

REVIEW

Asthma, nasal polyposis and ulcerative colitis: a new perspective

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Introduction

Asthma, nasal polyposis and ulcerative colitis are diseases of unknown cause, characterized by a Th2-type inflammatory response. In the past 40 years there has been a marked increase in the prevalence of these diseases, comparable with an epidemic [1].

Background

In 1950 Francis L. Weille first proposed that intrinsic asthma and nasal polyposis are caused by an 'allergy virus' [2]. In 1956 Weille and Gohd [3] cultivated and passaged in chick embryos an unknown virus from nasal polyp tissue, using as a test for the presence of the virus an increase of the protein concentration in the allantoic fluid. In 1966 Weille [4] showed that the serum from patients with nasal polyposis contains antibodies to nasal polyp antigen, and the serum from each patient cross-reacts with the antigen from the other patients. In 1970 Popova et al. [5] also found that the serum and polyp fluid from patients with nasal polyposis contain antibodies to nasal polyp antigen, but they interpreted their data in favour of an autoimmune aetiology of nasal polyposis.

In 1979 Gitnick and coworkers [6] isolated 60 nm viral particles from colonic filtrates obtained from ulcerative colitis patients. Part of the data reported were later found to be invalid by McLaren and Gitnick [7], and in 1984 Yoshimura et al. [8] were unable to reproduce Gitnick's work. These negative results can be explained by the very low productivity of the virus and the absence of overt cytopathic effects in host cells, problems also encountered by Weille and Gohd, who were unable to passage the virus more than nine times and could not detect any cytopathic effects in infected chick embryos. In 1988 Szczeklik [9] proposed that aspirin-induced asthma results from a chronic viral infection, a concept still considered viable in current literature [10–12]. More recently, Hogg [13, 14] proposed that latent viral infections are important aetiological factors in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD).

The hypothesis

Asthma, nasal polyposis and ulcerative colitis are caused by a lentivirus that infects the fibroblasts of the lamina propria of the bronchial, nasal or intestinal mucosa, respectively. The infected cells secrete a viral protein, the envelope glycoprotein, which

acts as an allergen. Individuals who respond to the infection with a Th2 reaction are susceptible to the disease, while individuals who respond with a Th1 reaction are resistant. In the fibroblasts the infection is not productive, and after the viral genome gets integrated into the host cell's genome, the envelope gene is actively transcribed. The secreted envelope protein acts as a decoy on the immune system by inducing a strong Th2 response, which interferes with the Th1 response that would lead to the clearing of the virus (see [15]). In asthma this inflammation is at the origin of bronchial hyper-responsiveness, and is a predisposing factor for the development of asthma after exposure to inhaled allergens (by lowering the threshold for an asthmatic response). The severity of the disease is determined by the degree of sensitization to the envelope glycoprotein, but other genetic factors may also be involved. I call this virus 'fibroblast-associated retrovirus' (FAR).

The secreted envelope protein elicits a typical Th2 response, with degranulation of mast cells and influx of eosinophils. Cytokines and mediators released by eosinophils and mast cells activate fibroblasts, enhancing proliferation and increasing protein synthesis [16–28]. As a result, more envelope protein is released, and a vicious cycle is initiated; under these conditions the disease is in an active state. Corticosteroids, by inhibiting both eosinophils and fibroblasts, break this vicious cycle and induce a state of remission. In the bronchi, the constant release of FAR envelope glycoprotein within the subepithelial layer leads to activation of eosinophils, release of transforming growth factor- β (TGF- β), and airway remodelling [29].

The concept of an internally generated allergen explains the findings that activated or degranulated mast cells are more numerous in the deep stroma of nasal polyps compared with the part near the surface [30–32], and that mast cells from the stromal compartment, but not those from the epithelium, release a significant amount of histamine after stimulation with anti-IgE antibodies [33]. Also, IgE-producing plasma cells are consistently found in the stroma of nasal polyps [34–38]. Similarly, an elevated number of cells expressing mRNA for the ϵ germ-line transcript and the ϵ heavy chain of IgE has been reported in the bronchial mucosa of asthmatics [39, 40], suggesting the presence of an unidentified, possibly viral, allergen [41]. Numerous IgE-producing plasma cells have also been observed in the intestinal mucosa of patients with ulcerative colitis [42–45]; again, there is evidence for a specific immune response to a yet unidentified antigen [46, 47].

An intriguing aspect of asthma and nasal polyposis is aspirin sensitivity, or better, non-steroidal anti-inflammatory drug sensitivity. An acute attack precipitated by aspirin is similar to an IgE-mediated anaphylaxis [11, 48], with release of mediators by mast cells [49–61], although no causative antigen has been identified. *In vitro* studies have shown that inhibition of cyclooxygenase (COX), in the presence of TGF- β or bradykinin,

leads to an increase in protein synthesis and secretion by fibroblasts [62–66]. As a consequence, fibroblasts infected with FAR will release envelope protein, causing highly sensitized individuals to respond with an anaphylactic reaction. The delayed and progressive time-course of the reaction [67, 68] suggests a protracted release of antigen by fibroblasts. This mechanism of aspirin sensitivity should be viewed in the context of a genetically altered arachidonic acid metabolism, where a marked down-regulation of COX-2 [69] leads to a low basal concentration of PGE₂ [32, 70, 71], which renders fibroblasts more sensitive to the effects of COX inhibition; an increased basal concentration and production of LTC₄, reported in aspirin-sensitive but not in aspirin-tolerant asthmatics [32, 49, 72–79], may also contribute to fibroblast activation [80]. Therefore, the sudden lack of the inhibitory action of PGE₂, together with an elevated concentration of LTC₄, leads to fibroblast activation and release of FAR envelope glycoprotein; subsequently, and for as long as COX is inhibited, a compensatory increase in the synthesis of nitric oxide [81–84] will exert a similar inhibition on fibroblasts [85], resulting in a refractory state. After aspirin administration, it may take 5 to 7 days before prostaglandin synthesis returns to normal [86]. Several substances have been shown to prevent or, in most instances, attenuate aspirin-induced asthma when administered prior to challenge [52, 58, 67, 68, 87–110]. Of these, PGE₂ and β -agonists act by preventing fibroblast activation and release of FAR envelope glycoprotein [63, 65, 111–115], while leukotriene receptor antagonists, cromolyn sodium, ketotifen and clemastine inhibit the anaphylactic reaction that follows the release of the envelope glycoprotein.

In the tissue FAR spreads by cell–cell contacts (at a speed of 1 to 2 cm per year). The infected fibroblasts show no abnormalities, although occasionally may present a pseudosarcomatous alteration, which has been observed in nasal polyps [116–122] and in the pseudopolyps associated with ulcerative colitis [123, 124]. In the bronchi the infection starts in the larger airways (causing asthma responsive to inhaled β_2 -agonists), and slowly spreads towards the small peripheral airways (causing asthma requiring steroid treatment). In the intestine the infection generally starts in the rectum and slowly spreads proximally, very often silently; viral or bacterial infections and food allergens can exacerbate the disease, or activate a silent infection. In the population FAR is transmitted by the oral–oral route and causes, in susceptible individuals, an influenza-like illness followed by the chronic disease.

Several other diseases are probably or possibly caused by FAR. Among these: interstitial lung disease (ILD), hypertrophic scars and keloids, nodular fasciitis, myxomatous degeneration of heart valves and pinguicula. In these lesions the virus probably originates from peripheral blood fibrocytes, which target injured tissues [125, 126]. FAR may also be a factor in the pathogenesis of COPD, by enhancing and perpetuating the inflammatory response caused by cigarette smoke. Furthermore, FAR is at the origin of vasoactive intestinal peptide (VIP) natural autoantibodies [127], which have a higher VIP-binding affinity in asthma patients compared with healthy subjects [128, 129]. The sequence from FAR envelope glycoprotein responsible for these antibodies is homologous to the sequence RSANFTDNAKTIIVQLNESV from the second conserved region of HIV-1 gp120 envelope protein (see [130, 131]); this sequence from HIV-1 also shows similarity with the equine

infectious anaemia virus envelope protein (e.g. gi1177059 and gi2627425).

Chloroquine and hydroxychloroquine have been shown to be effective in the treatment of asthma [132, 133], ulcerative colitis [134] and ILD [135, 136], presumably because of their anti-inflammatory activity. Since these drugs inhibit the production of the envelope glycoproteins of HIV-1 [137, 138] and of the avian reticuloendotheliosis virus (a type C retrovirus) [137], it is possible that their therapeutic efficacy is also due to inhibition of the production of FAR envelope glycoprotein.

Conclusions

We should not be surprised if diseases well characterized and much studied, but still of unknown aetiology, are found to be caused by novel infectious agents [139–142]; many important pathogens still wait to be discovered! But how could this new virus be isolated and sequenced? By constructing a complementary DNA expression library from nasal polyp tissue, and screening it with the patient's serum. What treatment could eradicate the virus? Immunotherapy with the envelope glycoprotein, or part of it, conjugated to immunostimulatory oligodeoxynucleotides [143], to induce a switch to a Th1 response.

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