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Spotlight

The IFN-high phenotype: A biomarker-driven breakthrough in colorectal cancer treatment

Lize Allonsius,[1,2] Luca Kelecom,[1,2] and Damya Laoui[1,2,*]
[1]Lab of Dendritic Cell Biology and Cancer Immunotherapy, VIB Center for Inflammation Research, Brussels, Belgium
[2]Lab of Cellular and Molecular Immunology, Brussels Center for Immunology, Vrije Universiteit Brussel, Brussels, Belgium
*Correspondence: dlaoui@vub.be
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Patient stratification is crucial for improving immunotherapy effectiveness. Acha-Sagredo et al. identified an interferon (IFN)-high immunophenotype and CD74 overexpression as predictors for immunotherapy response in colorectal cancer (CRC). This signature, involving cytotoxic T cells and antigen-presenting macrophages, was found in both mismatch repair-deficient and -proficient CRCs. CD74 overexpression could serve as a biomarker, enabling personalized CRC treatment.

Despite improvements in screening methods, colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide. Immune checkpoint inhibitors (ICI) improved outcomes for certain patients; however, response rates remain limited, with only 50% of mismatch repair deficient tumors (dMMR) responding, while MMR proficient (pMMR) tumors being largely resistant. Therefore, identifying predictive biomarkers is crucial for improving patient stratification and expanding immunotherapy benefits, as conventional markers such as tumor-mutational burden (TMB) and PD-L1 expression remain suboptimal. Acha-Sagredo et al.[1] identify an interferon (IFN)-high immunophenotype, characterized by heightened immune activation, as a crucial biomarker for ICI responsiveness. Laser capture microdissection followed by RNA sequencing enabled the precise separation and analysis of normal epithelium, tumor epithelium, and stromal compartments, providing detailed insights into the tumor microenvironment (TME). The researchers observed that regardless of TMB, certain dMMR and pMMR tumors exhibited increased infiltration of cytotoxic T cells (CTLs) and tumor-associated macrophages (TAMs), which overexpressed genes involved in antigen processing and presentation. The authors propose a model in which IFNγ produced by CTLs enhances antigen presentation in both TAMs and cancer cells. Importantly, the presence of this antigen-presenting TAM phenotype correlated with better ICI response regardless of the ICI used (Figure 1).

Using spatial transcriptomics, Acha-Sagredo et al. revealed overexpression of CD74 (MHC class II invariant chain), CXCL9, CCL5, and CXCL10 in both TAMs and tumor cells adjacent to IFN-producing CTLs in IFN-high samples. Notably, this TAM phenotype was previously suggested as a favorable predictor of patient outcomes and ICI response, with the CXCL9:SPP1 ratio proposed as a more accurate indicator of TAM polarity than the outdated M1/M2 classification.[2] Moreover, Kinget et al. demonstrated that interactions between proinflammatory TAMs and CTLs and a spatially embedded HLA signature correlated with positive outcomes following ICI treatment in kidney cancer, further emphasizing the role of TAMs and antigen presentation in predicting ICI efficacy.[3]

Previous CRC studies have also highlighted the importance of IFNγ as a predictor of survival. Llosa et al. reported that a subset of dMMR patients with high CTL and Th1 infiltration, characterized by high IFNγ production, exhibited upregulation of multiple immune checkpoints, suggesting potential benefit of ICI.[4] Similarly, in other cancer types such as gastric cancer and hepatocellular carcinoma, patients with an IFNγ-responsive, CTL-associated, and MHCII-enriched gene signature exhibit better prognosis and improved progression-free and overall survival following ICI treatment.[5,6]

However, an IFN-high phenotype is not always associated with favorable immunotherapy responses. As such, chronic IFNγ signaling can drive ICI resistance by epigenetically and transcriptomically reprogramming tumors—for instance, by upregulating ligands for multiple T cell inhibitory receptors.[7] This underscores the need for caution when therapeutically promoting sustained IFN signaling, as prolonged exposure may inadvertently induce immunosuppressive effects.

Acha-Sagredo et al.[1] found consistent CD74 overexpression in IFN-high samples, regardless of CRC subtype or stromal/epithelial compartments, prompting the authors to propose CD74 as a marker of the IFN-high ICI-responsive phenotype. *In vitro* co-cultures confirmed that IFNγ produced by CTLs directly induced antigen presentation and concomitant CD74 expression. The authors quantified CD74 protein expression using the stroma proportional score (SPS), defined as the proportion of $CD74^+$ stroma cells relative to all stroma cells defined by immunostaining. The CD74 SPS outperformed other scoring methods and was further validated across multiple cohorts.[1]

Previous studies support CD74 as a predictive marker, linking it to antigen presentation and improved anti-tumor immunity. As such, CD74 expression on TAMs was positively associated with CTL activation and favorable prognosis in HCC patients.[8] Recently, Wang et al.,

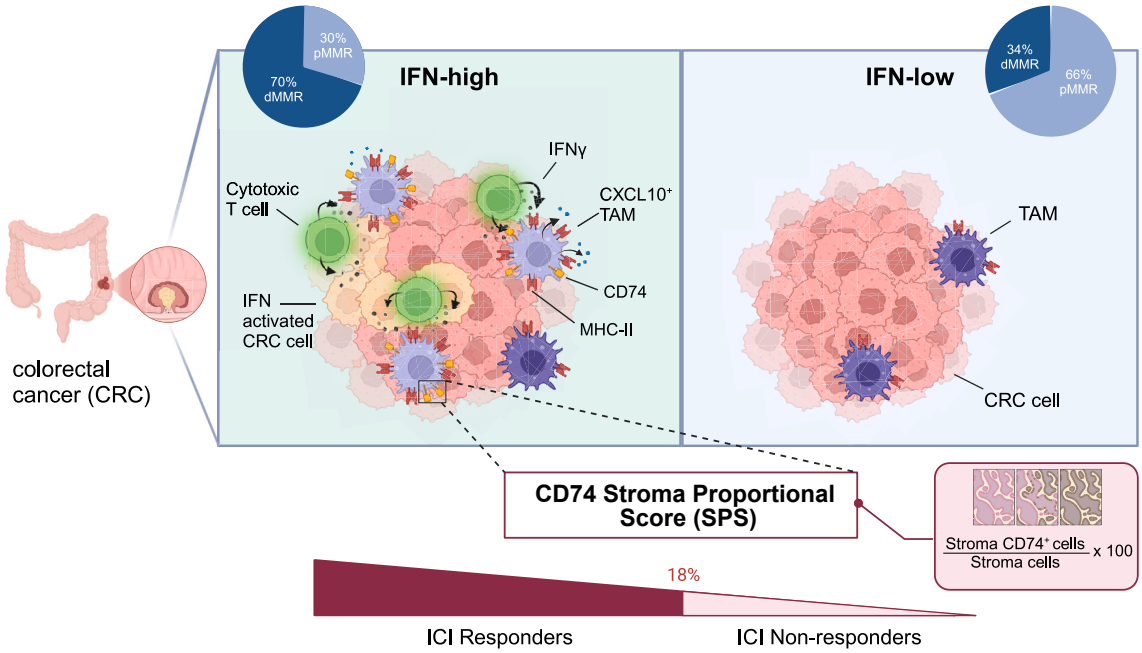

Figure 1. The IFN-high immunophenotype is associated with an improved response to ICI in CRC

IFN-high tumors exhibit an inflamed microenvironment highly infiltrated by CTLs secreting IFNγ, subsequently inducing antigen presentation and CXCL10 and CD74 expression in TAMs. IFN-low tumors are less inflamed, with fewer immune interactions. Pie charts indicate the proportion of dMMR and pMMR tumors in each group. The stroma proportional score (SPS) is calculated as the percentage of $CD74^+$ stroma cells relative to the total stromal cell population. A lower SPS is associated with non-responders to immunotherapy, with an 18% threshold separating responders from non-responders.

identified CD74 as a marker for an inflamed TME enriched in HLA and CTL infiltration, which correlated with responsiveness to treatment with a PD-1/CTLA-4 bispecific antibody in advanced solid tumors.[9] Similarly, in bladder and esophageal cancer, CD74 expression is linked to improved ICI outcomes and increased immune cell infiltration.[10] In contrast, some studies reported immunosuppressive roles for CD74 through interactions with macrophage migration inhibitory factor (MIF)[11] or amyloid precursor protein (APP).[12] These contrasting roles underscore the complexity of the function of CD74 and the need to clarify its context-dependent effects and relevance across large patient cohorts.

Despite these complexities, the identification of the IFN-high phenotype as a marker for immunotherapy response in CRC offers a new framework for patient stratification. High IFN signaling, marked by concomitant antigen presentation and CD74 overexpression by TAMs, could predict ICI response, irrespective of TMB and MMR status. Linking these findings with previous studies suggest that CD74 may be a potential biomarker for CRC and other cancers. Moreover, Acha-Sagredo et al. challenge the traditional paradigm that associates immunotherapy responsiveness primarily with dMMR status, revealing that a subset of pMMR CRC tumors with an IFN-high immunophenotype are amenable to ICI treatment, potentially improving outcomes for these populations. Future research could explore therapeutic strategies to modulate or leverage the IFN-associated immune signature, potentially combining these with ICI to achieve more durable responses. Additionally, the development of diagnostic tools capable of rapidly and accurately assessing these molecular characteristics, such as CD74 expression, could represent a significant advancement in precision oncology, paving the way for more effective and personalized treatment strategies.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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