Gelsolin in idiopathic pulmonary fibrosis: a new target supports a central role for epithelial injury in disease pathogenesis

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Idiopathic pulmonary fibrosis (IPF) is a highly heterogeneous condition and is likely to be initiated by many different forms of lung injury. Injury to the alveolar epithelium followed by aberrant repair is, however, recognised to be a central pathogenic mechanism in IPF.[1] Histologically, there is evidence of epithelial cell hyperplasia and proliferation, particularly adjacent to fibroblastic foci, but also areas of epithelial apoptosis and denudation.[2] In murine models of pulmonary fibrosis, inhibition of components of apoptotic signalling pathways abrogates both alveolar epithelial cell death and fibrosis. This has been achieved by treatment with caspase inhibitors or with antibody blockade of the Fas death receptor, these results being confirmed in mice deficient in murine Fas (lpr) or its ligand, gld.[3 4] The mechanisms of epithelial cell apoptosis in human IPF are not clearly defined, although there is evidence that the Fas pathway may be upregulated resulting in caspase-dependent apoptosis.[5] A recent paper has shown that apoptosis of epithelial cells derived from patients with IPF is specifically associated with markers of endoplasmic reticulum stress.[6]

In this issue of *Thorax*, Oikonomou and colleagues (***see page 467***) show that gelsolin—a regulator of cellular cytoskeleton dynamics—is upregulated in patients with IPF or fibrotic non-specific interstitial pneumonia, but not in other forms of interstitial lung disease, and that increased gelsolin expression correlates with reduced pulmonary function.[7] The authors also studied mice deficient in gelsolin and showed that they are protected from bleomycin-induced inflammation and fibrosis, with reduced neutrophil emigration to the lungs, marked reduction in epithelial cell apoptosis and reduced collagen production. Further experiments in an acute lung injury model suggested an intrinsic deficit in emigration of gelsolin-deficient neutrophils into the lungs, in keeping with other studies and with the cytoskeletal functions of gelsolin.[8] Nonetheless, adoptive transfer experiments, placing wild-type bone marrow into gelsolin-deficient mice and vice versa, showed that it was gelsolin expression in the resident tissue cells of the lung (as opposed to leucocytes) that was required for development of fibrosis.[7]

How does this fit with our knowledge of the biology of gelsolin? Gelsolin is a multifunctional protein which has a potent actin filament severing ability. This contributes to the rearrangements of the cellular cytoskeleton that underpin the motility of viable cells, with gelsolin deficiency reducing motility of inflammatory cells but increasing contractility of fibroblasts.[8] In addition, however, gelsolin is a specific target of caspase-3, the central "executioner" protease of apoptosis.[9] Cleavage of gelsolin during the later stages of apoptosis generates an N-terminal cleavage product (N-GSN) that causes cytoskeletal collapse resulting in apoptotic cell detachment and nuclear fragmentation, and it is the absence of this function that appears to be important in preservation of gelsolin-deficient alveolar epithelial cells following bleomycin injury.[7 10] Gelsolin-deficient cells are shown to be protected from apoptosis in vitro, despite the presence of active caspase-3 and the efficient cleavage of other known caspase substrates.

In the light of these elegant studies, the authors speculate that actin-modifying drugs or specific targeting of the N-GSN gelsolin fragment might prove useful therapeutic strategies in IPF. Certainly their data support this idea, although inevitably there are some unanswered questions. The longer term phenotype of gelsolin-deficient epithelial cells that have received a pro-apoptotic insult but survived is unclear. The authors show that the cells have active caspase-3 and that other important cellular targets (eg, those involved in DNA repair) still undergo caspase-mediated cleavage and inactivation. Thus, gelsolin cleavage may be too far downstream in apoptotic signalling pathways for long-term cell rescue, and the longer term survival and proliferative potential of these cells—which are likely to have DNA damage—requires further study. Moreover, the ability of these "rescued" epithelial cells to initiate other pathological features of IPF is potentially important. The authors convincingly show reduced levels of KC, the principal neutrophil chemokine in mice and a functional homologue of human interleukin-8 (CXCL-8), and it would also be interesting and important to study other pathological events such as release of transforming growth factor β (TGF-β) and angiogenic factors from these cells following bleomycin treatment.

Gelsolin deficiency is not always associated either with reduced apoptosis or with amelioration of injury in other disease models. In a model of pulmonary ischaemia, defects in cytoskeletal remodelling in gelsolin-deficient mice were associated with increased permeability of the pulmonary endothelium.[11] Gelsolin deficiency also results in worsening of ischaemic brain injury in mice.[12] Fas-mediated liver fibrosis is exacerbated in gelsolin-deficient mice in association with selective apoptosis of sinusoidal endothelial cells, again suggesting that gelsolin has an important role in the maintenance of vascular barrier functions.[13]

Although not the main focus of these studies, the paper by Oikonomou and colleagues again demonstrates that neutrophilic inflammation is a component of bleomycin-induced lung injury in mice, as it is of human IPF where higher neutrophil counts are associated with more rapid disease progression.[14] Reduced lung injury in gelsolin-deficient mice was associated with reduced neutrophil counts as well as with reduced alveolar epithelial cell apoptosis, compatible with a role for neutrophils in disease progression. However, the adoptive transfer experiments show that inhibition of epithelial injury reduces recruitment of wild-type neutrophils, suggesting that this inflammation is a consequence rather than a cause of epithelial injury.

Another interesting feature of this paper is the way in which gelsolin was identified as being worthy of study in IPF. The same group previously undertook expression profiling, comparing bleomycin-treated and untreated mice.[15] Gelsolin was one of a group of genes shown to be upregulated in bleomycin-treated mice and to be

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biologically plausible as a known TGF-β target gene. The results presented in the current paper emphasise the potential utility of this approach for target identification in diseases of unknown aetiology.

Competing interests: None.

Thorax 2009;**64**:461–462. doi:10.1136/thx.2008.110577

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Has ISAAC told us as much as it can? Where now?

Martyn R Partridge

Readers of a certain age may recall the use of diets in the management of peptic ulcer disease, their replacement by the introduction of increasingly complicated surgery such as highly selective vagotomy, and the subsequent discovery of the critical role of *Helicobacter pylori* infection in the causation of this (and other) diseases. What will the denouement for asthma be in 5, 10 or 15 years?

The output of the International Study of Asthma and Allergies in Childhood (ISAAC) over the last 14–15 years has told us a lot.[1–3] We now know that the prevalence of wheeze in the past 12 months amongst both 6- to 7-year-old and 13- to 14-year-old children varies only a little within countries but widely between countries. In the countries which have taken part in sequential phases of ISAAC, we know that in some the prevalence continues to rise, in others it has plateaued, whilst in others the number of affected children has fallen over a decade. The latest ISAAC report (***see page 476***) further contributes to this knowledge by informing us of data from a further 128 new centres.[4] The results again demonstrate rates of current wheeze that, for example, vary from a third of New Zealand 13- to 14-year-old children having a current wheeze to <1% responding positively to this question in Tibet. Trends in the "new" countries are in general similar to those shown in 1997, with the highest rates being in English language countries and South America, higher rates in Western than Eastern Europe, and lower prevalence in Africa and Asia. However, there is considerable heterogeneity in rates within some regions, with Mexico having rates much lower than the rest of South America, and Sri Lanka having rates higher than many other parts of Asia. In an attempt to explain these differences the authors have looked at one variable, economic development, and demonstrated higher prevalence in more affluent countries, but interestingly also noted that whilst overall prevalence was lower in countries with lower incomes, the severity might have been higher. They speculate that this could reflect lower understanding of the significance of wheeze as a marker of asthma in those countries, but also speculate that it might reflect either less good asthma care or a more adverse environment in these countries. The previous ISAAC time trends paper[3] also necessitates speculative interpretation. That some countries experience a rise in prevalence a few years later than occurred in other countries is perhaps not difficult to comprehend. The fact that other countries experience a plateauing of prevalence is similarly interesting, comprehensible and encouraging. That others have experienced a decline in prevalence over a 10-year period is much harder to explain. The ISAAC team cannot really help us here and have suggested that whilst treatment may affect severity it would not have affected prevalence. Whether that interpretation is correct if the questions relate to wheezing is debatable, and others have studied and queried the effects of treatment, repeated questioning of children and thresholds for diagnostic labels on studies of prevalence.[5 6]

ISAAC has been an extraordinary epidemiological study carried out with rigour and enthusiasm. It has told us much, and as with any study one can speculate as to the accuracy of parts of the data, and the authors repetitively discuss methodology and statistical pitfalls in their reports. However, there can be little doubt from ISAAC and from other studies of prevalence done using the same methodologies amongst the same aged children in the same places at different times,[7–9] that in many countries the prevalence of this condition has, at least until recently, increased dramatically. However, we do not yet have a preventive strategy such that we can advise either individuals or governments how they might reduce the chance of children being born with this condition, or a tendency to it. We know that the condition will have resulted from an interaction between a susceptible host and the environment and that whilst genetic factors will play a significant part in that host susceptibility, they will not have changed over the last decade or two. Interest has therefore focused upon the interactions with the environment. Special interest and study have been focused on rates of exposure to infections in early life, to the degree of exposure to

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