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Review

Immunotherapy and patients treated for cancer with microsatellite instability

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Summary

Microsatellite instability (MSI) is a tumor phenotype linked to somatic or germline (Lynch syndrome) inactivating alterations of DNA mismatch repair genes. A broad spectrum of neoplasms exhibits MSI phenotype, mainly colorectal cancer, endometrial cancer, and gastric cancer. MSI tumors are characterized by dense immune infiltration and high load of tumor neo-antigens. Growing evidence is accumulating on the efficacy of immune checkpoint inhibition for patients treated for MSI solid tumors. We present a comprehensive overview of MSI phenotype, its biological landscape and current diagnostic methods. Then we focus on MSI as a predictive biomarker of response to immune checkpoint inhibition in the context of colorectal cancer and non-colorectal tumors.

Mots clés
Cancer de l'endomètre
Cancer colorectal
Checkpoint immunitaires
Déficience du système de réparation de l'ADN

Résumé

Immunothérapie et patients traités pour cancer avec instabilité des microsatellites

L'instabilité des microsatellites (MSI) est un phénotype tumoral lié à l'inactivation somatique ou constitutionnelle (syndrome de Lynch) des gènes de réparation des mésappairements de l'ADN. Un

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Nivolumab
Syndrome de Lynch

large spectre de localisations tumorales présente un phénotype MSI, principalement le cancer colorectal, le cancer de l'endomètre et le cancer de l'estomac. Les tumeurs MSI sont caractérisées par un infiltrat inflammatoire important et une charge importante en néo-antigènes tumoraux. Les stratégies thérapeutiques ciblant les points de contrôle immunitaires semblent efficaces chez ces patients. Cette revue de la littérature présente les conséquences physiopathologiques et les méthodes diagnostiques du phénotype tumoral MSI, pour s'intéresser ensuite à l'épidémiologie des tumeurs MSI et aux données actualisées concernant l'immunothérapie chez les patients présentant des tumeurs MSI, cancer colorectal et autres tumeurs solides associées au phénotype MSI.

Introduction

The human tumor phenotype, referred to as microsatellite instability (MSI), is associated with inactivating alterations in mismatch repair (MMR) genes [1–3]. MSI was first observed in inherited tumors associated with Lynch syndrome (LS) and later in sporadic colorectal, gastric and endometrial cancers [4]. The MSI and microsatellite stable (MSS) tumor subtypes are mutually exclusive and represent 15% and 85% of colorectal cancers (CRC), respectively. MSI tumors develop through a distinctive molecular pathway characterized by genetic instability in numerous microsatellite DNA repeat sequences throughout the genome (for review, see [5,6]).

MMR deficiency is not a direct transforming event. Most oncogenic alterations found in MMR-deficient (dMMR) tumors are somatic mutation events that occur as a result of MSI [7–9]. The MSI process is expected to be oncogenic when it affects DNA repeat sequences that have a functional role. Over the past 20 years, studies have reported several loss of function truncating mutations in coding repeats. Mutations in some of these coding repetitive sequences undergo positive selection during tumor development due to the growth advantage they confer to tumor cells. Importantly, the MSI-driven pathway to cancer also leads to the synthesis of aberrant and potentially immunogenic neo-antigens by the tumor cells. A likely consequence is that MSI tumors are highly infiltrated with cytotoxic T cell lymphocytes (CTLs) expressing activation markers, as well as Tc1 and Th1 phenotypes [10]. More generally, elevated expression levels for CTL/Th1/cytotoxicity markers are thought to constitute strong and independent predictors of relapse and overall survival in CRC patients regardless of their molecular phenotype, with a high density of lymphocyte infiltration consistently shown to be a strong indicator for prolonged survival [11].

Two signals are required to initiate an adaptive immune response by T cells: MHC-antigen peptide recognition by the T cell receptor (TCR) and co-stimulation *via* an array of receptors interacting with cognate ligands on antigen-presenting cells (APCs). Signaling *via* inhibitory receptors is necessary to regulate co-stimulatory receptor activity to ensure a measured response. However, during cancer progression, tumor-infiltrating T cells have been shown to display increased, chronic expression of different negative immune checkpoints (CK) like PD-1, LAG-3, and TIM-3, which cause T cells functional exhaustion and unresponsiveness [12]. These exhausted CD8T cells fail to proliferate in response to antigen and lack critical anticancer effector functions such as cytotoxicity and IFN gamma cytokine secretion [13]. Such data gives the rational to develop antibodies that target these regulatory molecules. They are called checkpoint inhibitors (CKI) and could boost anticancer immune response. Importantly, the development of monoclonal antibodies (mAb) targeting CKI is going to revolution cancer therapy. Recent clinical trials demonstrated that mAb targeting PD-1/PD-L1 could induce a major response in many types of cancers [14]. However, the clinical benefit in most tumor types was only observed in about 20% of patients, thus leading to the development of comprehensive studies, which could explain differences between responders and non-responders and help generate predictive biomarkers for response to these therapies. Some reports suggest a better efficacy in tumors expressing PD-L1 and infiltrated by myeloid cells. Although PD-L1 is a predictive marker of efficacy for anti-PD-1/PD-L1 therapies, it is not an ideal marker because of poor sensitivity and specificity. Rivzi et al. made the important observation that, in lung cancer, tumors with high rates of mutation and high rates of neo-antigens share better sensitivity to PD-1 mAb [15].

Recently, it was shown that MSI tumors were likely to persist in their hostile immune microenvironment because of immunoescape and dramatic co-overexpression of CK-related proteins [16]. Based on these findings, in 2015, Le et al. evaluated the clinical activity of an anti-PD-1 CKI (pembrolizumab) in a cohort of metastatic carcinoma patients with or without MSI [17]. The results of this phase 2 study, together with results from another phase 2 study evaluating nivolumab (anti-PD-1 mAb) with or without ipilimumab (anti-CTLA-4 mAb) [18], convincingly showed that MSI status was able to predict clinical benefit from CK blockade therapy. Thus, only tumors displaying MSI are likely to respond to PD-1 blockade, suggesting that MSI neoplasms are probably a useful model to study immune determinants associated with good response to anti-PD-1/PD-L1 mAb, or more generally to CK blockade therapy.