Schistosomal Cor pulmonale: A Fluke in the Fas Lane?

J.L. Robotham

Department of Anesthesiology, University of Rochester Medical Center, Rochester, N.Y., USA

The paper by Salama et al. [1, this issue of Respiration] correlating elevated serum Fas levels with cor pulmonale in schistosomiasis (caused by a subgroup of trematodes – flukes) may have broad implications for respiratory physicians. The Fas receptor and Fas ligand (CD95) system, being respectively related to the TNF-receptor (R) and the TNF families, is increasingly being appreciated as having similar complex and temporal relationships to the evolution of acute and chronic disease as do TNF and TNFRs [2–4]. While the focus on Fas/FasL regulation of apoptosis has taken center stage, it is seems likely that as with TNF/TNFR, such a potent system will be found to have multiple immunological regulatory roles [5–7]. Additionally, the evolving understanding of how metalloproteinase ‘sheddases’ such as TACE may either enhance or diminish the inflammatory consequences of TNF and its receptors is now being paralleled by studies of metalloprotease cleavage of membrane bound FasL (mFasL) [8–12]. The ability of soluble(s) TNF to propagate a lethal inflammatory process if released in large amounts (e.g. meningococcemia), must be appreciated while understanding that membrane bound (m)TNF normally plays the dominant role in the autocrine or paracrine signaling regulating localized acute and chronic disease states [13, 14]. Paradoxically, the shedding of mTNF or mTNFRs may also serve to reduce the degree of host induced injury in response to an infectious agent or injury [2, 15]. It should therefore not be surprising that a similar complex array of events will likely be elucidated within the Fas/FasL system and its interactions with the immune system.

It is with this background that Salama et al. [1] showed that increased levels of soluble Fas (sFas) correlated with the severity of the pulmonary hypertension in a population of 15 men with schistosomal cor pulmonale. The serum levels were significantly greater than those found in two control populations: men with cor pulmonale secondary to COPD and aged matched healthy men. While the study has some clear weaknesses, (e.g. no control populations with schistosomiasis without cor pulmonale), it does highlight an emerging body of science suggesting that Fas/FasL may be critical to understanding one of the most prevalent disease states affecting the human race. It also provides insights into how future understanding of the molecular regulation of apoptosis, inflammation and genetic variability in both host and parasite may be used to prevent morbidity and mortality in schistosomal lung disease, and very likely, lung disease in general [16–20]. The role of apoptosis in defining the evolution of disease is emerging as a fundamental principle in understanding lung inflammatory disease states from sepsis to emphysema [17, 21].
Five species of the parasite causing schistosomiasis are known in 76 countries with over one billion people living in endemic areas [19–22]. Global travelers in increasing numbers are returning home from endemic areas manifesting acute and chronic disease. Over 200 million people are estimated to have a relatively benign intestinal wall involvement associated with a localized inflammatory response. Over 20 million are severely ill with hepatic or urological involvement, and a subset, reported between 5–54%, have evidence of pulmonary involvement manifested by ‘angiomatoid’ pulmonary vasculitis caused by a granulomatous inflammatory response to ova trapped and killed in the circulatory bed. If the granulomatous response is both widespread and vigorous, mechanical obstruction of the vascular bed follows resulting in pulmonary hypertension. A parallel process is observed in the liver producing hepatic fibrosis and portal hypertension. The different schistosomal species have varying genetic predilections for different organ beds allowing long term propagation in the human host with ‘tricks’ including the ability to coat themselves with host antigens to decrease the inflammatory response [22]. The human host after first killing the ova through an inflammatory response, subsequently responds to the release of antigen from the ova by selectively upregulating lymphocyte Fas mediated apoptosis specifically in the granuloma thus mitigating further host damage [6, 23, 24].

The long term survival of the parasite species is dependent on the host surviving, i.e., a vigorous prolonged inflammatory response producing hepatic failure or cor pulmonale and death is not in the best interest of either the parasite or the human host. Over millennia a genetic ‘truce’ has evolved between parasite and host [6, 23, 24]. The focus of Salama et al. [1] on sFas now becomes understandable. As importantly, the interaction of FasL as a membrane bound or soluble ‘death effector’ must also be understood. Fas by definition must be membrane bound in order to act in its receptor role binding with FasL to initiate the apoptotic process in its resident cell. The critical study cited by Salama and coworkers to support their hypothesis that increased sFas would inhibit apoptosis, thus limiting granuloma formation and preventing cor pulmonale, paradoxically shows that sFas is increased in humans with lupus and increasing sFas in mice produces an inflammatory autoimmune disease [5].

The complexity of possible outcomes is further illustrated by experimental studies in mice showing that transfection of mice to increase sFas production reduced the degree of hepatic apoptosis following an antiFas triggering antibody [25]. The common mechanism of sFas binding to FasL and sTNFRs binding to TNF would appear to be preventing the ligand from triggering apoptosis by ‘capturing’ soluble ligand and thus preventing it from binding to membrane bound receptors. sFas results from a ‘shed-dase’ cleaving mFas or by production of a genetic mutant, as reported by Cheng et al. [5] in which the mRNA coding region for the transmembrane portion of mFas is missing, resulting in production and secretion of sFas. Either pathway may reduce the number of mFas receptors available to initiate apoptosis. An elevated sFas by limiting apoptotic signaling and thus maintaining a vigorous inflammatory response could produce a cellular response that will be fatal for the organism. However, studies in human lupus have shown that an elevated sFas correlates with the degree of organ damage present but not with the disease activity [26]. This is indeed a key question that Salama’s group must address in future studies, i.e. is the elevated sFas simply a manifestation of diffuse chronic (multi)organ damage with a cumulative ‘shedding’ into the interstitium and blood stream from a large cell mass in severely damaged organs, or specific evidence of active schistosomal lung disease? Could the increased sFas be from the same or a variant of the human Fas mRNA producing sFas reported by Cheng et al. [5] be a relatively common genetic defect stimulating inflammation or a counter-regulatory response reducing the inflammatory response via apoptosis?

Genetic or pharmacological manipulation of the Fas/ FasL system will likely be very tricky with respect to timing and dose, just as manipulation of the TNFR/TNF system has been found to be in acute disease [27]. Successful intervention in chronic TNF disease states is possible with anti-TNF therapy, e.g. rheumatoid arthritis [28]. However, whether anti-TNF or anti-Fas/FasL therapy will be effective in severe chronic schistosomal disease remains to be studied.
References


