In a Murine Pancreatic Adenocarcinoma Model, Visceral Surgery Significantly Alters the Cellular and Humoral Components of the Anti-Tumor Immune Response

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Abstract

Especially in the early stages of pancreatic tumors, surgery is the most crucial component of multimodal treatment ideas for oncological patients. While the impact of primary tumor excision on immune function has been examined in a number of studies, the effects of visceral surgery unrelated to a primary tumor on the organism that is carrying the tumor and on the primary tumor itself are still not entirely known. We coupled a mouse model of medically induced immune failure with an orthotopically implanted pancreatic cancer (SID). Over the course of 28 days, mortality and overall health, including body weight, were observed. MRI scans were used to monitor tumor growth on days 8 and days 27 after tumor implantation. The numbers of immune cells in the blood and spleen as well as the serum cytokines were measured on day 28. Compared to the control groups, SID causes a substantial worsening of the overall condition and a decreased increase in body weight in tumor-bearing mice. Mortality and tumor growth rate were unaffected. Following SID, tumor-bearing animals had more neutrophils and macrophages in their spleens. Additionally, peripheral blood levels of neutrophils and macrophages both increased. The data could help establish a fundamental knowledge of how the immune system and tumors interact as well as lead to fresh ideas for immunotherapeutic treatments.

Keywords: Pancreatic ductal adenocarcinoma • Surgically-induced immune dysfunction • Murine pancreatic carcinoma model • Anti-tumor immune response • Immunotherapy

Introduction

For up to a few weeks after surgery, immunosuppression is a side effect of the treatment. Both the innate immune system and the acquired immune system are impacted by immunological dysfunction. The innate immune system functions as the body's initial line of defence against foreign pathogens, aids in wound healing, and controls tumorigenesis and the antitumor immune response. It works closely with the adaptive immune response and stimulates it. The actions of cytotoxic T-cells, which are subjected to different inhibitory signals (regulatory T-cells, IDO expression, and expression of inhibitory surface molecules) inside the tumor microenvironment, are associated to specific anti-infectious and anti-tumor immune reactions. The stimulation of the hypothalamic-pituitary-adrenal axis results in postoperative immunosuppression, which is mediated by the actions of corticosteroids and catecholamines on the cells of the innate and adaptive immune systems. The clinical effects of this Surgery-Induced Immunosuppression (SII) include an increased risk of postoperative local and systemic infections, difficulties with wound healing, and a worsening of the oncological prognosis in cases when the surgery was performed on a patient with a tumor. In multimodal therapy plans for cancer patients, surgery is a crucial component. However, it has also been demonstrated that the surgical process and the accompanying stressors raise the risk for the emergence of cancer metastasis and local recurrence. This behavior has been connected to a number of mechanisms. Among them, SII causes the reduction of cellular immunity, which has the effect of allowing latent or clinically inactive tumor cells to bypass the immune system. However, by reducing the levels of tumor-related anti-angiogenic substances, the excision of the main tumor itself also appears to have an impact on the emergence of local and distant recurrence.

The majority of in vivo and in vitro investigations have examined the impact of SII on cancer metastasis and recurrence in the context of original tumor excision. In this type of animal, it is challenging to distinguish between the effects of perioperative immunosuppression and the effects of the removal of the underlying tumor because primary tumors have been found to suppress the formation of metastasis. Furthermore, it has been demonstrated that the immunological microenvironment of a metastatic tumor differs significantly from that of a primary tumor. In the current study, a mouse model combining an orthotropic pancreatic cancer model and the model of surgery-induced immunosuppression was used to analyze the impact of non-tumor related surgery on the growth and prognosis of pancreatic carcinoma (SID). In order to better understand the relative significance of both occurrences, the individual and combined effects of the presence of the original tumor and the surgical trauma on the immune system were comprehensively characterized in this mixed model.

Discussion

The potential of Pancreatic Ductal Adenocarcinomas (PDAC) to significantly alter and block both the local and systemic immune response is one of their distinguishing features. Therefore, surgeries intended to remove the underlying tumor have an impact on immune state not just through mechanisms related to the SII but also through the subsequent absence of immunomodulating signals provided by the primary tumor. In order to evaluate the effect of SII on both the growth of the main tumour itself and survival, we used a mouse model combining an orthotopically implanted PDAC with SID. The findings in this research unmistakably demonstrate that SII brought on by visceral surgery unrelated to the original tumor does not result in an acceleration of tumor growth or a decrease in overall survival. However, tumor-bearing animals tended to gain less weight and SII significantly worsened their overall condition.

SII had no effect on overall survival in the current trial. In this study, SID dramatically decreased the longevity of tumor-bearing animals compared to the unoperated control mice, despite similar tumor growth in both experimental groups. In contrast to the current study, the survival analysis' follow-up period was much longer at 60 days following PDAC implantation. Given that the main proportion of mortality in the groups examined in that study was observed between 20 days and 60 days, and the present study was designed to evaluate mortality for a period of only 28 days, the difference in the length of the observation period may be the cause of the discrepancies between the findings of the two studies.

Our findings suggest that SID worsens the overall health of tumor-bearing mice. This is corroborated by the propensity for less weight gain in the first 28 days after tumor implantation and a much higher stress score. It is well known that surgical stress causes a multifactorial physiological response that includes the production of glucocorticoids and the neurotransmitters adrenaline and norepinephrine. It is well recognized that the metabolic changes that ensue, especially those that affect protein catabolism, have a direct impact on how mice gain weight. This is consistent with our observat-

-ion that the group of mice with tumors undergoing SID tend to gain less weight even if the tumor-bearing mice's bodies are already catabolic.

In line with earlier research, we found no evidence that SID had an impact on the tumor's growth when it was measured by an MRI scan on days 8 and days 27 after the tumor was implanted. The growth of the tumor is only one component of the disease's progression; the most complicated aspect is the interaction between the immune system and the growth of the tumor. SII does not affect the growth of tumors in the first line, although it may cause changes at the cell level and in the Tumor Microenvironment (TME). Further research is taken into account to support this claim.

The tumor produced by the 6606PDA cell line is thought to be useful in characterizing a number of aspects of cancer immunology because it has been demonstrated that inflammatory cells surround the carcinoma but do not permeate it. Additionally, it is recognized that the tumor derived from this cell line represents a growth of a moderately differentiated glandular tumor. As a result, we draw the conclusion that the model we have described here may be beneficial for analyzing the effects of non-tumor surgery on "cold" tumors with glandular development patterns and, consequently, in a common form of PDAC.

PDAC has an immunosuppressive immunological milieu, and up to this point, immunotherapeutic treatments for this tumor form have largely yielded disappointing outcomes. This is primarily owing to the pancreas tumor's many immune escape mechanisms (i.e., the release of immune-suppressive chemokines or cytokines by the tumor and the establishment of a barrier of fibroblasts and collagen). Numerous clinical investigations with various immunological treatment plans for PDAC are now being conducted. The mouse model we've provided could be useful for researching how different immune treatment modalities are affected by non-tumor-related surgery.

It is crucial to have a thorough understanding of how visceral surgery, one of the multimodal treatments for PDAC, affects the immune system of animals that have tumors. According to our concept, SII is characterized by immune system alterations that primarily inhibit the anti-tumor immune response.

In mouse models of PDAC, it has been demonstrated that elevated levels of cytotoxic CD8+ T cells and T-helper 1 T cells promote the anti-tumor response. In human PDAC patients, higher concentrations of these cell types are associated with increased survival. Both CD8+ and CD4+ T-cell populations had decreased in tumor-bearing rats in our model following SID, demonstrating that a diminished anti-tumor immune response caused by trauma from surgery is unrelated to the underlying tumor. To address the local implications of this result, more characterization of the tumor infiltrating T-cell populations in this model is required.

The TME's fundamental elements, Tumor-Associated Macrophages (TAM) and Tumor-Associated Neutrophils (TAN), have a significant influence on the biological behavior of PDAC. A worse prognosis for PDAC patients is correlated with more M2 polarized TAM. Similar to this, lower survival in PDAC is correlated with greater TAN levels in the TME. Interestingly, it has been demonstrated that the spleen, not just the bone marrow, is a crucial source of TAM and TAN, both of which are continuously replenished by the spleen throughout tumor growth. It is noteworthy that in the combination paradigm used in this investigation, the tumor-bearing animals' spleen macrophage and neutrophil counts rose following intercurrent SID. The peripheral blood also contained more macrophages and neutrophils. These results indicate that surgical stress increases the splenic reservoir of neutrophils and macrophages that can infiltrate the developing main tumor. To support this notion, more histological examinations of the original tumor and the spleen are needed. It has been demonstrated that TGF- causes TAN to exhibit pro-tumor phenotype. Both IL-4 and IL-13 have been found to directly promote the proliferation of KRAS-mutant tumor cells while suppressing the anti-tumor immune response. It has been demonstrated that SID therapy raised the levels of both cytokines in the spleen of tumor-bearing animals. Given that there was no difference in tumor growth between the experimental groups in the trial described here, it is still unclear how clinically significant the observation is. This question should be addressed in an experimental context with a longer follow-up because the follow-up in our experimental environment was rather brief. Following SID treatment, IL-10, which is known to have tumor-promoting effects, was also elevated in the serum of mice with tumors.

Together, these data imply the existence of an internal environment that favors the inhibition of an anti-tumor immune response in tumor-bearing mice following SID.

In this study, we demonstrate how surgical techniques affect mice with pancreatic tumors immune systems on a systemic level. To fully understand the whole picture of an immunomodulating effect of non-tumor related abdominal surgery in tumor-bearing mice, additional research based on the findings in the present publication is necessary. To determine the local effects of the noticed systemic immune system changes, a histological examination of the original tumor is first necessary. Both the tumor cells and the TME can have local immunosuppressive effects in pancreatic cancer through a variety of different methods. To put the systemic changes found in our work into context, a thorough examination of the immune cell infiltration in the main tumor and of its TME is required. Additionally, the immune cell types affected by the modifications revealed in this work require a thorough phenotyping. In order to ascertain if the observed clinical and immunological effects of SID in tumor-bearing animals will eventually result in variations in tumor growth and survival, our model should be evaluated in an experimental environment with a long observation period following SID.

PDCA can be split into different subtypes according to the immune cell composition of the microenvironment, and each subtype is linked to distinctive clinicopathological traits and the existence of mutational alterations in the tumor cells. The tumor microenvironment appears to be influenced by the mutational status of the malignant cells that make up the PDCA and serves as the foundation for additional molecular PDCA classifications. It would be interesting to determine whether the changes in the systemic immune status described here may have an impact on the development of a particular PDCA phenotype over a longer follow-up period, even though the mutational status of the orthotopically transplanted tumor cells in our experimental model was similar in the different experimental animals.

Conclusion

In conclusion, the findings provided here showed that surgery-related trauma had a significant negative impact on the animal's immune system. Numerous altered immune parameters have been identified as being crucial to the host's immunological anti-tumor response. When developing new immunotherapeutic techniques for PDAC, it is important to consider how surgery alters the immune state because anti-tumor immunotherapy is a potential therapie option in many solid tumors but has largely failed in PDAC so far.

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