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

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av

PETER FALK

Fakultetsopponent:
Docent Bertil Casslén
Lunds universitetssjukhus, Lund

Avhandlingen baseras på följande delarbeten:

I. Overproduction of transforming growth factor-β1 (TGF-β1) is associated with
   adhesion formation and peritoneal fibrinolytic impairment.
   Holmdahl L, Kotseos K, Bergström M, Falk P, Ivarsson M-L, Chegini N.
   Surgery 2001;129:626-32

II. Differential regulation of mesothelial cell fibrinolysis by transforming growth
    factor beta 1.
    Falk P, Ma C, Chegini N and Holmdahl L.
    Scand J Clin Lab Invest, 2000;60:439-448

III. Sodium hyaluronate increases the fibrinolytical 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-β1,3 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
   in manuscript
EXPERIMENTAL MODELS OF THE HUMAN PERITONEAL ENVIRONMENT: EFFECTS OF TGF-β AND HYALURONAN

Peter Falk, Department of Surgery, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital-Östra, S-416 85 Göteborg, Sweden

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-β1 and fibrinolytic components were measured in peritoneal tissue in patients (I). In models response to increased levels of TGF-β1 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-β1 levels in adhesion tissue were associated with adhesion formation and TGF-β1 correlated to plasminogen activator inhibitor-1 (PAI-1). Increasing levels of TGF-β1 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-β1-2 were found compared to plasma. The levels of TGF-β1 in peritoneal fluid correspond to the levels found to increase MC proliferation in vitro.

CONCLUSION
Increased levels of TGF-β1 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-β1 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


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