

Chapter 5

Common Cold and Flu



The common cold is a very common viral infectious disease, as its name indicates, which no one can avoid during their whole life. Medically, the mortality rate of this disease has been known to be zero. Even flu, which is more morbid and toxic than the common cold, has a mortality rate near around zero. Most of the causative agents of the common cold are viruses, especially RNA viruses, such as the rhinovirus, corona virus, adenovirus, Coxsackie virus, and so on. Even though there are some common colds of bacterial origin, actually, their proportion is very small. In addition, they can be treated successfully by potent antibiotics, whereas optimal regimens for the successful eradication of the common cold of viral origin are not available yet. The main symptoms of the common cold, although they depend upon the initial site of infection, are runny nose, mild fever, throat pain, cough, and headache (rare). Because the common cold is a disease occurring only in the respiratory system, especially in the upper respiratory system, physicians usually call it a URI (upper respiratory infection). Therefore, before explaining the common cold in detail, the structures of the respiratory system will be reviewed briefly.

Structures of the Respiratory System

Respiration can be defined as gas exchange between O_2 and CO_2 , which takes place in the lungs (pulmonary respiration, in which O_2 moves from air space to capillaries, while CO_2 moves in the opposite direction) as well as in tissues (tissue respiration, in which O_2 moves from blood to cells, while CO_2 moves in the opposite direction). The final goal of respiration is to supply all cells in the body with O_2 , one of the important components for power generation, and to expel out CO_2 generated in the cells during the power generation process. The respiratory system is a group of structures for pulmonary respiration, consisting of an air conduction portion and a respiratory portion (Fig. 5.1).

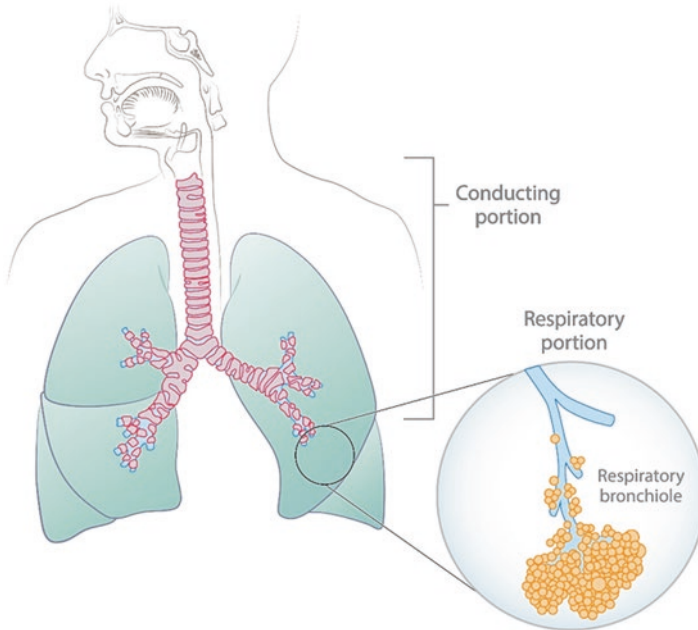


Fig. 5.1 Respiratory system consists of conducting and respiratory portion. The nose, pharynx, larynx, trachea, bronchus, and several divisions of bronchioles to terminal bronchiole are included in conducting portion. Respiratory portion, where the gas exchanges take place, contains respiratory bronchiole and alveoli

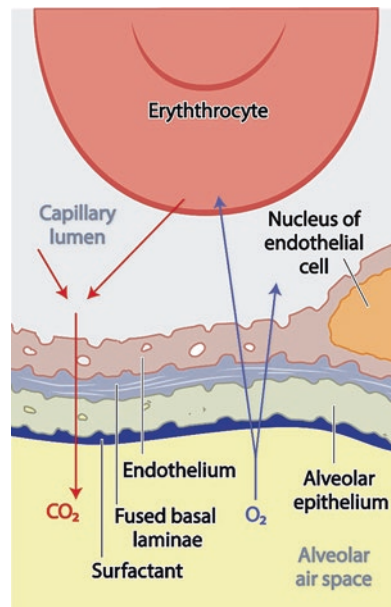
The air conduction portion is composed of the nasal cavity, pharynx, larynx, trachea, bronchus (divided in a dichotomous manner more than 20 times), and finally terminal bronchiole in that order from outside to inside, where gas exchange never takes place, but gases (O_2 or CO_2) are transported from the outside to inside or vice versa. The main functions of the air conduction portion are conditioning the air for pulmonary respiration as well as air conduction as its basic function. Conditioning of the air includes three actions, (1) air cleaning, (2) air warming, and (3) air moistening. Interestingly, the nasal cavity, the first part of the conduction portion, has complicated structures for conditioning of the air such as dome-shaped nasal alae (their inner space is the nasal ventricle), making air warm and moistened by slowing the air speed, and three shelves (inferior, middle, and superior conchae) projected from the nasal septum in the nasal cavity, making air warm, moistened, and clean by increasing the contact of the ingested air with typical respiratory mucosal epithelium having moisture and warmth from the rich capillaries by causing air turbulence, in addition to its basal function, air conduction. Especially, mucin secreted from the typical respiratory epithelium of the nasal cavity is so sticky that it gets rid of the particulate materials such as dusts and microorganisms easily through their adhesion to the sticky mucin, which is called the “air cleaning process.” The larynx also has its proper function, phonation, for which it has several

small cartilages and small muscles connecting each cartilage, besides its air conduction function. Needless to say, the air passing through the entire air conduction portion is fully conditioned air, e.g., cleaned, moistened, and warmed appropriately, arriving at the respiratory portion. The air conduction portion from the bronchus to the terminal bronchiole is called the bronchial tree, which also has a typical respiratory epithelium on their luminal surface. The typical respiratory epithelium consists of several cell types: (1) tall columnar cells are the most abundant ones and have numerous cilia on their apical surface; (2) mucous goblet cells, looking like a typical wine glass, have many polysaccharide-rich mucin droplets on their surface; and (3) there are some miscellaneous cells.

Functionally, all cilia of the tall columnar cells are fully covered by spreading out the polysaccharide-rich mucous droplets produced by mucous goblet cells, forming the mucociliary blanket. The sticky mucin component laid on the cilia adsorb chemical substances, tiny particles, and even microorganisms, which are removed effectively by one-way movement (from inside to outside) of the mucociliary blanket. Therefore, a substantial amount of mucous fluid drains from the bronchial tree into esophagus, a pathway to the GI tract that is the crossroads in the laryngopharyngeal area between the respiratory and GI tracts, every day in humans.

The respiratory portion starts from the last and smallest bronchiole, called respiratory bronchioles, which have alveoli intermittently on their way to the terminal portion of respiratory pathway, the alveolar sacs, which are composed of numerous alveoli. Wide networks of capillaries cover the external surface of each alveolus, forming the blood air barrier, consisting of the alveolar epithelium and endothelium of its covering capillary, and the fused basal laminae present between them (Fig. 5.2).

Fig. 5.2 Blood-air barrier. O_2 (blue arrows) in the air inhaled into alveoli gets through the blood-air barrier into the capillary, while CO_2 (red arrows) transported from cells to the alveolar capillary is penetrated to the alveolar space through the blood air barrier, which consists of alveolar epithelium, fused basal lamina, and capillary endothelium



Conclusively, O_2 in the alveoli moves into blood capillaries through the blood air barrier, while CO_2 in the blood capillaries is transported to the air spaces in the alveoli through the blood air barrier, eventually evacuated to the outside of the body.

Pathogenesis of the Common Cold

There is no doubt in the fact that the direct initiating factor of the common cold is low temperatures, i.e., coldness, especially relative coldness, which means a sense of feeling cold due to an unexpected sudden change in the temperature from high to low. Here, coldness does not mean an absolute extremely low temperature routinely experienced in both arctic areas year-round. Therefore, although the outdoor temperature can be higher than $30\text{ }^\circ\text{C}$, people attending a meeting in a room where the air-cooling system is operating well with the indoor temperature kept around $24\text{--}25\text{ }^\circ\text{C}$ cannot help but feel cold for a relatively long time, and they can catch the common cold. Generally speaking, traditionally, the incidence rate of the common cold during the hot summer has been very low. In the Korean proverb, “Even the dogs do not catch colds in May and June of the lunar calendar.” Understanding that May and June in the lunar calendar indicate a midsummer time, it means that Korean people rarely catch cold in the midsummer time. However, nowadays, the rate has become relatively high such that it is very common to see cold patients during the summer time because air-cooling systems are found everywhere. It is no wonder to see that the incidence rate of the common cold is not particularly high in the arctic areas where absolute coldness persists year-round, as well as during the cold winter time, when severe cold temperatures persist, because they do not usually feel cold due to routinely being exposed to severe coldness as well as having low viral colonization due to severe low temperatures. Actually, relative coldness means the temperature at which people feel cold in real life. When people feel cold or chilly, a couple of responses take place in their body to keep the core body temperature constant ($37.5\text{ }^\circ\text{C}$). First, vascular constriction around the inlet area of air occurs, typically the mucous membrane of the nasal cavity, resulting in a reduction of mucus secretion containing various antiviral soluble mediators, such as interleukins, $TNF\text{-}\alpha$, $IFN\text{-}\gamma$, and so on, and followed by an explosive increase in the nasal viral flora such as adenovirus and rhinovirus by their rapid proliferation. The nasal viral flora proliferates easily in the relatively cold weather, which causes the relative humidity to become low. A relatively low temperature and dryness are good conditions for viral proliferation and invasion to the body. Dryness usually causes injuries in the nasal mucosa, which supplies the route for the initial viral invasion. When the human physical defense system weakens or is broken and viral proliferation increases, the balance between the human body defense system and the viral flora tends to shift to the viral flora, resulting in catching the common cold. That is the reason why there are common cold or flu outbreaks in the late fall season and the transitional season from the hot summer to the cold winter. When the common cold starts just after a prolonged exposure to relative coldness, the first symptom of the

common cold is usually a runny nose, which functions to wash out the increased viral flora so that the number of virus infected cells decreases. Moreover, people in good physical condition ordinarily do not catch the cold, while people who are not healthy ordinarily due to prolonged fatigue, overwork, or insomnia usually catch the cold. Once people catch the cold, the next symptoms after a runny nose are a sore throat and systemic fever. A sore throat means that tissue invasion by the proliferated viral flora has started, followed by inflammation which usually consists of four classical signs of redness, swelling, pain, and heat. Systemic fever is a very important innate defense. The higher the body temperature is to some extent, the lower the proliferation rate of the virus is. Therefore, normal body temperature itself (37.5 °C) is a very important body defense against bacterial or viral infection. Actually, bacterial or viral proliferation is strongly inhibited by high temperatures (higher than 37.5 °C). Because it takes a little time (minimally 2–3 days) to activate the adaptive, specific immunity for invading bacteria or a virus, the body defense system uses the high fever as a non-specific defense tool immediately upon viral infection, which works in a very short time. That is the reason why early use of antipyretic agents should not be done for a high fever occurring in the common cold or flu. However, a high fever should be cautiously controlled by pediatricians in the case of young-aged people in whom brain damage is likely to be caused by febrile convulsions. Acute symptoms of the common cold are usually terminated within 3 days, at the longest 5–7 days, before the specific adaptive immune system is fully active, unless a secondary bacterial infection is also present. There are a couple of reasons why actually vaccines for the common cold are not available. One is that the common cold comes from an imbalance between the human defense system and the normal viral flora, which normally reside at the initiation part of the respiratory system such as the nasal cavity and nasal or oral pharynx so that they usually do not induce new immunity against the normal floral virus. The second reason is because there are more than 200 viruses that cause the common cold. The third reason is because the common cold has been called a self-limited disease in which it takes just a few days to be cured so that mainly the innate immunity must work but the adaptive immunity does not need to be activated for the eventual termination of the common cold.

One more thing is to be considered seriously; the common cold and flu are totally different. The flu is never a severe cold. Clinically, it is not easy to tell the flu from a common cold, although there have been some differences in clinical symptoms. Briefly, the main symptoms of the common cold are runny nose, mild fever, cough, and sometimes sore throat, while those of the flu are high fever, myalgia (muscle pain), headache, sore throat, and generalized weakness (lethargy) (Table. 5.1).

Unlike the common cold, which is usually not infected by a foreign pathogen but is just a kind of battle between the body defense system and the normal flora of viruses residing in the upper respiratory system, the flu is a disease caused by an influenza virus infection. Thus, the common cold takes place at any time year-round whenever people feel coldness for a relatively long time, while flu outbreaks occur only during some restricted periods (in Korea from October to April of the next year) when the influenza virus is prevalent.

Table 5.1 Differences in clinical symptoms between the flu and the common cold

	The flu	The common cold
Runny nose	Yes (less common)	Yes (very common)
Cough	Yes (less common)	Yes (common)
Sore throat	Yes	Yes
High fever	Yes	Rare (low-grade fever)
Headache	Yes	Rare
Myalgia	Yes	Rare
Lethargia	Yes	Rare

Change in the Common Cold or the Flu

In March 2003, the WHO reported officially that a new unidentified fatal disease has appeared in Hong Kong. It was discovered that the disease is a kind of variant of the common cold caused by a variant coronavirus, which supposedly originated from musk cats raised by some farmers in Guangdong, China, in November 2002. The coronavirus is a single-stranded RNA virus and has a species specificity as the causative viral agent of infection. However, a genetically modified coronavirus of the musk cat has a new capability to infect beyond the interspecies barrier. It was not just the matter of crossing the interspecies barrier. Even though its genetic structure has changed, it is just one of the new causative agents of the common cold, which causes people to become infected with the common cold. Unfortunately, some of the patients infected by this variant coronavirus have died. The autopsy of the dead cases revealed that the specific cause of death was viral pneumonia, which rarely occurs in routine common cold patients. Since then, the common cold caused by the variant coronavirus is called severe acute respiratory syndrome (SARS). Epidemiological data show that the mortality rate of SARS has reached around 10% (about 780 people dead out of about 83,000 patients), which is high enough to cause people to panic, considering that the mortality rate of the original common cold is near zero.

At the end of March 2009, a new strain of type A influenza virus was reported for the first time from a 10-year-old child admitted to one clinic located in San Diego, USA, with the chief complaints of high fever, cough, and vomiting. It turned out to be a novel swine-origin influenza A (H1N1) virus that caused the infection. Thereafter, this novel flu has spread out to the whole world, resulting in the occurrence of more than 130,000 patients and dead cases of more than 800 people. Fortunately, this novel flu could be controlled successfully by the administration of Tamiflu, which does not have any treatment effects on the seasonal flu despite having the same serotype (H1N1). Therefore, many researchers think that the actual mortality rate of this novel swine-origin influenza A might be more than 10%. Influenza virus has two kinds of antigens, which consist of hemagglutinin (H) and neuraminidase (N). Hemagglutinin has 15 subtypes (H1~H15), while neuraminidase has 9 subtypes (N1~N9). A combination of H subtypes and N subtypes makes theoretically 135 sub-serotypes of influenza A virus such as H1N1, H3N2, H5N1, H7N9, and H15N9. According to scientific reports, humans are usually infected by

influenza virus with low numbers of H (H1~H3), while avian are usually infected by influenza virus with high numbers of H (H5~H15). The H protein is known to be used for viral attachment to the host cell, after which the virus proliferates using the replication machinery of the host cell. The H protein has high species specificity. Unfortunately, this principle has been broken, welcoming a new millennium, in 2000. In late 2003, shocking news was reported that some people living in East Asia had been infected by a highly pathogenic avian influenza (AI), for which their serotype was H5N1, which had never been reported before in human medical history at that time. Even worse, this H5N1 avian influenza showed an extremely high mortality rate (about 70%), even though its infectivity is low. However, there is good fortune in this misfortune because infection cases between humans have not been identified yet. Recently (spring 2013), a new serotype of AI has appeared in some areas of China, for which the serotype is H7N9. According to some reports presented at the meeting of "Options for the Control of Influenza" held in Cape Town from September 5 to 9, 2013, this new AI is expected to have a higher infectivity and toxicity than H5N1 AI, and in the fall of 2013, a pandemic of this new AI was forecast by the Centers for Disease Control and Prevention (CDC) of the USA.

Vitamin C Against the Common Cold

In Korea, for the last 20 years, the number of people taking a couple of grams of vitamin C daily has increased steadily such that in 2017, it was presumed that about 15 million people were taking a megadose of vitamin C daily. The most frequent cases, which I have observed by telephone or e-mail interviews, have been many people taking a megadose of vitamin C for more than 4–5 years, and for a couple of years, they have never caught a cold, which they used to suffer from one to two times a year when they did not take a megadose of vitamin C. Twelve years ago, I was asked to meet a CEO who was in his mid-50s and suffered from multiple episodes of a cold yearly for more than 30 years. He was admitted regularly to a hospital for 1 month due to pulmonary complications from the cold. Immediately after meeting with me, he started to take a megadose of vitamin C daily. Since then, he has never caught a cold for more than 10 years. This longitudinal study has very meaningful value in estimating the effects of vitamin C on the common cold, even though it is only a single case.

Clinical studies on the effects of vitamin C on colds presented by some clinicians have shown generally negative results. Regular vitamin C consumption may decrease the duration of cold symptoms but does not affect the symptom severity or act as a prophylaxis (Heimer et al. 2009). The failure of vitamin C supplementation to reduce the incidence of colds in a normal population indicates that preventing a cold by taking routine megadoses of vitamin C is not rationally justified for community use. However, evidence suggests that it could be justified in people exposed to brief periods of severe physical exercise or cold environments (Douglas et al. 2007). Their conclusion is that vitamin C does not have a curative or preventive

effect on colds but shortens the duration of the illness. The common cold is a self-limited viral disease. For a curative treatment, the optimal dose of vitamin C and the right method of administration should be considered. According to a pharmacokinetic study of vitamin C after oral administration, it is most desirable to take vitamin C every 6 h because vitamin C has a 6-h cycle of metabolism as mentioned in Chap. 1, the Introduction. Actually, when it is orally administered, it reaches peak concentration in the peripheral blood 3 h after the administration, and it comes back to the basal level of concentration 6 h after the administration. However, almost all clinical experiments on the effects of vitamin C published so far have been performed on a single dose of vitamin C. Furthermore, the daily vitamin C dose used in the above published papers was less than 1000 mg. In addition, it is actually impossible to perform clinical experiments that can confirm if vitamin C can cure or prevent a cold because a cold has a short period as a self-limited disease. Once cold patients visit the clinic for treatment, the number of viruses is too high to be controlled by any potent medication such that the balance between the host and the virus is shifted to the virus and the patient usually becomes severely ill. During such an active phase of the cold, no drug can stop the disease process of a cold from occurring in the upper respiratory tract. Vitamin C can prevent the onset of a cold if people follow a strict regimen taking a megadose of vitamin C three times daily because it can inhibit the initial phase of viral proliferation, when the number of viruses is not so high and still controllable by the host defense system (Furuya et al. 2008). That is the case with Tamiflu, which has been used for successful prevention of the swine flu (H1N1). The correct method of administering Tamiflu is to take it within 48 h after the occurrence of fever. If it is taken 48 h or later after a fever occurs, it has no effect on the treatment of swine flu. Considering the operating mechanism of Tamiflu, which binds to the hemagglutinin protein of the influenza virus and inhibits viral attachment to the host cell resulting in failure of viral replication using the replication machinery of the host cell, Tamiflu does not cure the cold but prevents it because Tamiflu blocks the initial proliferation of the influenza virus.

In Vivo Experiment Showing the Effects of Vitamin C on the Flu

There have been some reports on the effects of vitamin C on the flu (Li et al. 2006; Sladkova and Kostolansky 2006; Banerjee and Kaul 2010). To observe the effects of vitamin C on flu, an in vivo experiment using *Gulo(-/-)* mice, which are unable to synthesize vitamin C like humans because the gene encoding L-gulonolactone oxidase is knocked out artificially, has been performed by my research team. The experimental animals were divided into three groups with six mice in each group: Group 1, wild-type, normal mice; Group 2, *Gulo(-/-)* mice without supplementation of vitamin C; and Group 3, *Gulo(-/-)* mice with supplementation of oral vitamin C. The mice in each group were infected with H3N2 influenza virus, and then,

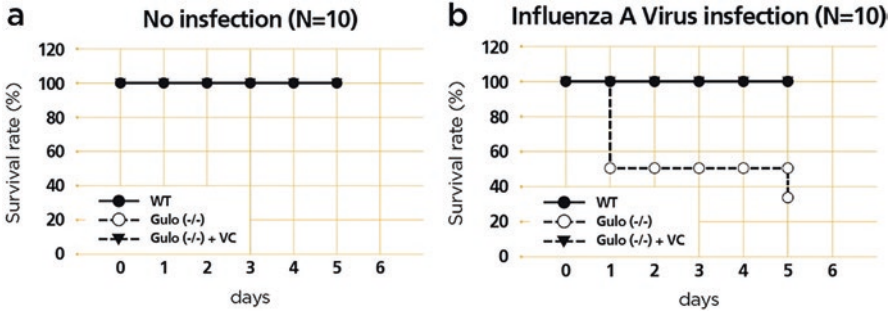
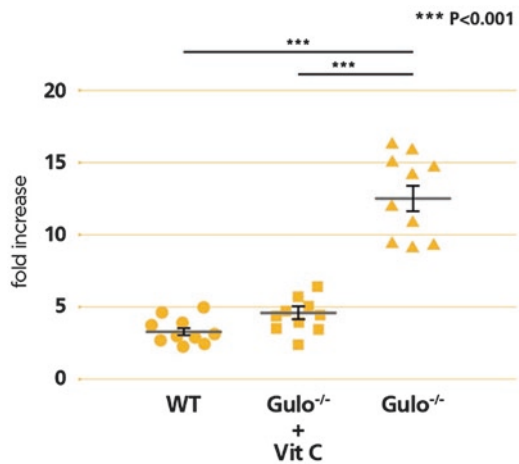


Fig. 5.3 Difference of survival rates among each groups. Only vitamin C-deficient mice ($Gulo(-/-)$) showed decreased survival rates by influenza infection (b), while no dead mice were observed in any groups without influenza infection (a). WT, normal mice group; $Gulo(-/-)$, mice group which cannot produce vitamin C like humans; $Gulo(-/-) + VC$, $Gulo(-/-)$ mice group fed with daily vitamin C in the drinking water. (Kim et al. 2013)

Fig. 5.4 Viral titration in the lungs from H3N2 influenza virus-infected mice using RT-PCR. The highest viral titer was observed in the lung of vitamin-deficient mice ($Gulo(-/-)$). WT, normal mice group; $Gulo(-/-)$, mice group which cannot produce vitamin C like humans; $Gulo(-/-) + VC$, $Gulo(-/-)$ mice group fed with daily vitamin C in the drinking water. (Kim et al. 2013)



the survival rate was checked. All the mice in the three groups showed symptoms of the flu such as fever, rhinorrhea, lethargy, and so on. Interestingly, 5 days after infection, 80% of the mice in Group 2 were dead, while no mice in Groups 1 and 3 died (Fig. 5.3).

The autopsies showed that the lung tissues from the dead mice were loaded with so much influenza virus, indicating that the mice in Group 2 died of viral pneumonia. However, the lung tissues from the mice in Groups 1 and 3, which did not die from the infection, did not have the influenza virus (Fig. 5.4) (Kim et al. 2013).

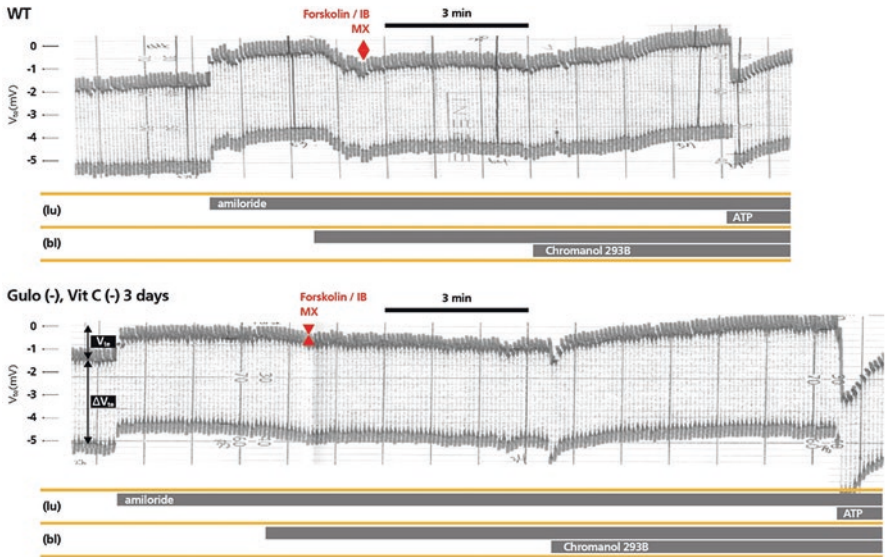


Fig. 5.5 Transepithelial voltage (V_{te}) and short-circuit current (I_{sc}) analysis. Vitamin C deficiency causes inhibition of cAMP-dependent secretion of chloride in the mouse airway epithelium so that the epithelium does not maintain fluidity on their surface, resulting in facilitation of viral invasion and proliferation

These results strongly suggest that vitamin C in a living body might prevent influenza virus from spreading down from the upper respiratory tract to the lower respiratory system such as the bronchi, bronchioles, and alveoli, even though the mechanism involved in the preventing process has not been elucidated yet. However, vitamin C deficiency causes inhibition of cAMP-dependent secretion of chloride in the mouse airway epithelium so that the epithelium does not maintain fluidity on their surface (our unpublished data) (Fig. 5.5).

The dryness of the mucosal epithelium facilitates viral proliferation and invasion. Furthermore, vitamin C deficiency dramatically decreases SVCT expression on the mucosal epithelium of respiratory tracts, leading to an abolition of the prevention effects of vitamin C from flu infection (our unpublished data) (Fig. 5.6).

In addition, levels of interferons (IFNs) in the bronchoalveolar lavage (BAL) fluid (Fig. 5.7), which have very critical roles in the defense of viral infection, are markedly low in vitamin C insufficiency group. However, levels of representative pro-inflammatory cytokines, such as TNF- α and IL-1 α and IL-1 β in BAL fluid, are

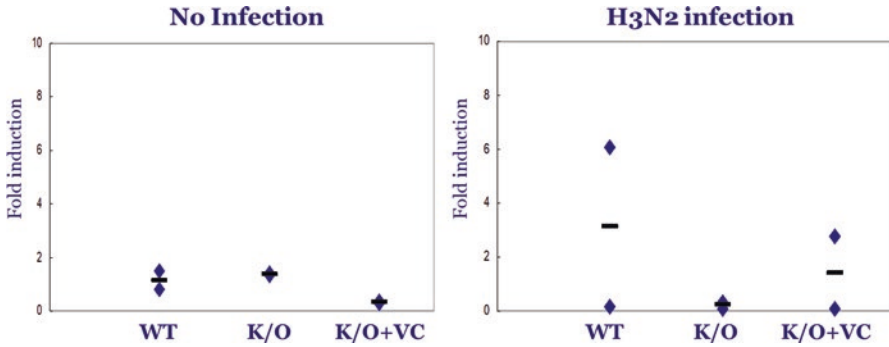


Fig. 5.6 SVCT2 expression in lungs from H3N2 influenza virus-infected mice using RT-PCR. Influenza infection induced increased expression of SVCT2 in the lungs of WT and K/O+VC groups, while it did not increase SVCT2 expression in the lungs of the vitamin C-deficient mice (K/O group). WT, normal mice group; K/O, mice group which cannot produce vitamin C like humans; K/O + VC, K/O mice group fed with daily vitamin C in the drinking water

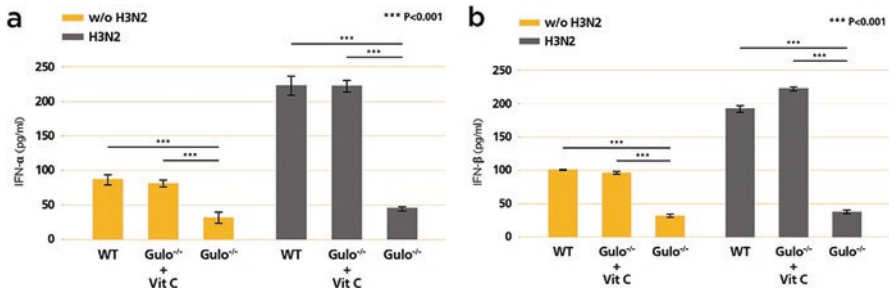


Fig. 5.7 Cytokine production in bronchoalveolar lavage (BAL) fluid (1). Vitamin C deficiency decreases production of IFN- α (a) as well as IFN- β (b), more significantly during H3N2 influenza infection. WT, normal mice group; Gulo(-/-), mice group which cannot produce vitamin C like humans; Gulo(-/-) + VC, Gulo(-/-) mice group fed with daily vitamin C in the drinking water

significantly high in vitamin C insufficiency group. Inflammatory cells are also markedly increased in BAL fluid (Fig. 5.8) (Kim et al. 2013).

These all in vivo data provide the immunological evidences that daily supplementation of high-dose vitamin C can prevent influenza infection and that, in extreme case, it can save the life.

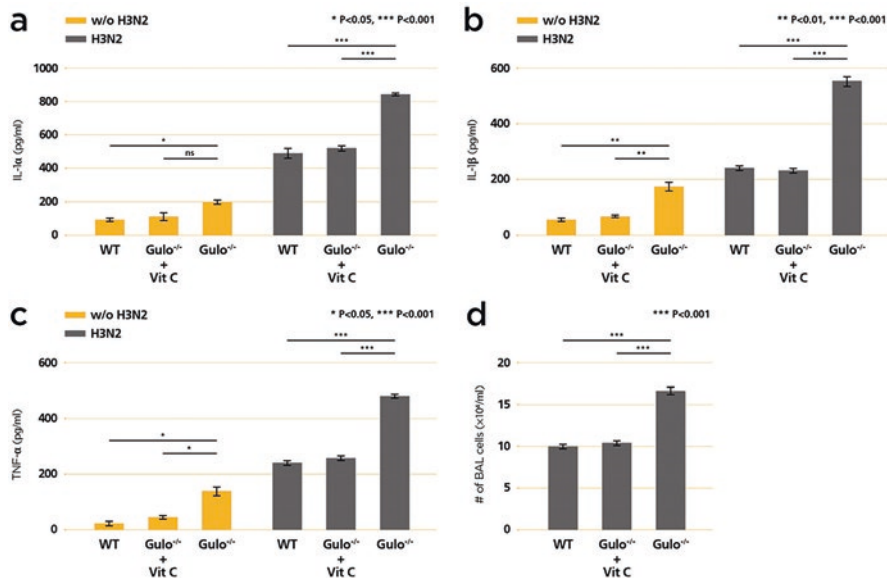


Fig. 5.8 Cytokine production in bronchoalveolar lavage (BAL) fluid (2). Vitamin C deficiency increases production of several pro-inflammatory cytokines such as IL-1 α (a), IL-1 β (b), and TNF- α (c), especially during H3N2 influenza infection, and it also causes increase of the inflammatory cells in BAL fluid (d). WT, normal mice group; Gulo(-/-), mice group which cannot produce vitamin C like humans; Gulo(-/-) + VC, Gulo(-/-) mice group fed with daily vitamin C in the drinking water

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