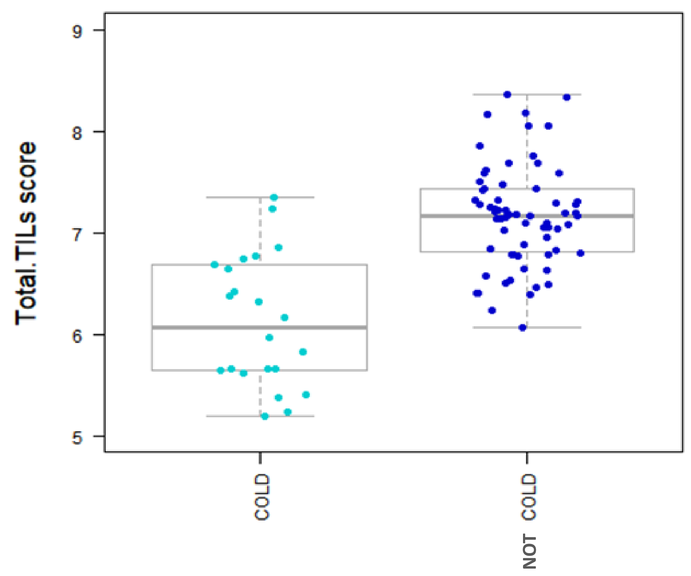

Figure 2. Tumor infiltrating lymphocyte score (TILs) in COLD and NOT COLD groups

Survival from the diagnosis of primary tumor in all patients (OS) and survival from the diagnosis of metastatic disease in metastatic patients (OS-MetDis) were lower in the COLD group than in the NOT COLD one, with p-values of 0.017 (HR=4.17; 95% CI:1.28-13.52) and 0.003 (HR=6.92; 95% CI:1.92-29.91) respectively (Figures 3-a and 3-b); on the other hand, no significant differences were observed in patients with not-metastatic disease (OS-NotMet; p-value= 0.86; HR=0.24; 95% CI:0.01-4.90).

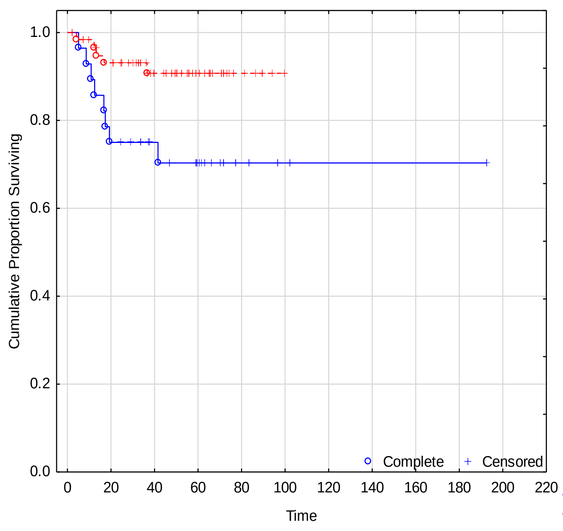

Figure 3-a. OS

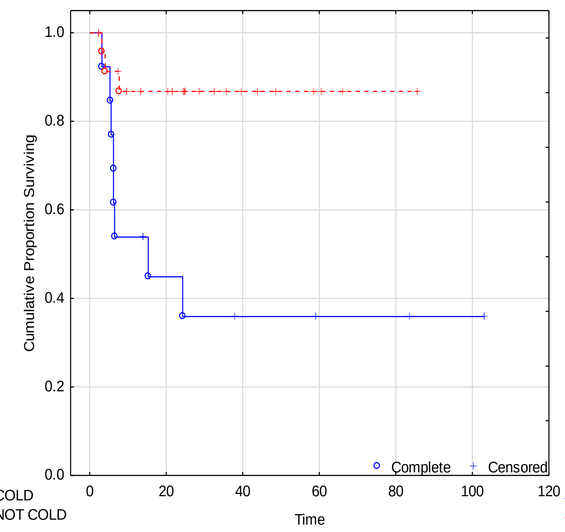

Figure 3-b. OS-MetDis

Conclusions

Our results demonstrate that immuno-related genes are heterogeneously expressed in dMMR CRCs, thus configuring two distinct groups: COLD and NOT COLD. They differ in clinical and pathological features, expression of several immuno-related genes, tumor infiltrating lymphocytes (TILs) density and prognosis. In addition, a predictive value of different sensitivity to immune checkpoint inhibitors could be suggested.

These results require further investigation in clinical trials.

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