

Host defenses

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Abstract

Repeated episodes of viral upper respiratory tract infections occur anywhere from four to eight times per year in healthy individuals. Local and systemic defense mechanisms exist to battle respiratory tract pathogens. Clinical manifestations are mainly due to host inflammatory response. Unfortunately, the host defense mechanisms are very often not sufficient to prevent subsequent/repeated episodes of infection(s). Further insight into the interaction of infectious agent and host immune response, genetic factors, and environmental factors is needed for a better understanding of why humans repeatedly and frequently suffer from infections with respiratory agents and develop a disease syndrome known as common cold.

Introduction

Human beings have come to accept common colds as a 'fact of life'. A cold is mostly a self-limited illness. However, when considered cumulatively, about 1 year of one's life span may be spent confined to bed, or at least at home, recovering from colds. More importantly, our responses to this infection vary significantly, both intra- and inter-individually. One explanation is that many viruses – over 100 serotypes of rhinovirus alone – cause this illness, thus manifesting disease in different manners. Nevertheless, even the same virus may be asymptomatic, or cause a mild illness in one person, while another person may develop a life-threatening illness. The exact mechanisms for these variations have yet to be elucidated, but interplay between the viral virulence factors, host immune response, and viral immune evasion strategies are likely involved. Viral infections may precede secondary infection by other pathogens, precipitate asthma exacerbations, cause severe disease in the lower respiratory tract, and even induce autoimmunity [1]. It is also important to acknowledge that uncomplicated common cold symptoms including sneezing, coughing, hypersecretion resulting in runny nose

and local inflammation itself may be interpreted as a complex host defense mechanism with the goal to eliminate the pathogen.

Local defense mechanisms

Nasal vestibule temperature regulation

Temperature of the nasal vestibule is the first host defense mechanism that a virus that causes common cold encounters. Increased incidence of colds during the cold winter months, and in those exposed to extreme cold weather gives us some insight into this defense mechanism [2]. A factor that contributes to the seasonality pattern of common cold may be cooling of the nasal mucosal epithelium, which inhibits mucociliary clearance as well as leukocyte phagocytic activity. On the other hand inhalation of warm vapor may alleviate nasal congestion associated with a cold. Nasal resistance as measured by a rhinomanometer increases with reducing room temperature [3], and that increase is more pronounced in summer than in winter. The latter may be due to cold adaptation of the nasal mucosa in winter.

Mucociliary clearance

Nasal airflow decreases and mucociliary clearance time is prolonged during colds. These changes correlate with abnormalities on sinus CT, and tend to be more common in allergic subjects [4]. Mucociliary clearance transport rate is markedly reduced during acute illness, and slight impairment may persist for about a month [5]. In addition, the number of ciliated nasal epithelial cells decreases, their regeneration slows down, and their beating frequency and intracellular synchrony are changed. Impaired nasal mucosal function in patients with rhinitis correlates with the rheological characteristics (viscosity, elasticity, adhesiveness, spinability, and pourability) of nasal mucus [6].

Nitric oxide (NO) regulates mucociliary activity, and has antiviral and bacteriostatic effects [7]. Increased production of exhaled NO in nasal and lower airways may play a beneficial role in clearance of rhinovirus infection [8].

Local/mucosal immune response

Approximately 90% of microorganisms infecting humans use the mucosae as entry portal. Thus, mucosal epithelia represent an important surface barrier for agents causing respiratory diseases like common cold. The mucosa is protected by numerous effectors of the innate immune system that closely work together with those of the adaptive immune system. Induction of

mucosal immune responses occurs in the respiratory tract in Waldeyer's ring, which includes nasopharynx-associated lymphoid tissue like adenoids and the tonsils, although the major part of organized mucosa-associated lymphoid tissue (MALT) is located in the gut (gut-associated lymphoid tissue, GALT, e.g., aggregated Peyer's patches and isolated B-cell follicles). At least 80% of all immunoglobulin (Ig)-producing plasma cells and blasts are located in intestinal lamina propria. Approximately 90% of terminally differentiated B cells produce dimers or large polymers of IgA, which are transported externally as secretory IgA (SIgA) by an epithelial component (membrane secretory component, SC) [9]. The bronchus-associated lymphoid tissue (BALT) is thought to represent a major site in which IgA isotype switch and differentiation of B cells occur [10]. Since this is not a constitutive feature of normal human lung, other parts of the human respiratory tract like the airway epithelium are believed to fulfill supporter functions, e.g., by constitutively producing interleukin (IL)-5, a cytokine with functions for the growth and differentiation of IgA-producing plasma cells [10].

IgA and IgM share the same transport mechanisms because both components contain a similar joining (J) chain [9]. SIgA is able to inhibit invasion and colonization of pathogens, and polymeric forms of Ig may even inactivate viruses inside of secretory epithelial cells and transport them back to the luminal side [11].

Nasal mucosal IgA production is activated during common cold. Salivary Ig secretion rate is reduced in patients with recurrent respiratory infections [12, 13]. Rhinovirus infection induces respiratory epithelial expression of human beta defensin (HBD), a potent stimulant of dendritic cells, suggesting that HBD may play a role in host response to this infection [14]. Influenza virus and respiratory syncytial virus (RSV) mobilize different proportions of immune cells to the nasal respiratory mucosa [15]. Larger numbers of myeloid dendritic cells, plasmacytoid dendritic cells, and monocytes, as well as higher concentrations of monocyte chemoattractant protein-1 concentrations are present in nasal wash samples of patients with influenza [15] (Fig. 1).

Breastfeeding

Common cold is of particular importance for infants. Therefore, when discussing local or mucosal immunology of common cold, it is necessary to briefly review the role of breastfeeding. The interaction between the innate and the adaptive immune system is a prerequisite for the successful defense against respiratory pathogens. This cooperation is of particular interest for newborns because of the immediate exposure to a broad variety of microorganisms after birth. In this context, breast feeding is important for two main reasons, (i) the transfer of antibodies, and (ii) the provision of immunomodulating properties. Lactating mammary glands reflect the status of the

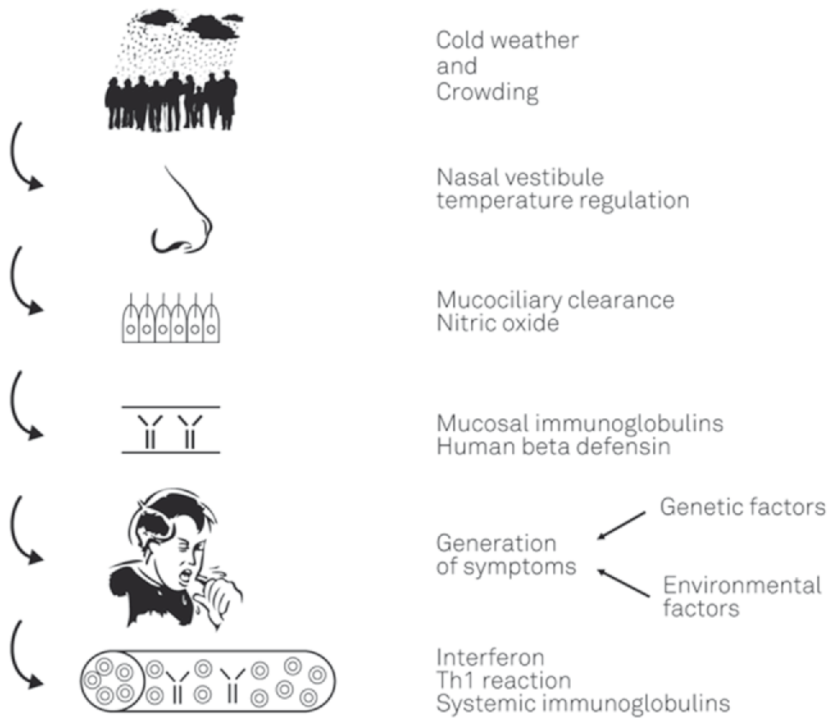


Figure 1. Stages of host defenses.

integrated mucosal immune system of the mother [9, 16] in both gut and airways. Secretory antibodies are targeted against infectious agents in the mother’s environment (which are likely to be encountered by the infant during its first weeks of life). SIgA from breast milk has been shown to exhibit specificity to a variety of common intestinal and respiratory pathogens [9, 16]. Interestingly, the protection is not only demonstrable in populations living in poor sanitary conditions. The beneficial effect has also been demonstrated in developed countries [17]. In a recent analysis of approximately 400 observational studies, it was shown that a history of breastfeeding was associated with a reduction in the risk of acute otitis media, nonspecific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis and asthma in young children [18]. In addition to the antibodies in the milk, numerous other factors are thought to protect the breastfed newborn. These are innate defense factors including lysozyme, lactoferrin, peroxidase, and complex oligosaccharides that may serve as receptor analogues as well as fatty acids and mucins. In addition, colostrum leukocytes ($\sim 4 \times 10^6/\text{ml}$) play an important role in the protection of the suckling newborn. Macrophages constitute 55–60%, neutrophilic granulocytes 30–40% and lymphocytes (mainly T cells) 5–10% of the cells in colostrums [9, 16, 17].

Systemic immune response/symptoms

The systemic immune response may be influenced by a variety of factors such as general condition, socioeconomic status, levels of maternal antibodies, gender or ethnic group. Because of the multiple interactions between the pathogen and the host's immune system, how local and systemic immune responses are distinguished depends on definitions. In the general population, adaptive immune response in the form of neutralizing antibodies develops in only about 50% of rhinovirus infections [19]. Immunocompromised individuals, including infants, the elderly, and those who are immunosuppressed either by underlying disease or iatrogenically, may suffer severe illness following a common cold [20, 21].

Type-I IFN represent the early, innate antiviral immune response [19, 22]. Even though this response may occur in only a third of patients, experimental administration of IFN reduces the severity of symptoms of the common cold [23]. T cell response to rhinovirus infection is serotype-cross-reactive, with Th1 reaction predominating [24, 25]. In patients with asthma, bronchial epithelial cells have a deficient innate immune response to rhinovirus infections [26]. In these individuals, impaired expression of IFN results in increased viral replication and impaired apoptotic response to rhinoviral infections.

Several weeks following rhinovirus infection, neutralizing antibodies develop in serum and secretions, representing an adaptive immune response [27]. High levels of rhinovirus homotypic serum neutralizing antibodies are associated with fewer and less severe infections [28]. This is not likely to be a reliable protective mechanism for an acute situation – recovery from illness usually occurs within 7–10 days, clearly before the development of these antibodies, and only about half of those infected actually develop them. Even though these antibodies may persist for up to 1 year, they are so specific that infection with other serotypes is possible.

For RSV infections, however, neutralizing antibodies have been found to contribute to viral clearance from the respiratory tract [29]. Also for RSV infections, a Th2 type immune response (favoring the humoral instead of the classical cytotoxic response) has been suggested to play a role in the pathogenesis of asthma [30].

For many viruses, the cytotoxic or cellular immune response is important for viral clearance. Systemic mediators but also epithelial-derived pro-inflammatory cytokines create a Th1-type cytokine environment within the infected tissue, necessary to eradicate the virus infection [31]. The lack of cytopathic effects in the respiratory epithelium contributes to the rapid recovery from common cold, when compared to other infections such as influenza.

Fever as a manifestation of the systemic immune response occurs during the course of an infection. For instance, 30–40% of RSV-infected individuals develop fever. Fever is also commonly observed during parainfluenza virus

infection, adenovirus infection [32] but less frequently during rhinovirus infection.

As already mentioned above under systemic immune response, a variety of factors may influence the clinical outcome and the disease severity of a common cold. Genetic factors have been described to play a role in the immune response since infants under 6 months of age with bronchiolitis associated with rhinovirus are more often IL-10 -1082 allele G non-carriers, i.e., homozygous for allele A (AA) [33].

There is ample evidence demonstrating an association between common cold symptoms and various inflammatory mediators. However, the role of specific mediators might be speculative until specific inhibitors have been studied in clinical trials. After rhinovirus infection, the proportion of infected nasal epithelial cells is low and there is not much support for direct viral cytopathic effects on the nasal epithelium [34]. Therefore, the pathogenesis of rhinovirus-induced disease is more likely due to inflammatory responses of the host, than to direct effect of the virus [34]. Although the link between the host's immune response to the clinical symptoms might be generally true for a variety of respiratory tract pathogens, it is safe to say that differences with respect to the interactions of individual pathogens with the host's immune system exist, resulting in a variety of clinical manifestations. For example, rhinoviruses are seen as typical pathogens causing common cold [34], RSV is known to cause common cold, but RSV is also a major producer of bronchiolitis, pneumonia and lower respiratory tract infection [35]. Adenoviruses may play a role in the pathogenesis of chronic obstructive pulmonary disease [36] and a respiratory coronavirus, the SARS-coronavirus is able to cause a severe acute respiratory syndrome resulting in high mortality [37, 38].

Rhinovirus infections of the nasal mucosa results in a number of symptoms including local vasodilatation and increased vascular permeability, due to cholinergic stimulation, manifesting in rhinorrhea, nasal obstruction and sneezing [20]. The host's response is mediated by pro-inflammatory cytokines, including IL-1 β , IL-6, IL-8, IL-11 and TNF, and chemokines, such as RANTES (regulated on activation, normally T cell expressed and secreted), which in turn attract leukocytes and dendritic cells [21]. Increased concentrations of IL-1, IL-6 and IL-8 have been reported in nasal secretions of symptomatic subjects with rhinovirus. The concentrations of IL-6 and IL-8 appear to correlate with the severity of common cold symptoms [34]. In addition to IL-1, IL-6 and IL-8, other pro-inflammatory mediators such as the kinins bradykinin and lysylbradykinin have been detected in nasal secretions of volunteers with rhinovirus-induced colds [34]. However, the role of these kinins in the pathogenesis of common cold symptoms is not clear. Although intranasal challenge of uninfected volunteers with bradykinin resulted in symptoms of nasal obstruction, rhinorrhea and sore throat, bradykinin antagonists failed to moderate common cold symptoms [34]. The reasons for this finding remain speculative at this point.

In summary, the picture of systemic host defense mechanisms is complex. Neutralizing antibodies are known to be generated against a variety of respiratory viruses. However, protective immunity appears generally weak and repeated infections are frequently observed.

Environmental factors, exercise, co-infections

People with more diverse social networks are less susceptible to common cold, produce less mucus, have more effective nasal ciliary clearance, and shed fewer viruses [39]. Possible explanations include increased motivation to care for oneself, manifesting in increased health-promoting behaviors and reduced psychological distress. The latter is associated with lower levels of epinephrine, norepinephrine, and cortisol, which affect cellular and humoral immune responses to infection.

Exercise may reduce the risk of upper respiratory tract infections by transiently increasing the leukocyte count or salivary IgA [40]. On the other hand, elite athletes suffer a higher rate of colds during intense training and competition season than recreationally competitive athletes [41].

Viral co-infection may occur in about 5% of cases of common cold [42]. Viral and bacterial co-infection is uncommon, occurring in <1% of cases [42]. The impact of these co-infections on the host defenses and the resolution of illness are not well understood.

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