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Letter to the Editor

Modulation of plasma complement by the initial dose of epirubicin/docetaxel therapy in breast cancer and its predictive value

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Sir,

I read with interest the recent paper by Michlmayr *et al*, 2010, describing the effects of neoadjuvant chemotherapy on serum complement factor expression (Michlmayr *et al*, 2010). The authors also reported increase in levels of the plasma protein inter-α-trypsin inhibitor (IαI), but they may have failed to appreciate the potential significance of this finding.

IαI is not an acute-phase protein, as the authors report in this paper; in fact IαI plasma concentration declines during acute inflammation, because of consumption and decreased liver expression (Daveau *et al*, 1993; Opal *et al*, 2007). Moreover, IαI heavy chain expression is downregulated in cancers, including breast cancer (Hamm *et al*, 2008). Furthermore, IαI does not simply have hyaluronan-binding properties; it inhibits cancer metastasis (Werbowetski-Ogilvie *et al*, 2006; Yagyu *et al*, 2006) and has strong anti-inflammatory properties (Zhuo *et al*, 2004). In fact, we showed that IαI inhibits complement activation, both through the classical and the alternative pathways (Garantziotis *et al*, 2007). Thus, the association of increased IαI and complement plasma levels is significant for at least two reasons. First, upregulation of IαI may be a regulatory mechanism inhibiting complement activation. As baseline IαI plasma concentration is substantial (0.1 – 0.5 mg ml^{-1}; Zhuo *et al*, 2004), even a modest relative increase of ~50%, as the authors report, would mean a significant absolute increase. As the observed increase in plasma IαI overrides the expected acute phase decline, powerful induction mechanisms may be assumed. Second, IαI is now in production in the United States and will soon be tested in a clinical trial for its effect in sepsis morbidity and mortality. As complement activation appears to have a role in the response to chemotherapy, factors that affect this activation, such as IαI, may be interesting as therapeutic agents. Furthermore, IαI levels may be predictive of response to treatment as well, as they are in sepsis (Opal *et al*, 2007).

In conclusion, I believe that IαI – complement interactions are important in the context of cancer progression and treatment, and these interactions should be highlighted in reference to the recently published paper by Michlmayr *et al*, 2010.

REFERENCES

Daveau M, Rouet P, Scotte M, Faye L, Hiron M, Lebreton JP, Salier JP (1993) Human inter-alpha-inhibitor family in inflammation: simultaneous synthesis of positive and negative acute-phase proteins. *Biochem J* **292**(Part 2)**:** 485 – 492

Garantziotis S, Hollingsworth JW, Ghanayem RB, Timberlake S, Zhuo L, Kimata K, Schwartz DA (2007) Inter-alpha-trypsin inhibitor attenuates complement activation and complement-induced lung injury. *J Immunol* **179:** 4187 – 4192

Hamm A, Veeck J, Bektas N, Wild PJ, Hartmann A, Heindrichs U, Kristiansen G, Werbowetski-Ogilvie T, Del Maestro R, Knuechel R, Dahl E (2008) Frequent expression loss of inter-alpha-trypsin inhibitor heavy chain (ITIH) genes in multiple human solid tumors: a systematic expression analysis. *BMC Cancer* **8:** 25

Michlmayr A, Bachleitner-Hofmann T, Baumann S, Marchetti-Deschmann M, Rech-Weichselbraun I, Burghuber C, Pluschnig U, Bartsch R, Graf A, Greil R, Allmaier G, Steger G, Gnant M, Bergmann M, Oehler R (2010) Modulation of plasma complement by the initial dose of epirubicin/docetaxel therapy in breast cancer its predictive value. *Br J Cancer* **103:** 1201 – 1208

Opal SM, Lim YP, Siryaporn E, Moldawer LL, Pribble JP, Palardy JE, Souza S (2007) Longitudinal studies of inter-alpha inhibitor proteins in severely septic patients: a potential clinical marker and mediator of severe sepsis. *Crit Care Med* **35:** 387 – 392

Werbowetski-Ogilvie TE, Agar NY, Waldkircher de Oliveira RM, Faury D, Antel JP, Jabado N, Del Maestro RF (2006) Isolation of a natural inhibitor of human malignant glial cell invasion: inter alpha-trypsin inhibitor heavy chain 2. *Cancer Res* **66:** 1464 – 1472

Yagyu T, Kobayashi H, Matsuzaki H, Wakahara K, Kondo T, Kurita N, Sekino H, Inagaki K (2006) Enhanced spontaneous metastasis in bikunin-deficient mice. *Int J Cancer* **118:** 2322 – 2328

Zhuo L, Hascall VC, Kimata K (2004) Inter-alpha-trypsin inhibitor, a covalent protein-glycosaminoglycan-protein complex. *J Biol Chem* **279:** 38079 – 38082

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