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Potential of memory T cells in bridging preoperative chemoradiation and immunotherapy in rectal cancer

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ABSTRACT

The management of locally advanced rectal cancer has passed a long way of developments, where total mesorectal excision and preoperative radiotherapy are crucial to secure clinical outcome. These and other aspects of multidisciplinary strategies are in-depth summarized in the literature, while our mini-review pursues a different goal. From an ethical and medical standpoint, we witness a delayed implementation of novel therapies given the cost/time consuming process of organizing randomized trials that would bridge an already excellent local control in cT3-4 node-positive disease with long-term survival. This unfortunate separation of clinical research and medical care provides a strong motivation to repurpose known pharmaceuticals that suit for treatment intensification with a focus on distant control. In the framework of on-going phase II-III IG/IMRT-SIB trials, we came across an intriguing translational observation that the ratio of circulating (protumor) myeloid-derived suppressor cells to (antitumor) central memory CD8+ T cells is drastically increased, a possible mechanism of tumor immuno-escape and spread. This finding prompts that restoring the CD45RO memory T-cell pool could be a part of integrated adjuvant interventions. Therefore, the immunocorrective potentials of modified IL-2 and the anti-diabetic drug metformin are thoroughly discussed in the context of tumor immunobiology, mTOR pathways and revised Warburg effect.

Current standard treatment for locally advanced rectal cancer is radiotherapy with 5-fluorouracil (5-FU) or oral capecitabine, followed by total mesorectal excision (TME). This regimen improves the local control with a local recurrence rate about 5% [1], but without significantly improving the long-term survival rate. The distal recurrence rate remains around 30% [2], representing the main cause of death in rectal cancer [3]. For this reason, oxaliplatin and targeted therapies, such as bevacizumab and cetuximab were evaluated in the neoadjuvant setting but with conflicting results (partially covered by our Section 2) [4–11]. To achieve risk-adapted and less toxic treatments, the approaches of omission radical surgery or radiotherapy, or intensity-modulated radiotherapy without chemotherapy are under investigation in selected subgroups of patients [12–15]. The success of immune checkpoint blockades in the treatment of advanced melanoma and lung cancer patients revolutionized oncology [16,17]. Recently, in colorectal cancer (CRC), the anti-PD-1 drug pembrolizumab was approved to treat metastatic/refractory microsatellite instability-high (MSI-H) patients [18]. Of note, MSI-H exists in about 15% of CRC [19], indicating that besides immune checkpoint blockades, other immune boosting approaches should be explored. Immunological memory is a fundamental feature of adaptive immunity. A higher density of memory T cells in CRC is a favorable prognostic factor for overall survival [20]; in contrast to the 'protumor' inflammatory markers at systemic level, such as neutrophil-to-lymphocyte ratio (NLR) and myeloid-derived suppressor cells (MDSC) (in-depth overviewed in our Section 3) [21,22]. With the increased understanding of the mechanisms that govern the formation of memory T cells, their ability to acquire longevity, and self-renewal, it becomes conceivable to adopt memory T cells to provide enduring anti-tumor effects.

Metformin, an anti-diabetic biguanidine, is probably the most exciting pharmaceutical in the pipeline of drug repurposing with over 100 clinical trials in oncology. While its antitumor properties are detailed elsewhere [23], we acknowledge here the intriguing fact that metformin as a mammalian target of rapamycin (mTOR) inhibitor might restate the pool of pluripotent CD45RO memory

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T cells. Of note, these immunocorrective effects are beyond the already identified immune checkpoints (as PD-1/PDL-1) that preferentially operate in more differentiated effector T cells within the tumor site [16,17]. Accumulating evidence suggests that effector T cells resemble tumor cells characterized by the Warburg metabolism and regulated by mTOR pathways to sustain proliferation [24,25]. In contrast, memory T cells rely more on fatty acid oxidation regulated via AMP-activated protein kinase (AMPK) signaling pathways [24,26]. mTOR inhibitors or AMPK activators including metformin therefore have a potential to initiate the effector to memory T cell transition [26,27]. Besides a metabolic switch, memory T cells require a second trigger to maintain their longevity/expansion, which is largely controlled through the CD122 chain (Rβ) of the IL-2 receptor [28]. Opposed to that, CD25 chain (Rα) signaling is responsible for the outgrowth of Tregs, a physiological mechanism to inhibit and shutdown T-cell stimulation [29]. Therefore, section 4 describes the state-of-the-art tools of molecular immunology, which offer an elegant solution to restrain (protumor) CD4 regulatory T cells (Tregs) in favor of (antitumor) memory CD8 T cells by using a CD122-biased IL-2. Our understanding is that an efficient re-instatement of T-cell memory at systemic level (blood and lymph nodes) could be obtained by the two key triggers: (1) graded mTOR inhibition by metformin and (2) optimal cytokine stimulation by a CD122-biased IL-2.

We believe that our review will encourage both researchers and doctors to (re)consider metformin for immunological evaluations with the following take-home messages: (1) mTOR inhibitors appear to favor T-cell memory and offer immunocorrection at systemic level, in contrast to PD-1/PD-L1 checkpoint inhibitors that operate in the tumor; (2) metformin, an anti-diabetic drug and mTOR inhibitor, is already repurposed for targeting tumor metabolism in ongoing clinical trials, yet needs a next round of repurposing for long-term immunocorrective interventions and (3) CD122-biased IL-2, preferentially expanding the memory T cells, may be incorporated with metformin to sustain the adaptive immune response.

Preoperative chemoradiotherapy in rectal cancer

The management of CRC, and particularly locally advanced rectal cancer, has historically established new standards of clinical research and medical care that illustrated the importance of (i) a multidisciplinary approach in treatment modalities, (ii) collaborative efforts in organizing international large-scale randomized trials, and (iii) a strong dedication of teams across the world to examine alternative interventions based on technical and pharmacological developments. Despite standing just at its beginning, the 21st century has already introduced into practice two major paradigms – the TME and preoperative chemoradiation, which together secure the loco-regional control in rectal cancer above 90%. While the procedure of TME is globally accepted as the only golden standard of radical surgery [30], the role of chemoradiation continues to broaden and evolve leaving enough room for pre- versus post-operative regimes, and radiation or chemotherapy alone versus their concomitant application [12–15]. As a result of successful German, Dutch, French, Polish and other trials, the European schools put forward preoperative 5-FU/capecitabine-based chemoradiation, which markedly decreases local tumor recurrence and seems to minimize the risk of patient under-treatment and hence the necessity to rely on further aggressive (and more toxic) adjuvant options [31–36].

Another paradigm shift may be referred to our growing understanding that the clinical stage of locally advanced cT3-4 node-positive rectal cancer represents, in fact, heterogeneous diseases with variable clinical outcomes [12,15,37]. Therefore, the optimization of personalized treatment plans may benefit from a patient-tailored separation of chemo- and radiotherapy, a recent and unexpected turn in the view of modern combined strategies that have guided treatment intensification for decades. As an example, the team of Schrag D et al. opted in their PROSPECT trials for intensified chemotherapy FOLFOX and selective radiation for non-responders only [38–40], while Valentini V et al. have chosen more radiation up to 54 Gy using high-precision IMRT-SIB, intensity-modulated radiotherapy with simultaneous integrated boost [41–43]. Those diverged programs, however, pursue the same twofold goal – to lower delayed toxicity/morbidity despite an increased tumor cytoreduction and to improve distant control in high-risk patients by restraining metastatic spread, the main cause of cancer-related deaths [14]. On the other hand, low-risk patients staged T3N0M0 with an upper rectal location might favor from an omitted over-treatment, linked to neoadjuvant chemoradiation [44,45], once the diagnostics of involved CRM (circumferential resection margin) and lymph nodes by MRI is improved [13,45]. CRM remains to be a critical objective parameter for treatment planning, and its narrow margin (less than 1–2 mm) next to a low tumor location and extended vascular, lymphatic and perineural invasion indicates an increased risk of local recurrence and compromised prognosis [46,47]. Yet, even a low-risk tumor may be understaged due to the limitations of CT/MRI scanning to address the micro-disease, a not infrequent situation discovered by postsurgical pathology that requires adjuvant interventions. This fine-tuning of disease-oriented chemoradiation, however, proceeds by slow and incremental steps since a differential analysis of risk groups (low versus intermediate versus high) would require a big cohort of randomized patients given the already excellent level of local control in the TME era. Therefore, overall survival rates as the primary end-point are hardly feasible, and many on-going phase II trials contain inherent shortcomings by re-focusing on non-inferiority, pCR by Dworak and short-term disease-free survival, including our own studies [48,49].

To improve distant control and overall survival rate, a number of intensified strategies based on oxaliplatin, targeted and biological agents have been recently explored. According to the results from the ACCORD 12, STAR-01, PETACC-6 and NSAPB R-04 randomized trials, the addition of oxaliplatin increased toxicity, but failed to improve the early and long-term endpoints, such as the pCR, disease-free survival and overall survival [4–7]. Conversely, in the phase III CAO/ARO/AIO-04 trial the addition of oxaliplatin was well tolerated, associated with increased pCR rate and disease-free survival [8,9]. In addition, preliminary results from the large multicenter FORWARC study demonstrated that the pCR rate was significantly higher in the arm combining mFOLFOX6 with radiotherapy compared to the arm of 5-FU with radiotherapy [8,9]. Among biological agents representing monoclonal antibodies, the EGFR blocker cetuximab showed disappointing low rates of pCR [10]. The VEGF blocker bevacizumab demonstrated a trend toward improved clinical outcomes but at the cost of increased surgical complications [11]. Altogether, significant advancements in the management of locally advanced rectal cancer have occurred over the last decades, resulting in improved local control rates. However, the risk of distant metastases remains an ongoing problem and the major obstacle to improve the survival rate, requiring novel strategies [50].

Immunobiology of colorectal cancer

Immunoprofiling of colorectal cancer at local and systemic levels

Over the last decade, inflammatory and immune biomarkers underwent extensive investigation in many tumor types, and CRC

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