Influence of Gastrointestinal Flora in the Treatment of Cancer with Immune Checkpoint Inhibitors

Význam gastrointestinální flóry v léčbě nádorů pomocí checkpoint inhibitorů

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Gastrointestinal (GI) flora contains an immense number of bacteria (1014), what is considered ten times more than eukaryotic cells in the entire body, and represents a complex, dynamic and diverse collection of approximately 1 000–1 500 different microbial species [1]. The GI bacteria play an essential role in nutrition and food digestion and in the modulation of antitumor immunity [2,3]. Interestingly, some of the GI bacteria, such as *Bifidobacterium spp, Listeria monocytogenes, Clostridium spp, Salmonella ssp, Shigella flexeneri, Vibrio cholerae,* and *Escherichia coli* have shown preferential accumulation in tumors compared to normal organs [4]. The use of probiotics, living bacteria or other microorganisms, has been recognized for their health-promoting effects for more than a century due to their role in preventing and treating various diseases including some types of cancers [5]. The maintenance of epithelial integrity, alleviation of lactose intolerance, enhancement of production of vitamins, stimulation of cell-mediated immunity, IgA production, and detoxification of carcinogens are among the properties of the probiotics; their beneficial effects are often bacterial strain-specific [6,7].

Monoclonal antibodies targeting inhibitory immune checkpoint inhibitors (ICIs) (i.e. anti-PD-L1/PD-1 and anti-CTLA-4) have demonstrated clinical activity in several malignances, including malignant melanoma (MM), renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), bladder cancer, head and neck squamous cell carcinoma, microsatellite instability-high colorectal carcinoma, Merkel cell carcinoma, and Hodgkin lymphoma; these antibodies have changed the practice of medical oncology in the last decade [8–10]. In MM and NSCLC for instance, up to 33% of unselected, previously treated patients and up to 45% of patients with PD-L1-positive tumors in the frontline setting achieve objective responses with the anti-PD-1 therapy [11,12]. However, there is still a significant number of patients who do not respond to such therapy and/or relapse after the response. Therefore, understanding the immune escape is crucial for applying the emerging treatment approaches that could enhance the efficacy of ICIs. There are several factors that may participate in the resistance to ICIs, both of immune origin, such as poor presentation and recognition of tumor antigens, recruitment of regulatory T-cells, unresponsiveness of T-cells, and non-immune origin, such as generation of neoantigens, derangement of the T-cell metabolism, genetic and epigenetic tumor changes, and angiogenesis. Into non-immune origin of resistance, we can also include the GI flora [13].

It has emerged from several recent human and animal studies that GI flora dictates the efficacy of ICIs in cancer immunotherapy. The first observations reported that the use of antibiotics during the course of transplantation was associated with increased frequency of the graft versus host disease (GvHD). The type of used antibiotics seems to have a predictor role in GvHD-related mortality. In animal studies, investigators found that imipenem-cilastin treatment of mice with GvHD reproducibly resulted in shortened survival compared with mice treated with aztreonam [14].

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Studies of patients with hematological malignancies who underwent allogenic bone marrow transplantation suggested that the diversity of the fecal microbiome at baseline plays a role in relapse/progression, indicating the potential use of the GI flora as a biomarker [15].

Two recent papers published in Science further point out the importance of GI flora for the efficacy of PD-1-based immunotherapy. In one of these papers, French investigators found that antibiotic consumption inhibited the clinical benefit of PD-1 blockade in a mouse model and in patients with advanced RCC and NSCLC. The non-responding patients showed low levels of bacterium *Akkermansia muciniphila*. After fecal flora transplantation from cancer patients who responded to ICIs into germ-free (GF) or antibiotic-treated mice, the efficacy of antitumor effects of PD-1 was recovered [16]. In the second paper, American investigators reported that differential composition of the GI flora influences the therapeutic response to anti-PD-1 therapy in preclinical models. In experiments with MM patients on anti-PD-1 therapy, they demonstrated that patients with high abundance of favorable GI flora i.e., *Rumonococcaceae* and *Faecalibacterium* had a higher density of immune cells and markers of antigen processing and presentation compared to those with *Bacteroidales*, suggesting that the GI flora may modulate the antitumor response mediated by antigen presentation and improve the effector T-cell function in the periphery and in the tumor microenvironment [17]. The same French group conducted a retrospective analysis of RCC and NSCLC patients treated in prospective trials with anti-PD1/PD-L1 inhibitors alone or in combination with antibiotics. In RCC patients, antibiotic treatment was associated with a significantly increased rate of primary progressive disease (PD) compared with patients who did not receive the antibiotics (73 vs. 22%). Progression-free survival (PFS) and overall survival (OS) were also significantly shorter in these patients (median PFS, 1.9 months vs. 7.4 months and median OS 17.3 vs. 30.6 months). In NSCLC patients, antibiotic treatment was not associated with an increase in PD, but they had a significantly shorter median PFS (1.9 vs. 3.8 months) and median OS (7.9 vs. 24.6 months) compared to the non-antibiotic-treated patients. Similar results were obtained in patients treated with antibiotics within 60 days of starting therapy, suggesting that the results would be seen with an extended timeline [18]. Another retrospective study reported 80 metastatic RCC patients treated in prospective trials with PD1/PD-L1 inhibitors alone or in combination with antibiotics. The antibiotic-treated patients were defined as patients who received them up to 1 month prior to the first dose of ICIs. In the antibiotic-treated patients, PFS was significantly decreased compared to the patients who did not receive the antibiotics, 2.3 vs. 8.1 months. The OS also showed a negative trend in the antibiotic-treated patients, but the data was too immature to make conclusions [19]. Altogether, these results confirm that antibiotics might be deleterious to patients treated with ICIs.

Other interesting results have shown that the immune defect of CTLA-4 efficacy was overcome by gavage with *Bacteroides fragilis*, by immunization with *B. fragilis* polysaccharides, or by adoptive transfer of *B. fragilis*-specific T-cells. Moreover, fecal microbial transplantation from humans to mice confirmed that anti-CTLA-4 treatment of MM patients favored the outgrowth of *B. fragilis* with anticancer properties. This study revealed the immunostimulatory role of *Bacteroidales* in the CTLA-4 blockade [20]. Another prospective study enrolled 26 MM patients treated with ipilimumab. The GI flora composition was assessed using 16S ribosomal RNA gene sequencing at baseline and before each ipilimumab infusion. The results showed that the baseline GI flora predicted the clinical response in metastatic MM patients treated with ipilimumab, and patients whose baseline microbiota was enriched with *Faecalibacterium* genus and other Firmicutes had longer PFS and OS [21]. In animals previously treated with antibiotics and further recolonized GI flora, the anti-CTLA-4 antibiotic-mediated anticancer responses were restored. This protection was associated with the capacity of *B. fragilis* to promote proliferation of ICOS+ regulatory T cells in the lamina propria, possibly via mobilizing plasmacytoid dendritic cells seen to accumulate and mature in mesenteric lymph nodes after *B. fragilis* monocolonization of GF mice treated with anti-CTLA4 antibody [22]. In agreement with such results and even more intriguing, another study in animals showed an unexpected role for commensal *Bifidobacterium* in enhancing antitumor activity, and its oral administration improved tumor control to the same degree as PD-L1-specific antibody therapy, with combination treatment nearly abolishing tumor outgrowth [23].

Based on these preliminary observations, it may be recapitulated that GI flora has a strong influence on the response to ICIs, although many questions about this relationship remain. Are certain antibiotics potentially more immunosuppressive than others? What is the mechanism whereby the GI flora communicates with the tumor microenvironment? What is the microbe or group of bacteria acting as immunostimulants, and would supplements with probiotics promote the antitumor immunity and the efficacy of ICIs? What is efficacy of ICIs in relation to different antibiotics and other antiviral and anti-fungal agents? Does GI flora have an impact in different tumors and in the use of ICIs as monotherapy or combined treatment? To answer all these questions, more preclinical studies and prospective clinical trials are strongly warranted.

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62 % u dosud neléčených pacientů [2]
- (n=29; 95% CI: 42 – 79)

33 % u předléčených pacientů [3]
- (n=88; 95% CI: 23 – 44)

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