**Background**

Intraabdominal adhesions are the most frequent post-operative complication of abdominopelvic surgery and are associated with significant morbidity, including infertility and potentially fatal small bowel obstructions. In the USA alone, the economic burden of adhesion related disorders exceeds $5 billion annually.

**Objective**

To characterize the temporal expression of substance P in the peritoneum after surgery and to examine its effect on tPA and PAI-1 early in adhesion formation.

**Methods**

**Surgery to induce adhesion formation**

1. Abdominopelvic surgery
2. Tissue injury, peritoneal trauma and localized hypoxia/ischemia
3. Fibrinous exudate and decreased fibrinolysis
4. Adhesion formation

- Adhesion formation is initiated by surgery-induced peritoneal trauma (Fig 1). The inflammatory response and the subsequent production of a fibrinous exudate leads to fibrin deposition within the peritoneum. With the normal healing process, peritoneal fibrin is rapidly degraded by the fibrinolytic system.
- However, our laboratory has shown that peritoneal fibrinolysis, which is regulated by the ratio of tissue plasminogen activator (tPA) to its principal inhibitor, plasminogen activator inhibitor-1 (PAI-1) is compromised after surgery via an increase in PAI-1 expression relative to tPA (Reed 2004) [Fig 2].
- This laboratory has also shown that inhibition of peritoneal substance P (SP) signaling with an antagonist to its cognate NK-1 receptor (NK-1RA) reduces adhesion formation by 50%, but only if administered within the first 6 hours (Cohen, 2007).
- Intraoperative administration of an NK-1RA has been shown to increase the expression of tPA relative to its inhibitor 24 hr after surgery [Fig 2], leading to greater fibrinolytic capability and diminished adhesion formation. However, little is known of how tPA, PAI-1, and peritoneal fibrinolytic activity are regulated in the critical 6 hr window within which the NK-1RA is effective.

**Fig 1: Formation of intraabdominal adhesions**

**Fig 2: Peritoneal fibrinolysis after surgery**

**Results**

**Peritoneal fluid substance P levels increase by 1 hour after surgery**

An intraoperative dose of an NK-1RA: A) increases tPA mRNA in peritoneal tissue at 6 hr post-op; B) decreases PAI-1 mRNA in peritoneal tissue at 6 hr post-op; C) increases the tPA/PAI-1 ratio by 1 hr post-op; and D) increases peritoneal fibrinolytic activity at 3, 12 and 24 hr post-op, all compared with operated controls.

**Conclusions**

Peritoneal substance P levels become elevated within the first hour after surgery, and trigger alterations in the peritoneal fibrinolytic capacity that persist for hours. Inhibition of substance P reveals two phases of fibrinolytic inhibition, a previously unknown one that peaks at 3 hours, and a delayed one that starts at 24 hours. These results indicate that substance P serves as an important early regulator and may be a key therapeutic target.

**References**