



Dean Harris, Department of Surgery, Cardiff University, WALES

### Peritoneal cytokines

Adhesions form as a result of the complex interplay between cellular and humoral factors involved in peritoneal wound healing, and represent an exaggerated and prolonged inflammatory response to trauma. Preservation of the integrity of the mesothelial monolayer is the prime factor in adhesion free healing. The single layer mesothelial lining, although easily damaged, heals by centripetal migration followed by cell proliferation<sup>i</sup>, resulting in rapid wound healing over 5-7 days. Separation of juxtaposed sub-mesothelial connective tissue during this critical time window seems to be the most effective strategy in preventing formation of the precursor fibrin bridge.

Maintenance of an effective mesothelial cell mass is as important as its continuous integrity. Whilst being the predominant source of intraperitoneal tissue plasminogen activator (tPA)<sup>ii</sup>, surfactant<sup>iii</sup> and hyaluronan<sup>iv</sup> with obvious consequences for fibrinolysis and peritoneal lubrication, the mesothelial cell also holds a pivotal role in the augmentation of the peritoneal healing process through orchestration of leucocyte trafficking<sup>v</sup>. By contribution to the peritoneal cytokine network<sup>vi</sup> and through interaction with resident macrophages, mast cells and fibroblasts mesothelial cells coordinates the leucocyte flux that results in resolution of inflammation and adhesion free healing. Through interleukin-6 (IL-6) signalling via its soluble receptor (sIL-6R) the pattern of chemokine expression is switched to limit neutrophil influx and promote a pro-resolution mononuclear cell population. Further work has implicated Th1 cells in the pathogenesis of adhesions, with the extent of adhesions tightly controllable through manipulation of T cell function and chemokine expression<sup>vii</sup>. Dysregulation of this process and failure of resolution, often driven by foreign material, persistent infection or trauma may play a causative role in adhesion formation leading to persistent mononuclear cell recruitment, fibroblast activation and permanent collagen and ECM deposition.

The challenge facing us is the prevention of inappropriate adhesion formation but preservation of the host response to intra-abdominal infection, sepsis and anastomotic healing. Such an approach would embrace an understanding of the peritoneal response to injury to include pro-migratory, anti-angiogenic and anti-inflammatory strategies. Such work in understanding the cellular and sub-cellular mechanisms underlying adhesion formation would refine the current preoccupation with the use of inert physical barrier separation of injured surfaces. It is hoped that progress will continue and new products designed with a clear remit of inhibiting or modulating endogenous pro-adhesion pathways will begin to enter the market.

- <sup>i</sup> Yung S, Davies M. Response of the human peritoneal mesothelial cell to injury: an in vitro model of peritoneal wound healing. *Kidney Int.* 1998 Dec; 54(6):2160-9.
- <sup>ii</sup> Ivarsson ML, Holmdahl L, Falk P, Molne J, Risberg B. Characterization and fibrinolytic properties of mesothelial cells isolated from peritoneal lavage. *Scand J Clin Lab Invest* 1998; 58(3):195-203.
- <sup>iii</sup> Beavis J, Harwood JL, Coles GA, Williams JD. Synthesis of phospholipids by human peritoneal mesothelial cells. *Perit Dial Int*, 1994; 14(4): 348-55.
- <sup>iv</sup> Yung S, Coles GA, Williams JD, Davies M. The source and possible significance of hyaluronan in the peritoneal cavity. *Kidney Int.* 1994; 46(2): 527-33.
- <sup>v</sup> Hurst SM, Wilkinson TS, McLoughlin RM, Jones S, Horiuchi S, Yamamoto N, Rose-John S, Fuller GM, Topley N, Jones SA. IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. *Immunity* 2001; 14(6): 705-14.
- <sup>vi</sup> Topley N. The cytokine network controlling peritoneal inflammation. *Perit Dialysis Int* 1995; 15:S35-40.
- <sup>vii</sup> Holsti MA, Chitnis T, Panzo RJ, Bronson RT, Yagita H, Sayegh MH, Tzianabos A. Regulation of Postsurgical Fibrosis by the Programmed Death-1 Inhibitory Pathway. *J Immunol* 2004; 172: 5774–5781.