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The perioperative immune/inflammatory insult in cancer surgery

Time for intervention?

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Within the tumor microenvironment, non-specific innate immune responses can suppress adaptive cytotoxic immunity and hence promote tumor progression. Surgery and trauma provokes high-grade, non-specific inflammatory responses that suppress cell-mediated immunity. Here, the surgical resection of neoplastic lesions is considered in the context of antitumor immunity, providing the rationale for development of perioperative interventions to maintain the immunological competence of the host.

The prognostic significance of immune or inflammatory responses developing within and around colorectal cancer is now well established. The prognostic value of lymphocytic infiltrates was actually first reported over 80 y ago (reviewed in ref. 1). Up to the mid-1980s, several studies reported that peritumoral lymphocytic or inflammatory responses were indicative of improved disease outcome among cancer patients.[1] Scoring methods for the assessment of peritumoral lymphocytic infiltrates were developed and validated in various centers, but largely failed to enter routine clinical practice due to issues of subjectivity and inter-observer variability (reviewed in ref. 1). Other scoring methods of immune/inflammatory infiltrates have been described, but it is only within the past 10 years that methods including the simplified Klintrup–Makinen score—a 4 point grade of inflammatory cell reaction at the tumor invasive margin have been repeatedly validated.[2] Recently, immunohistochemistry has enabled researchers to examine the cellular make up of intratumoral immune responses, and with such work it is apparent that lymphocyte-dominated tumor infiltrates are powerful indicators of improved disease outcome. In particular, an intact cytotoxic $CD8^+$ T-cell response is critical, and when present predicts a marked reduction in the risk of disease recurrence following curative surgical resection.[1]

Immunohistochemical studies suggest high-grade peritumoral infiltrates are composed of coordinated adaptive and innate immune responses[3]. When such responses are absent (i.e low grade inflammatory responses), only innate or myeloid derived cell types remain.[3] This may be consistent with observations by others indicating that uncoordinated and non-specific innate immune responses can suppress T-cell activity and override the immune competence of the host.[4] As a result, strategies to limit innate, non-specific immune responses should be sought. In summary, the maintenance of an intact, coordinated cell-mediated immunity within the tumor microenvironment is associated with improved disease outcome. Conversely, once this coordination is lost, non-specific myeloid inflammatory responses predominate and may compromise antitumor immunity.

Several immunomodulatory treatments have recently been implemented with success into clinical practice for the treatment of prostate cancer and melanoma.[5] In general, these therapies—including Sipuleucel-T and ipilimumab—aim at restoring adaptive antitumor immunity within neoplastic lesions, a strategy that effectively delays disease progression (based on results from several well powered Phase 3 clinical trials).[5] It can be anticipated that similar strategies may prove effective in the treatment of multiple tumor types, especially those in which immune responses have been ascribed a significant prognostic value (e.g., colorectal cancer).

Modern antineoplastic therapies generally consist of a multimodal approach, but surgical resection remains central to achieving a cure in patients affected by gastrointestinal cancer. Therefore, it is of interest to consider the process of surgery and its potential complications in the context of tumor immunity (**Fig. 1**). Surgery and traumas of any kind are associated with generation of a systemic inflammatory response and upregulation of innate immune responses resulting in suppression of cell-mediated immunity.[6] It is increasingly appreciated that the "immunological hit" caused by surgery

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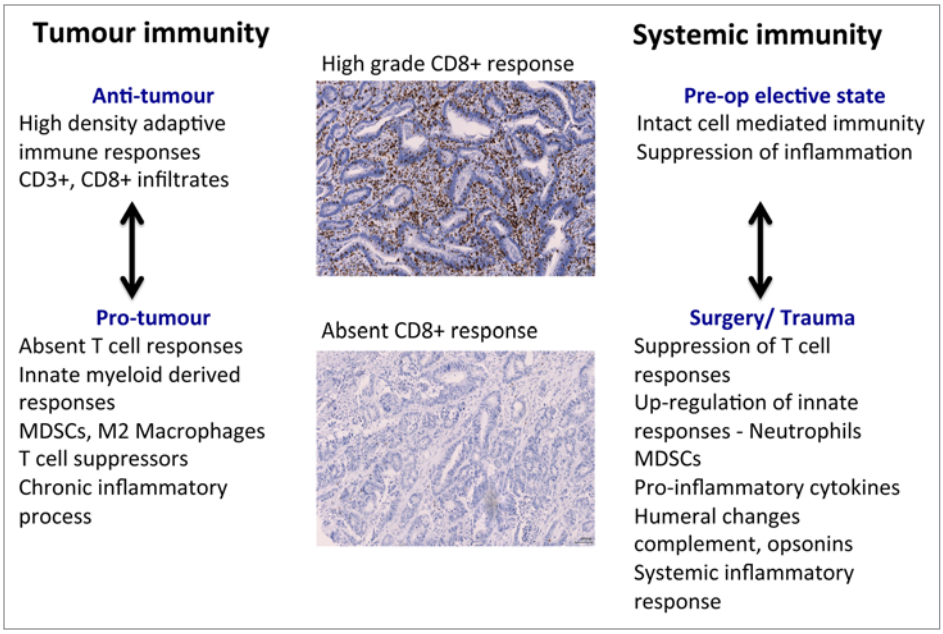

Figure 1. Balancing pro and anti-tumor responses in the tumor microenvironment and systemic circulation during the perioperative period. MDSC, myeloid-derived suppressor cell.

may compromise the antitumor immune defenses of the host. Furthermore, this "hit" can be compounded by various pre-operative factors. Indeed, patients may present as an emergency case with hemorrhage, obstruction or perforation, all of which are associated with a high-grade systemic inflammatory response.

The presence of emergency presentation or a pre-op systemic inflammatory response confers a higher risk of recurrence independent of stage.[7] Furthermore, development of post-operative complications are important prognostic factors. For example, anastomotic dehiscence is associated with a 2-3 fold increased risk of recurrence after surgery,[8] and the development of any post-operative septic complication (irrespective of whether it involves the surgical site, the respiratory system or the urinary tract) further augments the recurrence risk.[9] These conditions potentiate the post-surgical systemic inflammatory response, resulting in the up-regulation of innate immune responses and the suppression of adaptive immunity. Therefore, surgery for cancer in the presence of emergency presentation and infective complications could be considered an 'immunological double hit' resulting in a compromised immune response to residual disease and prolonged recovery additive to the damage already caused. This is consistent with the negative prognostic value attributed to the presence of a systemic inflammatory response in patients affected by most tumor types at any stage of the disease.[7]

As oncologists begin to employ immunomodulatory therapies in patients with non-resectable advanced-stage tumors, little attention has been focused on early-stage resectable neoplasms. It is clear that a range of tumor-extrinsic factors tumor influence disease outcome in the perioperative period (e.g., age, presence of comorbidities, presentation, post-operative complications, transfusions). All these factors can actually be related to the presence of a systemic inflammatory response and the impairment of effective cell-mediated immunity. Therefore, the perioperative period represents an opportunity for clinicians to intervene early, acting to suppress high-grade non-specific systemic inflammation and maintaining effective the immunological competence of the host. Such strategies may support the effective clearance of circulating cancer cells or occult micro-metastases. This period of time lasts for approximately a week and therefore interventions are likely to be inexpensive, yet potential benefits for patients may be large. Simple strategies to be implemented in this setting include the administration of anti-inflammatory agents (non-steroidal anti-inflammatory drugs, corticosteroids), and an aggressive prophylaxis for patients at risk of perioperative complications (emergency presentations, patients with significant comorbidities). Accumulating evidence indicates indeed that such simple immunomodulatory therapies can safely be employed in the perioperative period.[10]

It is increasingly clear that the interaction between tumors and their host is a complex process, key to determining disease recurrence and patient survival. The success of multimodal anticancer regimens is likely to increase if these target both neoplastic lesions and the immune/inflammatory responses of the host to surgery in the perioperative period.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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