Review Article

The significance of tumor-associated immune response in molecular taxonomy, prognosis and therapy of colorectal cancer patients

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Abstract: The importance of host immune response in colorectal cancer (CRC) has been constantly revealed through the last 10 years. A number of relevant immune markers have been introduced as prognostic and are now been used alone or in combination with each other in clinical practice. Efforts establishing a worldwide consensus on the implications of immune-profiles in conjunction to other factors are designed in the right direction in order to more effectively categorize patients with CRC in groups that might benefit from currently used or future applied therapies. On the other hand, a number of clinical trials have evolved the application of immunotherapies in patients with CRC both in the adjuvant and palliative setting.

Keywords: Colorectal cancer (CRC); immune response; therapy

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men (10% of all cancers) and the second in women (9.2% of all cancers) worldwide (1). Mortality rates remain high despite the fact that new operative and oncological therapies have been applied. Almost half of the patients undergoing treatment with curative intent will survive up to 5 years. Nevertheless, a substantial 25% of the conventionally classified [AJCC/UICC Tumor-Node-Metastasis (TNM) classification] stage I/II CRCs recur despite pathologically confirmed complete surgical resection and no evidence of residual tumor burden or distant metastases (2). The reason for that remains unclear but it definitely implies that the TNM classification does not have the needed accuracy for predicting outcome in all stages. Several other ways have been proposed to classify CRC. These rely on tumor cell characteristics, including morphology, molecular pathways, mutation status, cell origin and gene expression-based methods and allows the distinction of multiple, yet overlapping subtypes (3-7). This overlapping could be bypassed with classifications not based on the neoplastic cells and their characteristics but on the immunologic profile of the tumor microenvironment, also named tumor-associated immune response or host immune response (8). This is an important determinant of outcome in human cancers (9,10). The prognostic impact of immune cell varies based on the type of cancer but in general high densities of T cells (CD3+), cytotoxic T cells (CD8+) and memory T cells (CD45R0+) are clearly associated with longer disease-free survival (DFS) and overall survival (OS) (10). More than one hundred published studies confirm the prognostic value of the immune cell infiltrates in patients with CRC. The observed association with improved survival is regardless of pathological stage (11). Moreover, efforts have been made to clarify whether lymphocyte subtyping adds additional prognostic information beyond the evaluation of inflammatory cells on routine haematoxylin and eosin (H&E) stained sections (12).

In this review, we try to highlight the impact of tumor-associated immune responses in the prognosis of CRC

patients and to present tools that can help distinguish those patient groups who would potentially benefit from future applied immunotherapies.

Methods for assessing immune response in colorectal cancer

To be used globally in a routine manner, evaluation of a novel marker should be simple, applicable in daily practice, feasible and inexpensive, reproducible, quantitative, standardized, pathology-based and powerful (13).

In order to improve the risk stratification for patients with CRC, many researchers have applied simple, specific T cell subtype immunohistochemistry-based density analysis. Density is graded as absent, weak, moderate or strong in three separate compartments: (I) invasive margin (IM); (II) tumor stroma (ST) and (III) cancer cell nests (CCN) (14).

Another immunohistochemistry-based score, the Galon's "Immunoscore", grades CD45R0 or CD3 and CD8 infiltration at both the IM and central tumor (CT) as either high (Hi) or low (Lo), according to the median number of positive cells. Patients are assigned to one of four prognostic groups depending on the total number of areas graded Hi or Lo (15).

A third method for assessing the local inflammatory response in CRC is the Klintrup-Makinen grade, an assessment of inflammatory cell infiltration only at the IM, using H&E stained sections. Patients are assigned to one of four prognostic groups depending on the intensity of the inflammatory cell reaction. Zero (0) denotes no increase of inflammatory cells, 1 denotes mild and patchy increase of inflammatory cells, 2 denotes a band-like infiltrate at the IM with some evidence of destruction of cancer cell islets and 3 denotes a very prominent inflammatory reaction with frequent destruction of cancer cells (16).

All methods seem to exhibit similar survival relationships in both node-positive and node-negative CRC, with a favorable prognostic impact of lymphocytic infiltrates (14).

"Immunoscore" versus TNM staging

The classification based only on tumor invasion parameters, has been shown to be valuable in estimating the outcome of patients in a variety of cancers (17). However, clinical outcome can significantly vary among patients within the same histological type and tumor stage (2,18). Histopathological analysis of colorectal tumors has revealed varying infiltration by inflammatory and lymphocytic cells (19). In depth intra-tumor analysis reveals that these immune infiltrates are not randomly distributed. Tumor-infiltrating immune cells appear to be localized and organized within dense infiltrates in the CT and at the IM of tumor nests. An underlying biology may be reflected by this immune reaction, as revealed by gene expression profiling and other assays. These gene-signature sets include evidence for innate immune activation, secretion of chemokines for innate and adaptive cell recruitment, expression of immune effector molecules and immunoregulatory factors (20,21). Large cohort studies (with sample sizes of 843 and 768 patients, respectively) have revealed that tumor immune infiltrate patterns in CRC are significant prognostic biomarkers, even after adjusting for stage, lymph node count and well-established prognostic tumor molecular biomarkers, including microsatellite instability (MSI) and BRAF mutations (22,23). When the "Immunoscore" was tested in two large independent cohorts (n=602), only 4.8% of patients, among those harbouring tumors with a high "I"4, relapsed after 5 years. In contrast, 72% of patients with a low tumor Immunoscore ("I"0 and "I"1) had relapsed and only 27.5% were alive at 5 years. Similar results have been obtained from other studies, illustrating that these "I"0 and "I"1 patients could have potentially benefited from adjuvant therapy (2,15,20,24,25). Mlecnik *et al.* showed that in CRC patients with TNM stages I/II/III, the best predictor for outcome among all clinical parameters was the Immune score. In Cox multivariate regression analysis, after adding the AJCC/UICC-TNM stages and the Immune score in the model, only the Immune score remained significantly associated with disease-specific survival and OS (HR 0.63 and 0.71, respectively, all $P<0.001$). Results were also confirmed in an independent cohort of 184 patients (Immune score: HR 0.42 and 0.64, respectively, all $P<0.001$) (15).

Immune response gene expression in colorectal cancer

Pentheroudakis *et al.* studied mRNA expression of seven immune response-related genes (CD3Z, CD8, CD4, CXCL9, CXCL13, IGHM and FOXP3) in patients with stage II and III colorectal tumors managed with oxaliplatin-based adjuvant chemotherapy and came to the conclusion that (10,26,27) only CD3 and CD8 can cluster the CRC patients into distinctive "mRNA-based Immune Score" high versus low (mIS) cases. CD3 is a marker of activated T lymphocytes, encoding a protein which forms the T cell

receptor-CD3 complex, important for coupling antigen recognition to several intracellular signal-transduction pathways. CD8 encodes a cell surface glycoprotein found on most cytotoxic T lymphocytes that mediates efficient cell-cell interaction with class I MHC antigen-presenting cells. However, the prognostic significance of mIS was restricted to a specific tumor stage and site. Specifically, only in patients with stage III right-sided colon cancer, a low immune response was associated with significantly inferior DFS (mIS-low, HR 2.28, 95% CI: 1.05-8.02) (28), while no prognostic impact was seen in left-sided tumors. In addition, a recently published novel 12-gene immune signature that was generated from miRNA/mRNA expression analysis, was shown to be an independent factor in predicting OS, as well as DFS in CRC patients (29).

In a more integrated analysis, spatio-temporal dynamics of intra-tumoral immune cells revealed that patients with diverse gene expression patterns have different clinical outcomes. Genes highly expressed in patients with prolonged DFS were related to cytotoxic T cell surface molecules, T helper cell surface molecules and chemokine-related functions associated to endothelial cell migration. In contrast, for patients with unfavorable outcome, an overexpression of genes with a role in IL-2 signaling and in the downregulation of adaptive immune responses was observed. This process seems to be complex and according to Bindea *et al.* evolves at each tumor stage. Densities of T follicular helper cells and innate cells increase, whereas most effector T cell densities decrease with tumor progression. The numbers of B cells increase at a late stage and have a dual effect, tumor-promoting and tumor-suppressive, depending on the complex fine regulation of the immune contexture. Chemokines, such as CXCL13 and IL-21 have a pivotal role in shaping the effective anti-tumor immune reaction in CRC (30).

Immune response and correlation with clinicopathological factors

In the Mlecnik *et al.* study the pT (depth of tumor) and pN stage (lymph node invasion), as well as the presence of bowel perforation were the clinical parameters significantly associated with survival. However, the Immune score was found to be the best predictor among all clinical parameters. In multivariate analysis only the Immune score remained significant for prognosis (15).

Various hypotheses have been generated for the impact of molecular processes on the intensity and nature of the host immune response. CRC can molecularly be divided into three groups: (I) chromosomal unstable (CIN); (II) microsatellite unstable (MSI); and (III) CpG island methylator phenotype (CIMP). Most of the cases arise through the CIN pathway, with various degrees of chromosomal number alterations and loss of heterozygosity. Mutations in specific tumor suppressor genes and oncogenes that activate pathways critical for CRC initiation and progression are accumulated in these cancers. Hypermutation characterizes the microsatellite unstable (MSI-high) CRCs, which represent 15% of all CRCs. Frame-shift mutations in MSI-high CRCs constitute a potential source of targetable neo-antigens (31). Epigenetic silencing of a mismatch-repair gene (MLH1) causes most of the MSI-high cancers [mismatch repair deficient (dMMR)] (6,32,33). This phenomenon occurs mostly in tumors of the CpG island methylator phenotype (CIMP-positive), though not all CIMP cases result in MLH1 promoter methylation. Consequently, a classification overlap occurs (6,33), while the degree of the host immune reaction varies in these overlapping subtypes.

dMMR tumors often contain intra-epithelial T cells in response to the expression of neo-antigens on the cell surface (34). This could be the explanation for the better prognosis observed in patients with dMMR tumors. Additionally, analysis of a cohort of 1197 patients confirmed the prognostic value of CD3+, CD8+ and CD45R0+ T cell infiltration in proficient-MMR (pMMR) CRCs (35). Other studies showed improved survival in patients with dMMR tumors and high density of cytotoxic CD3+ lymphocytes (36,37). In another large study with 768 CRCs, dMMR tumors were positively associated with CD45R0+ cell density, although the survival benefit associated with tumor infiltrating CD45R0+ cells was independent of MSI status (22). Accumulating data suggest that complex factors regulate the connection of the MSI status with that of the host immune response.

Discordant classification problems could potentially be solved by a consensus gene expression-based classification system for CRC, taking into account all the key components linked to tumor, stroma and host cellular functions. A group of experts recently published in *Nature Medicine* a proposal, after showing interconnectivity between six independent classification systems. Significant biological differences in the consensus molecular subtypes (CMS) support a new taxonomy for this disease with distinct molecular groups: (I) CMS1 (MSI immune) with a hypermutated profile, microsatellite unstable, CIMP-positive with strong immune

activation; (II) CMS2 (canonical) with epithelial, marked WNT and MYC signalling activation and frequent somatic copy number aberrations; (III) CMS3 (metabolic) with epithelial, evident metabolic dysregulation and frequent KRAS mutations; and (IV) CMS4 (mesenchymal) with prominent transforming growth factor-β activation, stromal invasion and angiogenesis. About 10–15% of CRCs represent a transitional phenotype and cannot be classified. The authors identified no specific gene aberrations reliably identifying any CMS type, apart from the nearly universal genetic activation of the receptor tyrosine kinase and mitogen-activated protein kinase pathways in CMS1 and CMS3. This supports the notion that tumors harbouring commonly assumed driver events in CRC still vary markedly in their biology, highlighting the very poor genotype/phenotype correlations in CRC. Important associations between the CMS groups and clinical variables have been observed. CMS1 tumors are frequently diagnosed in females with right-sided lesions and present with higher histopathological grade. On the other hand, CMS2 tumors are mainly left sided. Finally, CMS4 tumors have a tendency to be more advanced (stages III and IV). In multivariate analyses, after adjustment for clinicopathological features, MSI status and presence of BRAF or KRAS mutations, CMS4 tumors had a worse OS and relapse-free survival. Superior survival rates after relapse have been found in the group of CMS2 patients (38). Of interest, the CMS1 population had a very poor survival rate after relapse, in agreement with recent studies showing worse prognosis for patients with dMMR and BRAF-mutated CRCs that recur (39-41).

The group of patients harboring MSI-high and BRAF mutated tumors with strong immunity could potentially benefit from immunological therapeutic interventions. On the other hand, CRC patients with RAS mutant tumors had significantly lower expression of a coordinated immune response, a fact that could be translated into unsuccessful immunological therapies (42).

Immune response and therapeutic implications

Chemotherapeutics like oxaliplatin, commonly used in 5-FU-based regimens, can stimulate a highly potent immune response by increasing neo-antigen release and presentation via antigen presenting cells (APCs), with enhancement of T cell responses and generation of memory T cells (43,44). Tumor cells can be susceptible to cytotoxic T lymphocytes by upregulation of "death receptors", such as FAS or TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) (45). Correale *et al.* reported a better outcome in advanced CRC patients treated with oxaliplatin chemotherapy or chemo-immunotherapy if previously an intense T-regulatory cell (Treg) infiltration was present in primary tumors, suggesting a reversal of immune suppression (46). These immunogenic effects of oxaliplatin on the host immune response could transform its conventional use as an empiric cytotoxic drug to an immunomodulatory drug that can be used in combination with potent immunotherapies in order to potentiate their effect.

Despite the fact that immunotherapies have been proven successful in other types of cancer, the majority is being evaluated in early-phase (phase I and II) clinical trials for CRC. Current immunotherapies for CRC fall into 8 broad categories: (I) monoclonal antibodies (MAbs); (II) checkpoint inhibitors and immune modulators (anti-CTLA-4, anti-PD-1, anti-PD-L1); (III) cancer vaccines; (IV) adoptive cell therapy; (V) dendritic cell therapies; (VI) oncolytic virus therapy; (VII) cytokines; (VIII) adjuvant immunotherapies (47). For the purposes of this review we only report immunotherapies with clinically significant results in phase II, as well as ongoing phase II and III CRC trials. All ongoing trials are summarized in *Table 1*.

Agents that target immune-checkpoint pathways, such as PD-1, PD-L1 and CTLA-4 have shown to have objective and durable responses in different types of tumors like melanoma, non-small cell lung cancer and renal-cell carcinomas. PD-1 is expressed on a large proportion of tumor infiltrating lymphocytes and when bound to its ligands, PD-L1 and PD-L2, leads to lymphocyte anergy. Chronic antigen exposure and various escape mechanisms hijacked by cancer can lead to high levels of PD-L1 expression on host, stromal and tumor cells, as assessed by immunohistochemistry. Compared to peripheral blood, PD-1 is upregulated in CD8+ T cells. In patients with localized CRC, PD-L1 expression was observed in 37% of pMMR and in 29% of dMMR CRCs (48). In other groups, PD-L1 expression was observed in 38% of dMMR but only in 13% of pMMR CRCs (49). In a recently presented phase II study, evaluating pembrolizumab (an anti-PD-1 monoclonal antibody), previously treated patients with dMMR CRC tumors had an overall response rate (ORR) of 62% and a disease control rate (DCR) of 92%. In sharp contrast, pMMR CRC patients had inferior responses (0% ORR and 16% DCR). At one-year median follow-up, the dMMR group maintained high response rates with median PFS and OS not reached, in contrast to the pMMR

Table 1 Ongoing trials

a/a	Category	Intervention	Trial phase	Trial characteristics [number of patients]	Results expected	ID (NCT)	Mechanism of action
1	Monoclonal Abs	1. Sym004	II	metCRC and acquired resistance to anti-EGFR MAbs [254]	Jul 2016	02083653	Targets 2 distinct EGFR epitopes
		2. Bavituximab + Capecitabine + RT	I	Stage II/III rectal adenocarcinoma [18]	Jun 2017	01634685	Targets the predominant immunosuppressive phospholipid exposed on tumor endothelium and repositions macrophages from the M2 to the M1 phenotype promoting dendritic cell cytotoxic T cell activation
		3. Urelumab + Cetuximab	Ib	metCRC [104]	Jan 2017	02110082	Agonistic antibody toward CD137, which is a co-stimulator expressed on activated NK and memory T cells
		4. Ensituximab	I/II	metCRC after 2 standard therapies [116[§]]	Jan 2018	01040000	Directed against the MUC5AC-related antigen, which mediates mucosal immunity (ADCC)
		5. MGD007	I	Refractory metCRC [158]	Mar 2017	02248805	Redirects CD3-expressing T cells to cancer cells bearing the glycoprotein A33 antigen, which is almost uniformly present in CRC
		6. Vanucizumab + FOLFOX	II	metCRC therapy naïve (150)	Dec 2017	02141295	Bispecific IgG1 antibody blocking Ang2 and VEGF-A
2	CP inhibitors	1. Pembrolizumab *vs.* investigator's choice	III	metCRC dMMR or MSI-high [270]	Sep 2019	02563002	Anti-PD-1
		2. Pembrolizumab + Romidepsin + Azacitidine	I	MSS metCRC [30]	Jun 2018	02512172	Anti-PD-1
		3. Nivolumab + Ipilimumab	II	MSI-high metCRC [96]	Jul 2017	02060188	Anti-PD-1 + Anti-CTLA-4
3	Cancer vaccines	1. IMPRIME + Cetuximab *vs.* Cetuximab	III	Recurrent or progressive KRAS wild-type CRC [795]	Dec 2016	01309126	The molecular pattern is recognized by receptors on innate immune effector cells, triggering a cascade of innate and adaptive immune responses
		2. AVX701	I	Stage III CRC [12]	Nov 2017	01890213	Alpha virus replicon (VPR) encodes the CEA
		3. HER2 vaccine	I	metCRC [36]	Jan 2017	01376505	Combination of 2 chimeric HER2 B cell epitopes
		4. OncoVAX + surgery *vs.* surgery	IIIb	Stage II colon cancer [550] (ADJUVANT)	Jul 2022	02448173	Stimulation of immune response to autologous (patient-specified) tumor cells

Table 1 (*continued*)

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a/a	Category	Intervention	Trial phase	Trial characteristics [number of patients]	Results expected	ID (NCT)	Mechanism of action
4	Adoptive cell therapy	1. Autologous TILs + Aldesleukin after cyclophosphamide, fludarabine	II	metCRC [290[§]]	Dec 2019	01174121	TILs are infused iv after cultivation/maturation and attack directly the tumor cells
		2. Anti-CEA-CART	I	CEA-positive cancer [75[§]]	Dec 2019	02349724	T cells modified with CEA targeted chimeric antigen receptor, thus killing the CEA-tumor cells
		3. CART-EGFR	I/II	Chemotherapy refractory, EGFR positive CRC with liver metastases [60[§]]	Dec 2017	01869166	Chimeric EGFR antigen receptor-modified T cells
		4. NK-cells + Bortezomib	I	metCRC [61[§]]	Jan 2018	00720785	Enhancement of NK-cells ability to kill cancer cells after injection of bortezomib
		5. CIK + CAPEOX or FOLFOX	II	Stage II/III colon cancer [210] (ADJUVANT)	Aug 2019	01929499	Peripheral blood mononuclear cells are isolated by apheresis. T cells are activated, expanded and differentiated by anti-CD3 in the presence of cytokines including IFN-γ, IL-1α, and IL-2
5	Dendritic cell therapy	1. NY-ESO-1157-165 pulsed dendritic cells + IL2 + adoptive T cell therapy	II	metCRC [22[§]]	Oct 2018	01697527	The vaccine made using the NY-ESO-1 protein may stimulate the engineered immune response to tumor cells
6	Oncolytic virus therapy	1. Reolysin + FOLFOX + Bevacizumab	II	metCRC [109§]	Mar 2017	01622543	Reovirus replicates in tumor cells that have an activated RAS leading to cell destruction and generated immune response
7	Adjuvant immunotherapy	1. Rintatolimod + IFN + Celecoxib + Surgery	I/II	Recurrent resectable CRC [50] (NEOADJUVANT)	Aug 2017	01545141	Chemokine-modulatory regimen that increases the density of TILs (rintatolimod is a toll-like receptor ligand)

[§], patient enrolment with different malignancies accepted. MAbs, monoclonal antibodies; metCRC, metastatic colorectal cancer; EGFR, epidermal growth factor receptor; RT, radiotherapy; NK, natural killer cells; CP, checkpoint; dMMR, mismatch repair deficient; MSI, microsatellite instability; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HER, human epidermal growth factor receptor; CEA, carcinoembryonalt antigen; TILs, tumor infiltrating lymphocytes; CART, chimeric antigen receptors on T cells; CIK, cytokine induced killer-cells; CAPEOX, capecitabine + oxaliplatin; FOLFOX, leucovorin + fluorouracil + oxaliplatin; IFN, interferon; IL, interleukin.

group (median PFS 2.3 months, median OS 5 months). Interestingly, dMMR tumors were highly mutated with approximately 1700 mutations *vs.* 70 mutations per tumor in pMMR cases (P=0.007). The mutational burden was significantly associated with efficacy (P=0.02) (50). The authors have recently announced the initiation of a phase III trial (named KEYNOTE-177) with pembrolizumab versus investigator-choice chemotherapy in MSI-high or dMMR stage IV CRC (NCT02563002). Another phase II clinical trial of nivolumab (anti PD-1) versus nivolumab combined with ipilimumab (anti-CTLA-4) in recurrent and metastatic MSI-high CRC is ongoing with first results expected at the beginning of 2017 (NCT02060188).

Antigen presenting cells (APCs) may also trigger the adaptive immune response by increasing the priming and the cytotoxic effect of tumor-specific CD8+ lymphocytes. Toll-like receptor agonists are able to activate APCs in this way. Conjugation to cetuximab (a MAb targeting the EGFR in RAS wild-type CRC) increases the innate signalling and the antitumoral effect of cetuximab (51). Similar boost-like immune effects by the so called "adjuvant immunotherapies" are under investigation with phase II clinical trials enrolling recurrent, irresectable CRC patients with a chemokine modulatory regimen combining IFN, celecoxib and rintatolimod (NCT01545141).

Imprime PCG is a vaccine that conjugates the innate with the adaptive immune response. This vaccine works synergistically with anti-tumor MAbs like cetuximab. Results from a phase II clinical trial showed doubling of overall responses that led to a phase III trial (PRIMUS), where first results are expected during 2016 (NCT01309126). While some immune-modulatory drugs trigger a broad pro-inflammatory response, imprime PCG selectively targets and activates neutrophils without inducing systemic pro-inflammatory cytokines that are attributed to adverse reactions (52).

Oncolytic virus therapy uses a modified virus that can cause tumor cells to self-destruct and generate a greater immune response against the cancer. Reolysin is such a virus therapy, which is especially effective in RAS-activated tumors (53). A randomized phase II study of reolysin in combination with FOLFOX plus bevacizumab versus FOLFOX plus bevacizumab alone in patients with metastatic CRC is underway and primary results are expected at the beginning of 2017 (NCT01622543).

Conflicting results have been presented on adjuvant therapy with the monoclonal antibody edrecolomab, which can potentially restore the immune responses of patients with resected CRC. One study showed improved survival (54), while two more randomized trials failed to reproduce any survival benefit (55,56).

Conclusions

Overall results of studies on immunotherapies for CRC patients yielded conflicting, or only preliminary data. In order to clarify the real effect of immune therapies, predictive biomarkers, able to identify CRC patients who might benefit from those patients with resistant tumors, need to be identified and validated. Moreover, insights in the function and regulation of the tumor host immune interaction need to be generated and studied. Encouraging, ongoing network efforts are heading to that direction.

It remains unclear what the immunological profile of the metastatic disease might be and if that might have a correlation to the primary tumor profile (57). The immunological therapeutic implications might have a critical impact only in the adjuvant setting and mainly in those patients with early stage disease, as immune escape mechanisms prevail in the metastatic tumor making it difficult for the immune response to control the malignancy. Nevertheless, recent data suggest that immune-modulating therapies hold promise for patients with advanced disease, with minimal normal tissue toxicity, highlighting the dynamic and powerful potential of the host immune system. Future research efforts will likely focus on devising more elaborate ways to manipulate the host immune response and on combining immunomodulation with chemotherapy and targeted therapies.

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Footnote

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