REVIEW

Pathological networking: a new approach to understanding COPD

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Developing new treatments for chronic obstructive pulmonary disease (COPD) is extremely challenging. This disease, chronic by definition, becomes apparent only after substantial—and probably irreversible—tissue damage has occurred. The observable phenotype is of a stable disease state whose progression is hard to influence and reversal of which appears almost impossible. Identifying key components of the pathological process, targeting of which will result in substantial clinical benefit, is a significant challenge. In this review the nature of the disease is examined and conceptual information and simple tissue models of inflammation are used to explore the pathological network that is COPD. From the concept of COPD as a disease network displaying the features of contiguous immunity (in which many processes of innate and adaptive immunity are in continual dialogue and evolution), refinements are suggested to the strategies aimed at developing effective new treatments for this disease.

> ''For every complex problem, there's a solution that is simple, neat, and wrong'' H L Mencken

> ''Any intelligent fool can make things bigger, more complex, and more violent. It takes a touch of genius – and a lot of courage – to move in the opposite direction'' Albert Einstein

Balancing the dilemma raised by these quotations is very applicable to chronic disease pathologies such as chronic obstructive pulmonary disease (COPD). On the one hand, simplification results in a lack of progress as we fail to appreciate the subtlety and complexity of the processes with which we engage while, on the other, demonstrating complexity may encourage nihilism and do little to advance therapeutic concepts. COPD is a multifaceted and slowly evolving disease where significant pathological changes are already present by the time of diagnosis. This presents substantial challenges with respect to understanding the pathological processes that lead to disordered structure and function in COPD, and to the development of effective therapeutic strategies in disease management. Inferences about the potential role of individual cytokines, inflammatory cells and histopathological patterns have proved to be poor predictors of the effectiveness of new treatments designed by logical criteria, and even for well-established drugs such as inhaled steroids there are still unresolved issues over dose and timing.[1 2] Here we propose that targeting single observable components of the pathological process is relatively unlikely to generate effective treatments, and instead consider conceptual and experimental evidence that suggests that combinatorial therapeutic approaches are more likely to yield valuable dividends.

A MULTI-COMPONENT DISEASE

Observational studies of the pathology of COPD and its interaction with exposures to candidate aetiological agents have identified several general processes that appear to be major contributions to ongoing disease.[3] Three key processes have received considerable attention: oxidative tissue damage, protease-mediated tissue destruction, and leucocyte-driven chronic inflammation.[3] Targeting oxidative damage using antioxidants such as N-acetylcysteine has shown efficacy in chronic bronchitis[4 5] but is relatively ineffective in established COPD.[6] Targeting tumour necrosis factor α (TNFα) to ameliorate inflammation has also been disappointing.[7 8] The use of inhaled steroids combined with long-acting β agonists to reduce exacerbation rates in more severe disease is now widely accepted, but their effects on mortality are still in doubt[1] and we have no effective strategies beyond smoking cessation to slow disease progression. Of concern, manipulation of the immune response shows trends to increased risk of pneumonia.[1 7] These data suggest that even relatively modest immunomodulators such as inhaled corticosteroids might further impact on local immunity already damaged by chronic inflammation and remodelling, rendering individuals to some degree more vulnerable to significant infections. Moreover, we lack the confidence that we are addressing the key processes that promote disease progression or clinical deterioration and, in some cases, are unsure that our agents achieve an appropriate concentration in the tissues where they are proposed to act.[6]

THE REASONS TREATMENTS FAIL

Why, then, do logical targets fail to deliver effective therapeutics, and can we learn from our failures as much as we can learn from our successes? Box 1 describes a range of reasons that might explain poor translation to treatment. Two of these—choice of outcomes and design of molecules—are beyond the scope of this review,

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Abbreviations: COPD, chronic obstructive pulmonary disease; IL, interleukin; RLH, RIG-like helicase; TNFα, tumour necrosis factor α; TLR, Toll-like receptor

Box 1 Potential reasons for treatment failure

The wrong target
- The target is a process not active in the disease
- The target is a process that is a minor contributor to the disease
- The target is a process that is an observable bystander but not a driver of pathology
- The target is a process that is not readily modifiable (eg, emphysema)

Pathological redundancy
- The target is an active component of the disease, but other processes or molecules are serving the same roles and the therapy fails to achieve an effective knock-down of pathology

The wrong outcomes
- The target is an active pathological process, but driving an outcome not examined in the study
- Neutralisation of the target requires a longer time to affect the outcome than was allowed for (or might be feasible) in the study

The wrong molecule
- The target is an active pathological process, neutralisation of which would be of clinical benefit, but the therapeutic agent has limited efficacy as a result of its pharmacokinetics, pharmacodynamics or adverse effect profile

but here we consider the choice of target and the effects of pathological redundancy.

It is apparent that the pathology of COPD comprises many processes.[3 9] Their contributions to disease are classically tackled by a strategy in which each process or strand is identified, and its unique relevance determined through selective targeting in vitro, in vivo and, ultimately, in clinical trials. This approach has much to commend it and has been highly successful in some settings such as the targeting of TNFα in rheumatoid arthritis, but it must also overcome three principal problems.

The first of these is that effectiveness requires a stringent and robust system for identifying targets, yet COPD is a poorly understood disease with a slow natural history that militates against easy validation of targets. Moreover, most assessments of the disease examine functional impairment rather than directly reflecting its pathology. Furthermore, the best opportunities for intervention may be when the disease is still in a subclinical or very early phase, but identifying such patients is challenging, let alone identifying the targets likely to result in effective therapies. The second challenge for approaches seeking specific individual disease targets is that increasing refinement of the nature of the target promotes the selection of pathways with substantial pathological redundancy. The third, and most difficult problem to overcome, is that treating observable pathology may not be treating the processes that either cause or maintain the disease.

To illustrate these dilemmas and develop integrative therapeutic approaches that may overcome them, it is helpful to consider two models: the disease landscape and the disease network. These differ from the more traditional ''linear'' or causal models of pathophysiology in several important ways, but provide a more realistic approach to how these differing mechanisms are likely to operate in practice.

The landscape of disease

We increasingly recognise that the state of health requires very active maintenance. While a variety of different stimuli (eg, infections, environmental pollution) will push the human organism away from the state of health, they will be counteracted by a complex and flexible defence and repair system which, through the institution of carefully graded responses, is designed to combat the insult and restore health (fig 1). In addition, natural cellular and matrix turnover is an energy-requiring process that has at its heart the renewal of body tissues and therefore limitation or removal of cumulative mutations and tissue damage. It follows that to perturb this state of health sufficiently that the outcome is development of disease, a considerable driving force and/or a very unlucky combination of circumstances is required. Figure 1A illustrates a concept in which health has forces acting upon it to cause disease states (eg, infections), but these are opposed by forces maintaining health (eg, the activity of the immune system). Like pushing a rock out of a crater, the generation of disease requires an active process, and immune/healing systems provide resistance to this. Importantly, if health is a stable state maintained by active processes, so also is disease. Recognition of this fact generates three major hypotheses. The first is that the event(s) that provide the escape from health to disease do not have to be present when disease is observed: consider the disease state of chronic renal failure secondary to a nephrotoxic drug, acute respiratory distress syndrome after toxic gas inhalation, or chronic COPD secondary to previous smoking. Similarly, tissue damage from one aetiology can release autoantigens from immune-privileged sites that are then targeted by the adaptive response, resulting in autoimmune disease.[10] Such mechanisms have been postulated for COPD, providing insights into the persistence of disease after cessation of smoking.[11] The second resulting hypothesis is that active processes are likely to be involved in the maintenance of the new stable state. Active maintenance of a disease state may result from misguided processes that are attempting to restore health but, as a result of functioning in a new context, are preserving disease. Alternatively, pathways normally responsible for restoration of health may not be able to fully achieve this goal, but function to keep disease in the configuration generating minimum pathology (fig 1B). Thirdly, these data highlight the fact that multiple processes will be in operation continually to preserve the status quo (be it health or disease). While accumulation of disease states might be considered to be a disorganisation of the healthy organism following the second law of thermodynamics and a trend towards chaos, in reality the diseased organism continues to show a very high degree of organisation that requires very active maintenance.

Diseases as networks

We are familiar with the concept of redundancy, where neutralisation of a pathway fails to impact on a process because other pathways that achieve a broadly similar end are maintained and possibly upregulated. It is possible to view failures of logically-targeted therapeutics as consequent upon redundancy in the pathology: stop interleukin (IL)-8 recruiting neutrophils and granulocyte chemotactic protein 2 (GCP-2; another CXC chemokine) might do it instead. An alternative view of health and disease is that the components maintaining the status quo act in a network. The worldwide web is a good illustration of such a network in which the majority of components (end user computers, known in network terminology as nodes) have few connections to other computers, but some central servers have many connections to other computers

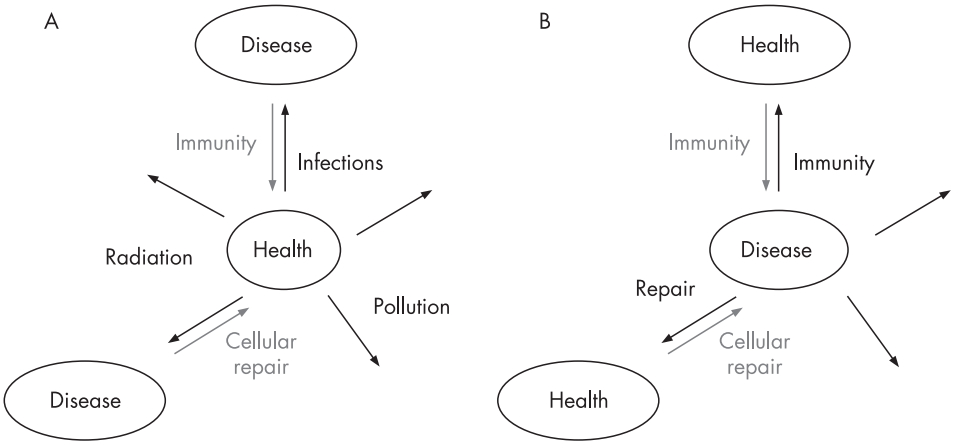

Figure 1 (A, B) The active maintenance of stable states. Preservation of health does not come about simply because stimuli driving disease have not been encountered: health requires continual active intervention of multiple systems to respond appropriately to an enormous variety of stimuli with preservation of normal tissue architecture and function. Chronic disease likewise represents another stable state maintained by active processes. In chronic disease, at best, systems whose role is to neutralise pathogens or heal tissue damage may act to delay further disease progression. At worst, processes normally maintaining health may function at the wrong intensity or in the wrong context to preserve or cause progression of the disease state.

(hubs). This kind of system is known as a ''scale-free network'' (fig 2) since small or large versions of the network exhibit largely similar characteristics, and this concept is readily applicable to biological systems.[12] Scale-free networks are hard to damage since the chances that an intervention will take out enough of the highly connected hubs is small. Likewise, perturbation of health tends not to cause disease because only a limited number of components of the network are usually affected. Equally, attempts to ameliorate disease by targeting of observable components of pathology are relatively likely to hit one or a few of the obvious network components, but these are relatively unlikely to be key hubs.

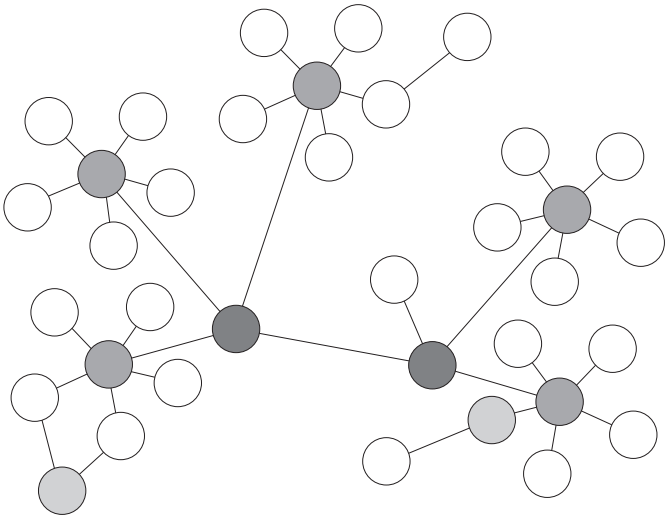

Figure 2 Scale-free networks. Many biological systems, similar to worldwide web, show features of scale-free networks. In these systems, the majority of system components have relatively few connections but some central hubs are highly connected. These networks are damage-resistant, and significant degradation of their function requires identification and neutralisation of one or more of these highly connected hubs. The components of the chronic obstructive pulmonary disease network can be visualised in several different contexts: for example, hubs may be principal cytokines and nodes cytokines for which there is marked pathological redundancy. Alternatively, in a process-centred network, specific processes such as protease function might comprise the hubs. It is hard to predict from observational studies whether, for example, individual cytokines seen to be upregulated in the disease are peripheral nodes whose function is locally limited or central hubs whose targeting is likely to result in a useful treatment. The identity of these hubs may be hard to ascertain, they may not be the most abundant cytokine or most obvious pathological component of the disease, and knowledge gained from one disease may not be directly applicable to another.

Hubs can, however, be identified and targeted. Steroids are multifunctional inhibitors of many components of the inflammatory network whose roles have been crafted through evolution to, in perhaps the majority of settings, target the key hubs of the inflammatory process. We are most at a loss therapeutically when steroids are ineffective, such as in the treatment of neutrophilic inflammation and many of the pathological aspects of COPD.[13 14]

Unfortunately, there is also no guarantee that a component that acts as a hub in one network will play the same role in another. Many key hubs are clearly based around early inflammatory cytokines that have orchestrating roles in inflammation such as IL-1 and TNF. Interestingly, targeting of TNFα is extremely effective in some inflammatory conditions (such as rheumatoid arthritis, inflammatory bowel disease and psoriasis), but has proved to be a less useful target in other conditions in which efficacy was expected, such as vasculitis[15] and COPD.[7] Even within rheumatoid arthritis, about one-third of patients show little response to this treatment for reasons that are still poorly understood. Targeting IL-1 is highly effective in some rare syndromes[16] and shows some promise in conditions such as juvenile idiopathic arthritis,[17] but is much less effective in rheumatoid arthritis.[18] Thus, the nature of the key hubs varies between diseases and, perhaps, within diseases over time.

We have previously proposed that defining the disease network can also be achieved at several levels of detail,[19 20] ranging from a process-centred network (where the nodes include definable organism responses to stimuli including leucocyte recruitment, scarring, tissue remodeling, etc.), through to the increasing complexity represented by networks of mediators or intracellular signalling pathways. Each of these networks shows features of being scale-free, where the principal hubs (therapeutic targets) are not necessarily obvious. This sensation, in which diving into one network merely displays another more detailed and complex one beneath it, is very analogous to exploring a fractal where patterns continue to repeat on a smaller and smaller scale. Before being overwhelmed by a dizzying complexity, we need to find ways of making sense of these networks at levels in which therapeutic intervention is feasible.

APPLYING THESE PRINCIPLES TO COPD

At the level of a process network, key components of the pathology of COPD are emerging. These have been reviewed in numerous excellent articles elsewhere[3 21] and, as noted above, are thought to centre round oxidant-mediated tissue damage, protease/antiprotease imbalance and leucocyte-driven inflammation. It is immediately apparent that these three central processes are intrinsically linked. For diseases such as COPD and asthma, where aspects of innate and adaptive immunity

and inflammation exist in continual dialogue and self-modifying systems, we have coined the term *contiguous immunity* to describe these networks.[20] Exploring the mechanisms of these linkages is challenging but of great interest. Here we are faced with the challenges of developing representative and informative in vivo and in vitro models.

One approach evolving in our laboratories and those of others is to develop simple models of tissue/leucocyte interactions in vitro. In an effort to model how inflammation is initiated and the events that might surround an exacerbation of airways disease, we started to examine coculture models of primary human tissue cells and leucocytes.[22 23] Most exacerbations of asthma are driven by viral infections: likewise, bacterial and viral infections are likely to be major contributors to exacerbations of COPD.[24] Additionally, matter derived from environmental and pathogenic bacteria (such as lipopolysaccharide, bacterial proteins and DNA) are a routine part of inhaled dusts, may cooperate with or be effectively delivered by particulate matter such as diesel exhaust particles,[25] and may be present at very high levels in association with some occupational exposures. Cigarettes are also a significant source of endotoxin, providing opportunities for many synergistic interactions between endotoxin and other components of smoke.[26] Infectious stimuli are sensed by a range of receptors with dominant roles for the Toll-like receptors (TLRs)[27–29] and a recently discovered family of antiviral receptors that are collectively becoming known as the RIG-like helicases (RLHs).[30 31] TLRs comprise a family of transmembrane receptors that detect and initiate responses to bacterial cell wall constituents, bacterial and viral DNA and bacterial RNA, as well as molecules associated with tissue damage such as HMGB1 and hyaluronan oligosaccharides.[32 33] Their activation is crucial for effective defence against pathogens and also, interestingly, for maintaining healthy tissues, since absent responses to gut commensal bacteria in TLR4 knockout mice are associated with impaired healing after inflammation.[34] Furthermore, signalling through TLR4 and TLR2 by hyaluronan may be important in the maintenance of epithelial integrity in the lung after inflammatory insults and in repair.[35] This dual role of TLRs in the maintenance/regeneration of healthy tissues, as well as responses to infective insults, emphasises the active nature of mechanisms maintaining health and suggests that targeting such pathways requires consideration of the timing and nature of inflammatory process in order to downregulate detrimental signals while preserving effective immunity and healing. It is also feasible to consider activation of TLRs as a potential prophylactic strategy—a concept perhaps best seen in the hygiene hypothesis, where stimulation of TLRs and other pattern recognition systems seems to underpin reduced risks of atopic disease in individuals exposed to high levels of endotoxin.[27] TLR agonists may also be able to confer protection against infectious pathogens.[36] The RLH family comprises intracytoplasmic proteins that detect and initiate responses to viral RNAs. They complement the function of TLRs to provide robust responses to viruses, but a link to healing has not yet been clearly demonstrated.

Tissue cells such as epithelial cells contribute substantially to immunity through their ability to act as barrier cells and produce antimicrobial molecules such as defensins,[20] and are a first point of contact with many of the exogenous stimuli driving COPD. Epithelial cells, airway smooth muscle and fibroblasts can all generate large amounts of cytokine, and can directly interact with or be infected by pathogens with responses being mediated by TLRs and RLHs. Leucocytes (resident or recruited) comprise a much smaller component of the lung tissue, although at sites of inflammation their numbers can be upregulated dramatically and rapidly (eg, lung consolidation in pneumonia). While many studies have examined the antimicrobial or inflammatory responses of each cell type in isolation, we postulated that the components of the lung immune system function best when acting as a collaborative network. It is now apparent that very small numbers of leucocytes can respond to pathogens with release of mediators such as IL-1 that then act to cause substantial local inflammatory responses from tissues to which they are adjacent.[22 23] We and others have shown that these networks are generic, since collaborative signalling to inflammatory stimuli such as TLR activators occurs in cocultures of leucocytes with epithelial cells, airway and vascular smooth muscle cells and endothelial cells.[18 37–45] When tissues are directly stimulated by mimics of viral infection capable of activating TLRs or RLHs, this further facilitates the responses of the tissue cells to signals arising from the leucocytes.[22]

These data suggest that initiation of inflammation may start with a phase of leucocyte/tissue cell cooperation controlled by mediators with ''hub'' roles such as IL-1, and that targeting IL-1 during early phases of acute exacerbations (or even during infections to prevent exacerbations) may be feasible. Once inflammation is underway, however, it is likely that other networks will be rapidly established, thus targeting IL-1 may only be useful at specific phases of the disease.[20] It may be that, at these points, development of chronic inflammation and tissue destruction resulting from protease/antiprotease imbalance may come to the fore.

In established disease the nature of the network is likely to be very different,[20] and may have contributions from many sources.[46] In asthma, alterations to tissue cell phenotypes in the epithelium and airway smooth muscle are important components of the disease phenotype,[20] underpinned by genetic or epigenetic modifications of cellular function. The extent to which such altered tissue phenotypes contribute to COPD is yet to be elucidated. Responses to chronic stimuli will be altered by the ratio of leucocytes to tissue cells, and by the potential continual recruitment of fresh peripheral blood monocytes which have a different phenotype to the more quiescent alveolar macrophage. Longer exposures to bacterial molecules such as endotoxin result in responses that are, interestingly, detuned through a process called endotoxin tolerance, and alveolar macrophages from smokers show clear evidence of tolerance to lipopolysaccharide.[47] This may even result in local immunoparesis in smokers[47] which may favour persistent microbial infection, currently an area of considerable interest in this disease. Exposure to infections that may be harder to eradicate as a result of immunoparesis, impaired barrier functions and mucosal immunity,[48] altered wound healing and chronic alterations to tissue cell phenotype may drive networks that are still poorly understood.

IDENTIFYING THE HUBS IN COPD

A common approach to disease is to identify components that appear as abnormal and to target them. Examples of this approach and its potential pitfalls are seen in asthma, where targeting of eosinophil recruitment was seen for many years as one of the great new hopes for asthma treatment. While a role for the eosinophil remains possible in airway remodelling,[49] anti-IL-5 treatments have been disappointing,[50] although the eosinophil remains a good biomarker of disease activity and phenotype.[51] The ability to design mouse models with highly specific phenotypes may have led to an overestimation of the role of eosinophils, and the same models have potentially driven an over-optimistic approach to targeting single specific cytokines. We need to be wary that we do not fall into the same trap with COPD: while the neutrophil may be important in COPD, there is a risk that it will turn out to be more of a

biomarker of disease severity than an aetiological factor (or, if it is an aetiological factor, it will be at a different point in the disease—such as early disease—or need to be targeted in combination with other pathological components). It seems that a series of integrative approaches are required both to phenotype the disease and rapidly evaluate the potential for new treatments.

Detailed phenotyping is required at multiple stages of disease to understand early disease (which might be potentially reversible), exacerbations (which are certainly treatable) and the stable state of chronic disease.[19] Linkage of phenotypes based on clinical and physiological characteristics or combinations of functional measurements to the underlying pathological change, whether defined macroscopically or microscopically, remains deeply challenging.[9 52–60] Currently, for chronic disease, the best we may be able to hope for is reduction in disease progression, since these established stable states are highly resistant to change, although of course strategies to regenerate tissue by drugs or stem cells may one day be of benefit. We have already argued that it is essential that national care pathways start to view linkage to research and disease phenotyping as a core component of good clinical care.[19] The pharmaceutical industry has a major emphasis on developing biomarkers of disease processes to enable rapid testing of drugs and, while this needs our support, correlating these with clinically meaningful processes and endpoints is likely to be the work of years. Until we get a better handle on modelling disease, for which we require good phenotypic data, the efficacy of new therapeutics will be hit and miss.

Alongside good phenotyping, we need model systems in which to determine whether observable components of pathology are network hubs or merely peripheral nodes. It is not enough to extrapolate from other diseases and models and assume that individual cells, cytokines and processes are important in a given pathology. A series of in vitro models of varying complexity, ranging from simple cocultures to more complex models of the airway wall comprising several cell types and scaffold proteins,[61] based on normal tissues and on those from patients, would have much to offer. Integration with results obtained from in vivo models[62] will provide further insights into the mechanism.

DEVELOPING NEW THERAPEUTIC STRATEGIES FOR COPD

Study of the human organism shows that, to resolve inflammation, multiple coordinated processes are required. Alongside an effective immune system, organisms have had to evolve effective resolution systems. Master regulators of these systems, such as corticosteroids, tend to interface with multiple pathways and exert their effects by multiple actions. Except where we directly use this axis ourselves, our effective anti-inflammatory agents tend to be blunderbuss-style tools, depleting whole leucocyte populations by targeting T cell replication, for example. Identifying key hubs remains difficult and, given our current limited understanding of COPD, prediction of the effects of removal of a single cell type or cytokine is very challenging. One approach is to look to the rapid evolution of monoclonal antibody-type drugs to provide a large bank of new targets that can be screened in phase I trials. Leaving aside issues of safety, since most of these antibodies are likely to be antagonistic rather than agonistic, implications for future drug costs and accessibility of such treatments in the developing world are a cause for concern, although standardisation of high-volume production methods may eventually result in these drugs being remarkably inexpensive.

An alternative is to take a leaf out of the book written by evolution and look not to develop a perfect magic bullet but to develop effective combination therapies. Such combinations may be temporal (ie, drug 1 for exacerbations of disease and drug 2 for chronic disease) and/or administered simultaneously to target multiple pathways. Understanding that disease processes occur in a network allows consideration that effective targeting requires neutralisation of multiple hubs. For example, chronic reduction of monocyte recruitment by a chemokine receptor antagonist may facilitate an environment in which pulmonary responses to innate immune stimuli become less over time. Coupled with identification and neutralisation of cytokines involved in tissue remodelling and reduction in oxidative stress, such approaches may yield useful dividends. In essence, steroid therapy is already a combination therapy since it exploits the organisms' natural complex resolution mechanism. Combined with long-acting β_2 agonists in COPD or asthma, additional benefits with respect to inflammation or exacerbation rate accrue.[1 63–66] Other examples of this approach have been encapsulated to some degree in the polypill debate for cardiovascular disease,[67] or the addition of N-acetylcysteine to azathioprine and prednisolone in the treatment of idiopathic pulmonary fibrosis.[68] Complicating this, each chronic immunosuppressing strategy may be subject to specific infective and non-infective risks, as illustrated by the effects of steroids on pneumonia rates,[1] the concern over an anti-integrin monoclonal antibody and risks of progressive multifocal leucoencephalopathy[69] and, in animal models, the effect of blockade of monocyte recruitment on Alzheimer's-like processes.[70]

Looking once again to steroids, we also need to be asking other questions of the state of health; for example, determining why chronic inflammation in response to pollution and dust exposure is not the norm and why many smokers do not get COPD. Tapping into the endogenous inflammatory brakes and restorative mechanisms seen in models of healthy inflammation may yield vital clues as to how to limit disease progression. The problems with combination therapies are clear: in particular, trial design at phase I/II level would be challenging in the extreme and, where combinations of therapies are exploited that use existing drugs or products of competing companies, problems will abound.

CONCLUSION

COPD is a slowly evolving disease whose pathology still contains many secrets. Consideration of COPD as a chronic network of inflammatory processes may allow new approaches to its modelling in vitro and the development of new treatments. Without a substantial effort to link clinical care to phenotyping, and a drive to develop a variety of integrated models of disease whose outcomes can link with clinical studies and inform work assessing the utility of biomarkers, development of new therapies will remain very ''hit and miss''. A better appreciation of the complexity of the interactions between the processes already identified in patients with COPD should permit better therapeutic targeting of the next generation of COPD treatments.

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