

**EXPERIMENTAL MODELS OF THE HUMAN PERITONEAL ENVIRONMENT:
EFFECTS OF TGF- β AND HYALURONAN**

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av

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Avhandlingen baseras på följande delarbeten:

- I. Overproduction of transforming growth factor- β 1 (TGF- β 1) is associated with adhesion formation and peritoneal fibrinolytic impairment.
Holmdahl L, Kotseos K, Bergström M, Falk P, Ivarsson M-L, Chegini N.
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- II. Differential regulation of mesothelial cell fibrinolysis by transforming growth factor beta 1.
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- III. Sodium hyaluronate increases the fibrinolytic response of human peritoneal mesothelial cells exposed to tumor necrosis factor alpha.
Reijnen M, van Goor H, Falk P, Hedgren M and Holmdahl L
Arch Surg, 2001;136:291-296
- IV. The antiadhesive agent sodium hyaluronate increase the proliferation rate of human peritoneal mesothelial cells.
Reijnen M, Falk P, van Goor H and Holmdahl L
Fertil Steril, 2000;74:146-51
- V. Studies of TGF- β ₁₋₃ in peritoneal serosal fluid during abdominal surgery and their effect on human mesothelial cell proliferation *in vitro*.
Falk P, Bergström M, Palmgren I, Holmdahl L, Breimer M and Ivarsson M-L
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BACKGROUND

Post surgical adhesion formation is still an unsolved problem and occurs when there is an imbalance between fibrin deposition and fibrin clearing capacity in the abdominal cavity. Transforming growth factor beta (TGF- β) is associated with fibrosis and hyaluronan has in several studies been showed to reduce adhesions. There are limitations to study mechanisms in humans, thus experimental models are needed. This work used *in vivo* and *in vitro* models to study effects of TGF- β and hyaluronan, and may further elucidate their involvement in peritoneal repair.

MATERIAL & METHODS

TGF- β_1 and fibrinolytic components were measured in peritoneal tissue in patients (I). In models response to increased levels of TGF- β_1 on fibrinolytical components in cultured mesothelial cells (MC) were investigated (II). Measurements of fibrinolytic components and proliferation by hyaluronan were investigated in MC (III & IV). TGF- β isoforms and fibrinolytic components were assessed in peritoneal fluid and plasma during surgery, together with mesothelial proliferation *in vitro* (V).

RESULTS

Increased TGF- β_1 levels in adhesion tissue were associated with adhesion formation and TGF- β_1 correlated to plasminogen activator inhibitor-1 (PAI-1). Increasing levels of TGF- β_1 decreased production of tissue plasminogen activator (t-PA) and increased PAI-1 release into the culture media dose dependently in cultured MC. The *in vitro* studies of hyaluronan on MC indicated an increase in fibrinolytic capacity and an increase in proliferation when added. In peritoneal fluid during surgery elevated fractions of TGF- β_{1-2} were found compared to plasma. The levels of TGF- β_1 in peritoneal fluid correspond to the levels found to increase MC proliferation *in vitro*.

CONCLUSION

Increased levels of TGF- β_1 in peritoneal tissue seem to be associated with adhesions, which in part might be explained by local decrease in fibrinolytic response from mesothelial cells. The clinical anti-adhesion effect of hyaluronan is unclear, but might partially be explained by increased fibrinolytical capacity and increased mesothelial proliferation. Low levels of active TGF- β_1 might increase mesothelial regeneration *in vivo* in combination with remained local fibrin degradation capacity found in the abdominal cavity during surgery. These findings might be of importance in the understanding of peritoneal repair.

Key words: Adhesion formation, experimental model, cell culture, mesothelial cells, peritoneum, fibrinolytic system, transforming growth factor beta, hyaluronan, proliferation