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REVIEW

Cytokine orchestration in post-operative peritoneal adhesion formation

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Abstract

Peritoneal adhesions are a near inevitable occurrence after laparotomy and a major cause of both patient and physician misery. To date, clinical attempts at their amelioration have concentrated on manipulating the physical factors that affect their development despite a wealth of experimental data elucidating the molecular mechanisms that underlie their initiation, development and maturation. However, the advent of targeted, specific anti-cytokine agents as directed therapy for inflammatory and neoplastic conditions raises the prospect of a new era for anti-adhesion strategies. To harness this potential will require considerable cross-disciplinary collaboration and that surgeon-scientists propel themselves to the forefront of this emerging field.

Key words: Postoperative peritoneal adhesion formation; Cytokines; Vascular endothelial growth factor

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INTRODUCTION

Post-operative peritoneal adhesion formation remains a considerable source of patient and physician frustration and a significant burden on hospital resources[1]. As the commonest cause of small bowel obstruction in patients who have previously undergone laparotomy, adhesions account for 40% of all cases of intestinal obstruction and 60%-70% of those affecting the small bowel. After a first such clinical episode, 53% of patients will go on to develop a second relapse, and 83% of these will have chronic symptoms[2]. Some 14% of those who manifest overt adhesive intestinal obstruction do so within 2 years of their initial surgery, with 2.6% requiring operative adhesiolysis for its relief[3]. Furthermore, approximately 20% of patients developing adhesional bowel obstruction do so at a remove of more then ten years after their index operation[4]. Post-operative adhesions are also a common cofactor in female infertility in those with prior laparotomy[5,6] and they add markedly to the technical complexity of any repeat abdominal operation. By doing so, they give rise to considerable surgeon frustration[7] and a heightened risk of patient morbidity[8].

For all these reasons, this iatrogenic complication weighs heavily on the balance books of health care providers. Indeed, in overall costs, the financial cost due to adhesion-related morbidity approximates the expenditure required for the surgical management of gastric or rectal cancer[9] and this is then further compounded by the cost of medicolegal claims and settlements. Finally, the considerable number of bed-days consumed by the sequelae and treatment of post-operative adhesions (indeed in Finland, adhesion-related admissions exceeds the number of bed-days appropriated to varicose vein surgery) also reinforces the urgency for developing effective means of adhesion abrogation.

Unfortunately, however, clinical strategies and therapies aimed at controlling or alleviating adhesion formation have been largely inadequate in their address of both ongoing human suffering[10] and economic cost[11]. To date these attempts have mostly concentrated on employing physical means to align[12-14] or separate[15] adjacent loops of bowel in the early post-operative period (so that any configuration of interloop bands is either organised or hindered respectively) or have focused on manipulating peritoneal fibrinolytic mechanisms[16-18].

CYTOKINE ORCHESTRATION IN POST-OPERATIVE ADHESION FORMATION

Adhesions however represent a form of secondary wound healing. Therefore the mesothelial tissue response to injury (occurring either directly due to handling and dissection or indirectly due to desiccation, cooling or relative ischaemia at sites both adjacent to and distant from the actual operative site) is initiated locally and thence both propagated and orchestrated by cytokine signaling. Although systemic[19] and genetic elements[20] may also influence the severity of the cascade and factors such as bacterial contamination can potentate it[21], interruption or manipulation of key cellular processes early in the response cascade would seem likely to markedly diminish all downstream events including the ultimate fibrotic endpoint. Furthermore, the increasing sophistication of anti-cytokine therapies now allows single components of complex cellular processes to be specifically targeted. In addition, potentially efficacious agents have already been proved both safe and useful in the management of anti-neoplastic[22] and anti-inflammatory conditions[23]. Therefore a new era in the approach to adhesion amelioration may be in the offing.

SPECIFIC TARGETTING OF SELECTED CYTOKINES

There has of course been a vast array of cytokines and chemokines implicated in the initiation, development and maturation of abdominal adhesions after laparotomy (Table 1) and therefore it may initially appear forbidding to try and narrow the therapeutic target most likely to lead to unopposed benefit. Tumor necrosis factor was one of the earliest cytokines investigated and certainly seems to represent one important factor. However its recent elucidation as a key mediator of the bacterial response to infection seems to mitigate against using monoclonal antibodies (already commercially available) to abrogate this cytokine early after intestinal operation[24]. Equally, the variability of action depending on the relative proportions of its isoforms and the central role it plays in wound healing would also seem to deter use of directed therapy against transforming growth factor-beta. Of the remaining candidate targets the majority only really have a slender evidence base to support their selection from out of the general post-operative molecular milieu. The one exception, at present, would seem to be vascular endothelial growth factor (VEGF).

Although this important signaling protein is best known as a potent angiogenic cytokine (and indeed may be proposed as having a role in the process of adhesion growth through the induction of new blood vessels into areas of operative tissue injury[25]), VEGF is now also well established as being directly involved in restorative tissue processes, including early inflammatory responses, as well as wound repair and remodeling *via* effecting fibroblast function[26]. Furthermore, the central role of VEGF in facilitating increased vascular permeability (essential for the early proinflammatory response to injury) as well as the subsequent deposition of the fibrin-rich matrix necessary for subsequent cellular migration and proliferation[27,28] would seem to make it a prime putative agent in the formation of peritoneal adhesions. It is not surprising therefore that VEGF has been consistently positively implicated (albeit non-selectively) in this process[29]. The realization that peritoneal mast cells both constitutively and inducibly express this cytokine[30,31] further suggests an intriguing link given that these cells are known also to be central to adhesion formation[32]. However, it may well be that rather than through direct secretion, mast cells effect the threshold concentration of this cytokine by exciting the egress of neutrophils and monocytes from the circulation into the peritoneum and that it is these cells that instead then contribute most to regional VEGF levels.

Regardless of its exact cellular origin, VEGF seems to represent an ideal target as its levels correlate with adhesion formation in animal models with its regulation (either positively[19] or negatively[32]) affecting the degree to which they form after peritoneal operations. The clinical success and safety of VEGF neutralization by a specific monoclonal antibody in the treatment of malignant diseases[33] adds further impetus to the need to try its pharmacological manipulation as an anti-adhesion strategy particularly as selective therapeutic targeting of the cytokine does not seem to disrupt operative wound healing in a clinically important fashion[34].

DETERMINATION OF CLINICAL EFFICACY

Clinical evidence of efficacy of anti-adhesion therapies is notoriously difficult to attain as second look-laparotomy to assess distribution and intensity of peritoneal reaction is not ethically justifiable (although may be possible in the case of certain gynecological procedures[35]). Additionally, the mere presence of adhesions, even if extensive, does not necessarily correlate with the incidence and severity of subsequent symptomatic episodes and long-term follow-up is required to determine the full-extent of the problems arising. These challenges are not however insurmountable as have been shown by those who advance the cause of bioactive substances[36,37] and the difficulties that would be encountered in establishing a progressing and adequately powered multi coated blinded study would be markedly outweighed by the huge benefit to patients of many differing specialties. With regard to monoclonal antibody therapies in particular, there now exists the opportunity to piggy-back on the human safety testing performed on this class of drug in alternative settings. While pursuit of molecular mechanisms for adhesion amelioration will undoubtedly still be expensive[38], the cost incurred by the management of adhesion-related morbidity[39,40] economically justifies considerable investment in any potential means of their attenuation.

CONCLUSION

There have long been a multitude of groups proposing

Table 1 Overview of literature to date regarding cytokine orchestration in postoperative adhesion formation. Included in the list are cytokines, chemokines, and proteases as well as trigger enzymes

Cytokine [Ref]	Mechanism investigated	*In vitro/vivo*	Species	Experimental model	Effect on adhesion formation
Heparin-binding growth factor[41]	Macrophage and neutrophil omental migration	*In vivo*	Mouse	(1) Partial hepatectomy (2) Omental adherence	Exacerbated by Midkine- omental inflammation reduced
HGF[42]	Mesothelial cell proliferation and migration	Both	Rat	Cecal abrasion	Exacerbated by local HGF gene transfer
IFN-γ, HGF[43]	Natural killer T cell activity	Both	Mouse	Cecal cauterization	Attenuated by HGF
IL-1[44]	Nonspecific inflammation	*In vivo*	Rat	Cecal abrasion	Exacerbated by IL-1
IL-1, TNF[45]	Proinflammatory markers	*In vivo*	Human	Adhesion samples	IL-1 & TNF-α associated with adhesion
IL-1, IL-6, TNF-α[46]	Cellular mediation	*In vitro*	Human	Peritoneal fluid sampling	Adhesions associated with IL-6 and IL-1
IL-10[47]	Natural antiiflammatory	*In vivo*	Mouse	Peritoneal injury	Attenuated by IL-10 but no effect with IL-10 mAb. No associated with IL-10 levels
IL-10[48]	Immunosuppression	*In vivo*	Mouse	Peritoneal injury	Attenuated by IL-10
IL-1b, TNF-α, TGF-β1, IL-10, IFNg, GM-CSF[49]	Inflammatory	*In vitro*	Human	Peritoneal fluid sampling	Only IFN-γ and TGF-β1 associated with adhesion formation. No association found with other cytokines.
IL-6[50]	Early proinflammatory effects	*In vivo*	Rat	Cecal abrasion with C_2H_5OH	Exacerbated by IL-6, attenuated by monoclonal Ab to IL-6
PAF[51]	Early inflammatory mediators	*In vivo*	Rat	Uterine horn abrasion	Adhesions and IL-6 levels attenuated by Lexipafant (PAF antagonist)
Substance P[52]	Substance P mediation	*In vivo*	Rat	Peritoneal ischaemic buttons	Substance P and TGF-β1 as well as ICAM-1 and VCAM-1 increased
TGF[53]	TGF isoforms	*In vivo*	Mouse	Serosal abrasion and apposition	Exacerbated by TGF-β3, attenuated by combined TGF-β1 and TGF-β2 mAB
TGF-β[54]	TGF-β regulation of extracellular matrix	*In vitro*	Human	Human fibroblast culture	Dichloroacetic acid inhibited fibronectin and collagen type Ⅲ expression
TGF-β[55]	Chemoattraction	*In vitro*	Rat	Cecal abrasion	TGF-β mRNA increased by trauma
TGF-β[56]	Mast cells	*In vivo*	Hamster	Uterine horn abrasion	Exacerbated by chymase inhibitor
TGF-β[57]	Chemoattraction	*In vivo*	Rat	Uterine horn abrasion	Exacerbated byTGF-β
TGF-β[58]	Mast cells	*In vitro*	Human	Cell culture	TGF-β and tryptase increased collagen
TGF-β[59]	Peritoneal repair	*In vivo*	Rat	Uterine horn abrasion	No antiadhesion effect of anti-TGF mAb
TGF-β[60]	Immunosuppression	*In vivo*	Rat	Small bowel transplant	Adhesions attenuated by tacrolimus
TGF-β[61]	Mast cells	*In vivo*	Rat	Uterus scraping	TGF-β increased by trauma, adhesions attenuated by chymase inhibition
TGF-β[62]	Cellular effects of Tisseel	*In vitro*	Human	Cell culture	Fibroblasts TGF-β reduced
TGF-b, MMP-9, TIMP-1[63]	Matrix factors	*In vivo*	Human	Sampled peritoneal fluid	Adhesion assoc with reduced MMP-9 but elevated MMP-9/TIMP-1 ratio
TGF-β/MDF[64]	Carboxymethylcellulose sponge	*In vivo*	Rat	Cecal denudation & apposition	Effect of sponge independent to cytokine release (barrier function)
TGF-β1[65]	Chemoattraction	*In vitro*	Human	Cell culture	TGF-β1 increased in scar tissue
TGF-β1[66]	Extracellular matrix	*In vivo*	Mouse	Cecal abrasion	Exacerbated by haploid insufficiency
TGF-β1[67]	Fibrinolysis	*In vitro*	Human	Biopsy sampling	Attenuated by TGF-β1 overexpression
TGF-β1[68]	Peritonitis	*In vivo*	Rat	Cecal ligation and puncture	Peritonitis upregulates TGF-β1 expression
TGF-β1[69]	Mitogenicity of macrophages & fibroblasts	*In vivo*	Rat	Small Bowel transection and re-anastomosis	Adhesions and TGF-1 levels attenuated by ACE inhibition
TGF-β1, MMP1&2, TPA, TIMP-1[70]	Cellular effects of seprafilm	*In vitro*	Human	Human fibroblast & mesothelial cell culture	No cytokine effect induced by Seprafilm (barrier effect important)
TGF-β1, TGF-β2[71]	Basal expression	*In vitro*	Human	Biopsy sampling	Sit-specific TGF-β1 & TGF-β3 expression
TGF-β1[72]	Cellular effects of changtong	*In vivo*	Rat/rabbit	Cecal abrasion	TGF-β reduced in rats
TNF, IL-1, IL-6[73]	Effects of gloves and powders	*In vivo*	Rat	Cecal abrasion	Adhesions increased by glove powder
TNF-α[74]	Proinflammatory effects of TNF-α	*In vivo*	Rat	Cecal abrasion	Adhesion formation attenuated by infliximab but no histological effect
TNF-α, IL-1[75]	Proinflammatory markers	*In vivo*	Rat	Cecal abrasion or small bowel resection	TNF-α appears a good biological marker for adhesion formation
TNF-α, IL-1[76]	Immunosuppression	*In vivo*	Rat	Cecal abrasion	Adhesion formation attenuated by mAbs to IL1 and IL-1/TNF-α
TNF-α, IL-6[77]	Proinflammatory mediators	*In vitro*	Mouse	Murine macrophages	Adhesion formation attenuated by hyaluronic acid and dexamethasone
TNF-α, MMP[78]	Mesothelium reaction to peritoneal injury	*In vivo*	Rat	Peritoneal wounding	No effect of MMP & TACE inhibition, TNF-α may not be adhesiogenic
TNF-α, TGF-β1[79]	PROACT to injured peritoneum	*In vivo*	Human	Tissue sampling	TNF-α and TGF-β reduced by heating
VEGF[80]	Angiogenesis	*In vivo*	Rat	Uterus-peritoneal scrub	Associated by angiogenesis
VEGF[29,32]	Vascular permeability	*In vivo*	Mouse	Peritoneal injury	Adhesions attenuated by Antiserum and monoclonal antibody
VEGF, basic-FGF[25]	Fibrovascular band formation	*In vivo*	Human	Adhesion samples	VEGF in endothelial cells associated with adhesion formation

VEGF, IL-6[21]	Bacterial Translocation	Both	Mouse	Caecal abrasion & suture	Adhesions attenuated by rBPI
VEGF, PlGF[81]	Pnenumoperitoeum	*In vivo*	Mouse	Lap. uterine horn model	Exacerbated by VEGF and CO_2
CCL 1-CCR 8[83]	Specific recruitment of peritoneal macrophages	Both	Mouse	Peritoneal ischaemic button & colitis-associated peritoneal adhesions	Unaffected by CCR8 gene deficiency and antiCCL1-neutralizing antibody
CD 28 T cell costimulatory pathway[84]	CD28 T cell costimulatory pathway/Inhibitor programmed death-1 pathway	Both	Mouse	Caecal abrasion	Exacerbated by CD28 T Cell costimulatory pathway but unaffected by death-1 pathway
Interferon-inducible protein-10[85]	Regulates influxing neutrophils, monocytes and lymphocytes	*In vivo*	Mouse	Peritoneal side wall injury	
Broad spectrum of chemokines[86]	Broad spectrum chemokine inhibitor NR58-3.14.3	*In vivo*	Mouse	Peritoneal traumatization	Adhesions significantly attenuated
MCP-1[87]	Fibroblast and mononuclear cell chemotaxis	*In vivo*	Mouse	Peritoneal injury	Attenuated by MCP-1 antibody
MCP-1[88]	Fibroblast and mononuclear cell chemotaxis	*In vivo*	Human	Cell culture	
MCP-1[89]	Fibroblast and mononuclear cell chemotaxis	*In vivo*	Human	Cell culture	
T cells, IL-17, CXC MPI-2/ CXCL8, CXCL1[90]	CD4+ T cells	*In vivo*	Mouse	Caecal abrasion	Unaffected by anti-IL-17 antibodies

HGF: Hepatocyte growth factor; IFN-γ: Interferon-gamma; IL: Interleukin; TNF-α: Tumour necrosis factor-alpha; TGF-β: Transforming growth factor-beta; GM-CSF: Granulocyte macrophage colony stimulating factor; PAF: Platelet activating factor; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase; MDF: Macrophage deactivating factor; TPA: Tissue plasminogen activator; VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factor; PIGF: Placental growth factor; MCP: Monocyte chemotactic protein.

novel, potential therapies for the attenuation of adhesion formation at a preclinical level- the onus now though is on leading surgeon-scientists to corral their endeavour and progress their preclinical expertise into the clinical setting. For a start, the most likely candidate cytokine must be agreed (in our mind VEGF would seem the most apposite) and the most appropriate means of affecting its activity (whether directly[32] or indirectly[21]) selected. Furthermore industry interest will need to be stimulated for its support for Phase Ⅱ and Ⅲ trials as well as for the subsequent manufacture and marketing processes is crucial. Above all, though it must be realized that the timing for a concerted attempt to prove that molecular manipulation of post-operative peritoneal formation has never been better.

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