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Perspective

Gene therapy for asthma: inspired research or unnecessary effort?

Gene therapy, in theory, is a relative simple undertaking for which there are two approaches. The easier is to become interested in a monogenic disease for which the gene has been cloned. In this case, the therapeutic gene is known and does not need to be selected from knowledge of pathogenesis. Cystic fibrosis (CF) is an obvious example of this process; ten phase one clinical studies have been reported without, as yet, consensus regarding the key function of the gene product, cystic fibrosis transmembrane conductance regulator. The more difficult approach is to focus on a polygenic disease with a significant enviromental contribution. Now sufficient understanding of the pathogenesis is needed to select a candidate gene, up or downregulation of which, it is hypothesised, will alter this process. Asthma is an obvious example of this latter approach. Is gene therapy research for this disease needed, and if so how can we go about it?

Asthma is characterised by attacks of cough and breathlesness, usually precipitated by an enviromental trigger. The sequence of pathogenesis is unclear but there is clearly a genetic predisposition. A number of candidate genes have been suggested, many of which are involved in the initiation and regulation of inflammation[1]. The key cell type in which expression of this predisposition is important is also unclear, but cells such as macrophages and lymphocytes, as well as perhaps the airway epithelium, have been implicated. Thus, the combined effect of several genetic alterations in several cell types may lower the threshold for an asthmatic to respond to an enviromental stimulus. Whether this threshold relates to the level of inflammation present is also unclear, but represents one possible pathological pathway.

The symptoms of the majority of asthmatics can be well controlled if the appropriate, already available, suppresive treatment is administered. Inhaled glucocorticosteroids (to control inflammation) and β_2-agonists (as bronchodilators) are the mainstay of therapy, are relatively well tolerated, and represent the benchmark against which new treatments will be measured. Gene therapy could offer benefit if it was more effective (better treatment for more patients), achieved a 'cure' or was easier to use.

Achieving more effective treatment could be focussed at the genetic predisposition itself or at events linking it with the enviromental initiator, but these are still visionary since the steps are unclear. Alternatively, the focus could be the downstream changes, probably related to inflammation. However, given the effectiveness of current treatment aimed at this target, this may be hard to achieve (see below). A 'cure' will need to be aimed at the visionary end of this spectrum and even if the 'right' gene is identified there is the further issue of gene delivery to the correct cell type. We consider either of these laudable goals unlikely to be achieved in the foreseeable future. The principal challenge in patients who respond to conventional therapy is to achieve effective delivery of care, so does gene therapy offer any new perspective for making treatment easier to use? Current evidence suggests that a transgene will be expressed for days to weeks in the airways using adenoviral or lipid-mediated gene transfer. Presently, therapy is given on a twice or four time daily basis. Thus, reduced frequency of administration leading to improved compliance is a possible benefit. However, in our view, for the majority of asthmatics, gene therapy appears to hold relatively little short-term promise.

Clearly, there is a group of asthma subjects with severe disease, often requiring long-term oral corticosteroids with their attendant side-effects. New, more effective and safer, treatments are urgently needed here, so what can gene therapy offer? As noted above, events prior to the enviromental trigger remain largely visionary at present. Controlling the environmental trigger seems to us an unlikely proposition. It may be possible to deliver a gene encoding decoys which would reduce the adherence of viruses or bacteria, often the cause of acute exacerbations, by mimicking their receptor sites. However, given the variety of organisms involved, as well as the many non-infectious triggers this seems a task Hercules would have baulked at. Which the 'effector' cells are that detect the environmental trigger and augment the characteristic inflammation is unclear, but probably includes non-resident macrophages. Targeting a nomadic cell, particularly one with an aversion for gene transfer, is likely to be very difficult. The epithelium, including afferent nerve endings, presents an easier target but one which may be less relevant for pathogenesis. Finally, the lack of a unified hypothesis for how the trigger induces inflammation, irrespective of cell type, further dampens our enthusiasm for this approach.

The inflammation provides another opportunity to arrest the pathogenic pathway. The effector cells recruit a number of inflammatory cell types using the production of chemoattractants. An example is the production of ICAM-1 which increases the adherence of neutrophils to respiratory epithelium[2]. Downregulation of these proinflammatory mediators is possible using antisense approaches. Oligonucleotide transfer efficiency

would have to be high, but more daunting is the redundancy built-in to this recruitment process. There are many already identified chemoattractants which can complement each others functions, and more can be expected.

On arrival, the inflammatory cells secrete a myriad of cytokines intended to remove the organism or allergenic particle. In asthma this process likely continues beyond the level required for such benefit, perhaps causing the patients' symptoms, although this is debated. Type 2 cytokines such as IL-4, and molecules such as adenosine, drive this process and one possibility would be to down-regulate their function[3]. As well as antisense strategies for such individual cytokines and mediators, a further possibility is to overexpress genes for secreted molecules such as interferon-γ or IL-12 which inhibit these type 2 responses. Further, there are cytokines such as IL-10, whose function it is to terminate the inflammatory process more proximal to these events. Of the very limited number of publications available to provide data rather than hypotheses in support of asthma gene therapy, interferon-γ[4] and IL-12[5] have been shown to be effective in animal models. The fearsome redundancy in the cytokine system, and the current inefficiency of gene transfer are key obstacles.

The use of secreted gene products may provide one way of circumventing the latter. The logical approach to the former would be to target the upstream controlling molecule responsible for disseminating the cytokine cascade. One candidate for this is the transcription factor NFκB. This is constitutively present within the cytoplasm bound to IκB molecules which retain NFκB within the cytoplasm, and hence maintain it in an inactive state. Pro-inflammtory stimuli induce phosphorylation of the IκB molecules leading to their degradation and the entry of NFκB into the nucleus where it induces transcription of the cytokine cascade. NFκB presents an attractive target for gene therapy, and studies outside the field of asthma have demonstrated success using IκB overexpression or the use of decoy oligonucleotides which mimic the genomic binding sites for NFκB. Again the current efficiency of gene transfer, and the uncertainty of which cell type needs to be transfected, remain obstacles. At least this approach may limit the redundancy argument, and for this reason is one which our laboratory is exploring.

In the current issue, Mathieu *et al*[6] have investigated another possible therapeutic approach aimed at reducing activated NFκB (and a further transcription factor AP-1). It is known that corticosteroids bind a cytoplasmic receptor, following which this complex can inhibit NFκB and AP-1 by direct protein-protein interaction. Over-expression of the glucocorticoid receptor *in vitro*, both decreased the activity of the transcription factors in the absence of glucocorticoids, whilst dexamethasone produced a further additive effect. Clearly, any such novel approach is to be welcomed, but we reiterate the obstacles noted earlier concerning cell type and gene transfer efficiency given that the glucocorticoid receptor is not a secreted protein.

We have tried to present the many obstacles we perceive to establishing gene therapy as a viable treatment in the near future. Both gene transfer efficiency and knowledge of asthma pathogenesis will increase and, we believe, provide the rationale for continuing the early studies of gene therapy for the severe asthmatics who urgently require such new approaches.

Eric WFW Alton
Uta Griesenbach and
Duncan M Geddes

Ion Transport Unit
Imperial College at the National
Heart and Lung Institute,
London SW3 6LR

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