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Prevention of Postoperative Infection and Micrometastasis by Preoperative Administration of a PPARγ Agonist following Colorectal Cancer Surgery

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I. Postoperative Host Responses and Infections

Several clinical studies have suggested that systemic inflammatory response syndrome (SIRS) following major surgical trauma is a main cause of postoperative infections and multiple organ failure. The underlying mechanisms of this increased susceptibility to infection due to postoperative immune suppression have been recognized as follows; release of endogenous immune suppressant, interleukin-6 (IL-6), prostaglandin E_2, and IL-10; Th1/Th2 balance shifts toward Th2 dominance, and the deactivation of monocytes. We have demonstrated that the Th1/Th2 ratio in patients with postoperative infection was significantly lower than that in patients without infection following colorectal cancer surgery[1]. Furthermore, preoperative immunonutrition by oral supplementation with a formula enriched with arginine, omega-3 fatty acids and ribonucleic acid improves the normalization of Th1/Th2 ratio and decreases the morbidity rate following colorectal cancer surgery[2].

Obesity, the most common nutritional disorder might be associated with postoperative infection morbidity rates. However, the molecular basis of the correlation between obesity and postoperative infection has not been fully clarified.

II. Adipokines and Surgical Stress

Dysfunction of adipose tissues is a risk factor for the development of various metabolic disorders, including hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome. Adipose tissues synthesize and secrete several proteins that play important roles in inflammatory processes. These proteins act as authentic hormones and are collectively called adipokines. They include tumor necrosis factor-α (TNF-α), adiponectin, leptin, Interleukin (IL)-6, angiotensinogen, and plasminogen activator inhibitor 1. Adiponectin is produced exclusively by adipose tissues and has anti-inflammatory properties that suppress TNF-α and IL-6 production from macrophages. This 30-kDa plasma protein has also been associated with visceral adiposity, insulin resistance, and various cancers, including those of the breast, endometrium, colon, stomach, and prostate. Leptin, which is a 16-kDa soluble polypeptide, was initially described as an adipocyte-derived hormone. Adipose tissue is a major source of leptin. whose circulating concentrations indirectly reflect body fat stores. Circulating leptin acts as acute-phase reactant that regulates proinflammatory immune responses. Furthermore, experimental studies have indicated that leptin deficiency increases susceptibility to bacterial infection.

Because adipokines responsible for inflammatory processes and immune responses, we have demonstrated

Table 1 Plasma adiponectin levels (μg/mL)

	before operation	POD 1	POD 7
uninfected group (n = 29)	7.81 ± 0.75†	6.01 ± 0.68†	7.46 ± 0.48†
infected group (n = 12)	3.82 ± 0.39	2.51 ± 0.29*	3.61 ± 0.43

The data are expressed as means ± SE. *$P < 0.05$ *vs.* the preoperative values in the same group; †$P < 0.05$ *vs.* patients with infections at the same time point. POD: postoperative day.

Table 2 Plasma leptin levels (ng/mL)

	before operation	POD 1	POD 7
uninfected group (n = 29)	4.32 ± 0.79†	7.74 ± 1.16*	2.57 ± 0.45
infected group (n = 12)	2.44 ± 0.45	5.88 ± 1.52*	2.24 ± 0.39

The data are expressed as means ± SE. *$P < 0.05$ *vs.* the preoperative values in the same group; †$P < 0.05$ *vs.* patients with infections at the same time point. POD: postoperative day.

that adipocyte dysfunction in surgical patients may affect their ability to resist nosocomial infections following surgery. We measured plasma adiponectin and leptin levels by enzyme-linked immunosorbant assay in 41 patients with colorectal cancer before surgery and on postoperative days 1 and 7[3]. The patients were divided into those with postoperative infections and those without infections. In both groups, the postoperative plasma adiponectin levels decreased transiently and then gradually recovered. However, the patients with infection had significantly lower adiponectin levels throughout the perioperative period than did the patients without infections (**Table 1**). Plasma leptin levels increased significantly on postoperative day 1 and then gradually decreased in both groups. Preoperative levels of leptin in patients with infection were significantly lower than those in patients without infections (**Table 2**). Logistic regression analysis revealed that a low preoperative adiponectin level was an independent risk factor for postoperative infection. These data suggest that a disorder of adipokine production from adipocytes is associated with the development of postoperative infections. A possible mechanism is that decreased adiponectin production promotes postoperative hyperinflammatory responses and enhances bacterial susceptibility by reducing the anti-inflammatory properties of adiponectin.

III. The Beneficial Effect of a Peroxisome Proliferators-Activated Receptor γ Agonist

Peroxisome proliferators-activated receptor (PPAR) γ is a member of the nuclear hormone receptor superfamily and is highly expressed in adipocytes. PPARγ is an important regulator of adipocyte differentiation and fatty acid metabolism. PPARγ activation by agonists is thought to be associated with anti-inflammatory effects and improves outcomes in rodent models of sepsis and hepatic ischemia/reperfusion injury. Furthermore, PPARγ agonists potentiate the antitumor effect of anticancer drugs by suppressing proliferation, angiogenesis, and downregulating NF-κβ and NF-κβ-regulated gene products in cancer cells. Pioglitazone, a PPARγ agonist, is a new class of antidiabetic drugs that improve insulin action without causing significant alternations in serum glucose levels of non-diabetic animals or humans. Pioglitazone enhances the expression and secretion of adiponectin in vitro and in vivo through the activation of its promoter. On the basis of the previous findings of us and others, we hypothesized that preoperative administration of pioglitazone would be able to prevent postoperative hyperinflammation and continuing immunosupperesion following major surgery. In this randomized clinical trial, we investigated that the effects of preoperative administration of pioglitazone (30 mg/

day for 7 days) on postoperative infection and micrometastasis following colorectal cancer surgery. Positive results of this study would suggest that PPARγ agonists are promising agents for the perioperative management of patients undergoing major surgery.

References

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