Energy Intake and Response to Infection with Influenza

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Abstract

Influenza is a worldwide public health concern, particularly with emerging new strains of influenza to which vaccines are ineffective, limited, or unavailable. In addition, the relationship between adequate nutrition and immune function has been repeatedly demonstrated. Mouse models provide strong evidence that energy extremes, including energy restriction (ER) and diet-induced obesity (DIO), have deleterious effects on the immune response to influenza infection. Both ER and DIO mice demonstrate increased susceptibility and mortality to influenza infection. The effects of ER are more pronounced during innate responses to influenza infection, whereas the effects of DIO are evidenced during innate and adaptive responses to both primary and secondary infection. There are striking similarities between ER and DIO during influenza infection, including impaired natural killer cell function and altered inflammation. Future studies must develop effective nutritional paradigms to offset the effects of these energy extremes on the immune response to an acute infection.

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INTRODUCTION

Seasonal influenza (flu) is a worldwide public health concern. The most recent statistics indicate that flu epidemics cause between 3 and 5 million cases of severe illness, and between 250,000 and 500,000 deaths worldwide (91). Although flu-related illness can seriously affect all age groups, those with the highest risks for influenza-related complications are children under the age of 2, adults over 65, and individuals who are immunocompromised or have chronic medical conditions, such as heart disease, pulmonary disease, or diabetes (62, 88).

The only known preventative for influenza disease is yearly vaccination to protect against circulating strains of influenza virus. There is clear evidence, however, that vaccination is not always effective in protecting from influenza disease in vulnerable populations. For example, influenza vaccination is 70% to 90% effective in protecting healthy individuals from influenza-specific disease. However, vaccination is much less efficacious in the elderly. Vaccination reduces influenza-induced illness by 60% and mortality by 80% in the elderly (62). Despite this, influenza and its secondary complications result in 200,000 hospitalizations and 36,000 deaths each year in the United States, and influenza is the fourth leading cause of death in individuals 65 years and older.

The emergence of a novel influenza strain, as seen with the swine 2009 influenza virus (H1N1), was of particular concern to the population under the age of 65. Although ~90% of influenza-related deaths occur from seasonal influenza in people 65 years and older, mortality from 2009 swine H1N1 during the early 2009 outbreak was highest among people 25 to 49 years of age (39%), followed by people 50 to 64 years of age (25%), and people 5 to 24 years of age (16%) (23, 46). A key issue during the 2009 swine H1N1 influenza outbreak was that the vaccine was limited in supply or unavailable. In fact, in many cases, immunization occurred during or after influenza outbreaks had already occurred. Since it takes several weeks to develop protective immunity to the vaccine, the usefulness of the vaccine in protecting from the circulating strains of influenza was questionable. These data mandate the need for studies that examine the primary immune response to novel strains of influenza to reduce the severity of disease in cases when vaccines may be limited or unavailable.

The emergence of swine flu also brought to the forefront the importance of proper health status in vulnerable populations during influenza season. In fact, population data stratified by health status indicated that severe cases of 2009 swine H1N1 influenza were associated with chronic lung disease (41%), hypertension (24.4%), diabetes (20%), immunosuppression (18%), neurologic disease, cardiac disease, and pregnancy (49, 88). Further analysis of population data indicated that both over- and underweight individuals demonstrated an increased risk of severity of infection to 2009 swine H1N1 (64).

During the 2009 swine H1N1 outbreak, obesity was, for the first time, reported as an independent risk factor for increased influenza severity, with 33% of infections in patients classified as obese. Morbid obesity [body mass index (BMI) >40] was strongly associated with hospitalization and death from 2009 swine H1N1 independently of any other comorbidity (64). Obesity (BMI >30) was the major factor observed for deaths among people >20 years old with no other recognized comorbidities. However, in all age groups, obesity (30< BMI <40) was not a significant risk factor for total mortality but was associated with extended time of hospitalization, prolonged mechanical ventilation, and time in the intensive unit care (19).

Collectively, this summary of population data supports the unequivocal need for a careful examination of the immune response to influenza infection, especially when vaccination is either ineffective against seasonal influenza or unavailable against emerging strains of influenza. In addition, the data indicating increased severity of influenza in over- and underweight individuals mandate the need for careful evaluation of the susceptibility and the severity of infection when energy balance is altered.

This review focuses on the effects of two nutritional states, energy restriction (ER), also known as caloric restriction (CR), and obesity, on the primary response to influenza infection in mouse models. These two nutritional paradigms have been selected because of their differential effects on the primary response to influenza infection. Undernutrition without malnutrition, characteristic of ER, is the only known nutritional paradigm that extends lifespan in rodent models (14). A typical ER diet (40% restriction) is achieved in mice by gradual underfeeding an isocaloric diet supplemented with proteins, minerals, and salts and reduced in carbohydrates (11). Studies in rodents have indicated that lifelong ER extends maximal lifespan by 20% to 30% and reduces the incidence of cancers and tumors (89). Although the effects of ER have been extensively studied on various immune parameters, data concerning the effects of ER superimposed during a primary infection, such as influenza, are limited.

Obesity can be studied in rodents by feeding a high-fat (40% to 60%) diet, known as diet-induced obesity (77), or in genetically obese mice, which are leptin-deficient (*ob/ob*) or lack leptin receptors (*db/db*). These transgenic models, although useful to study obesity, have limited clinical relevance because only a small percentage of obese humans suffer from mutations in the leptin-associated genes (27). Furthermore, the use of *ob/ob* and *db/db* transgenic mice in studying pulmonary infections is complicated because these animals have undersized airways and lungs (74, 75). This review focuses on studies that have used DIO to assess the immune response to influenza because we can directly compare and contrast the results of studies that have used dietary manipulations (ER or DIO) to assess the immune response to influenza. These studies have consistently used the same strain of influenza, specifically the eighth isolate from Puerto Rico (PR8) in 1934, and unless noted this strain of virus has been used in the discussed studies.

PRIMARY RESPONSE TO INFLUENZA

Innate Immunity

The primary response to influenza is illustrated in **Figure 1**. Influenza infects lung epithelial cells and replicates (16, 39). Initially, cytokines are released from dendritic cells, macrophages, and lung epithelial cells, which produce signals that activate and recruit immune cells to the site of infection to limit early virus replication in lung (42, 45). Influenza infection has been shown to induce high levels of inflammatory cytokines in response to infection, which include type I interferon (IFN-α/β), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-12, IL-18, MCP-1 (CCL2), and MIP-1α/β (CCL3/4) (6, 10, 15, 38, 51). The coordinated release of these cytokines is critical

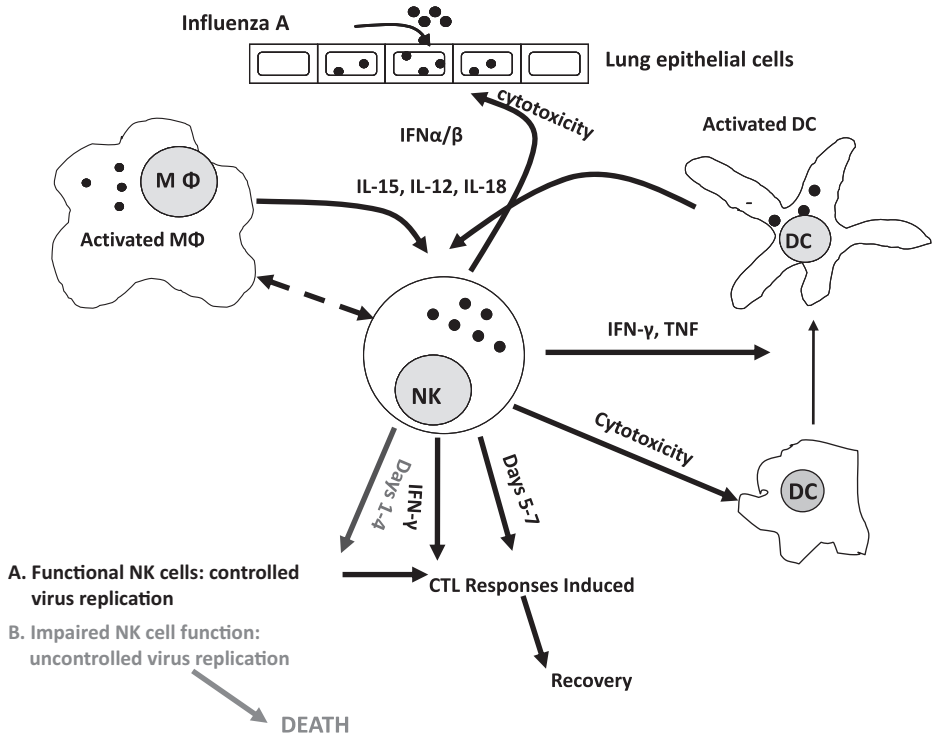

Figure 1

Proposed role of NK cells and DCs during early influenza infection. (*A*) During days 1 through 4 of infection, NK cells control virus replication leading to recovery from infection. (*B*) When NK and/or DC function is impaired, such as during ER or DIO, lung virus titers accumulate and impair the induction of a CTL response. CTL, cytotoxic T lymphocyte; DCs, dendritic cells; DIO, diet-induced obesity; ER, energy restriction; IFN, type I interferon; NK, natural killer; TNF, tumor necrosis factor.

for establishing immune cell communications necessary for an effective immune response to recover from influenza (42).

Natural killer cells. One of the first immune cells to respond to influenza infection is natural killer (NK) cells, large granular lymphocytes that recognize and kill virally infected cells, without prior antigen exposure. Cytokines, including IL-12, IL-18, and TNF-α, can induce the proliferation and activation of NK cells, which then produce IFN-γ within hours through the first few days of infection (8, 54, 66, 73). These activated NK cells bind to influenza-infected cells and release the cytolytic components perforin and granzyme, which subsequently kill infected cells.

The critical role that NK cells play in controlling virus infection, including influenza, has been well-established in ex vivo and in vivo studies. Ex vivo studies have shown increased numbers, percentages, and cytotoxic activity of NK cells as early as one day after infection, which helps to limit virus replication in the lung (68). However, in vivo studies have shown a critical dependence on NK cells during the early response to influenza infection. When NK cells were depleted in vivo prior to influenza infection, NK-depleted mice demonstrated marked weight loss and death within the first 5 to 6 days of infection (68, 81). Additional in vivo studies have also shown that influenza infection is fatal in mice lacking the gene for Nkp46, which is a receptor on NK cells that recognizes viral

hemagglutinin (HA) on infected cells (33, 58). Thus, it is clear that NK cells are a critical component of the early innate immune response to influenza infection.

NK cells also play an important role during the transition from the innate to adaptive immune response to influenza. NK cell–derived IFN-γ activates accessory cells, including macrophages and dendritic cells (34, 35). The activation of accessory cells further controls lung virus burden during infection, until an antigen-specific CD8+ cytotoxic T lymphocyte (CTL) response can be achieved (3, 7, 28, 61). Thus, NK cells are essential to support an efficient CTL response that is required for viral clearance and recovery from infection (47, 48). Importantly, NK cells work in concert with CTLs during influenza infection: CTLs produce IL-2, which feed back on NK cells and increase IFN-γ production; IFN-γ stimulates CTLs, which then clear virus, leading to recovery from influenza infection.

Adaptive Immunity

Dendritic cells. Dendritic cells (DCs) are resident in all tissues, including lung, to provide an immediate response to invading pathogens such as influenza (36). In general, DCs are present in an immature, highly phagocytic state and mature upon uptake of an antigen (76). DCs recognize various infectious stimuli through the expression of a wide range of pathogen-associated molecular patterns (PAMPs), in particular toll-like receptors (TLRs) (72). Maturation of DCs involves the upregulation of costimulatory molecules such as CD80 and CD86 as well as chemokine receptors, for stimulating naïve T cells and homing to draining lymph nodes, respectively (5, 37).

Based on function, there are at least two distinct subsets of mature DCs; plasmacytoid DCs (pDCs) and conventional DCs (cDCs). Upon stimulation, pDCs produce large amounts of IFN-α/β (29, 93). The majority of PAMPs expressed by pDCs are virus-associated, including TLRs 7–9. Importantly influenza, an ssRNA virus, can specifically activate TLR7 and other virus-associated TLRs (20, 36). Therefore, pDCs are important in stimulating both the innate and adaptive cells during an influenza infection through the production of IFN-α/β. Although they are not major type I IFN producers, cDCs are the primary cells responsible for antigen presentation. Conventional antigen presentation involves the presentation of intracellular antigens in major histocompatibility complex (MHC) I and extracellular antigens in MHC-II (4, 5). Stimulation of naïve T lymphocytes by DCs provides the critical link between innate and adaptive immunity.

T cells. Antigen is loaded onto MHC I or II and is presented by DCs to naïve T lymphocytes. T cell receptor interactions with MHC, in combination with costimulatory molecules on the T cell and the DCs, induce clonal expansion and differentiation of naïve T cells into antigen-specific effector T cells. Depending on cytokines produced in concert with antigen presentation, a T helper type I (Th1) or type II (Th2) response is developed. Influenza infection typically is characterized by production of cytokines such as IL-12 and IFN-γ that induce a strong Th1 response (6, 38). This results in the differentiation of antigen-specific CD8+ T cells into mature CTLs that recognize and kill infected cells using cytolytic molecules (86). Thus, the generation of an efficient Th1 response plays a critical role in viral clearance and recovery from infection (21).

Importantly, host nutritional status has been repeatedly shown to influence the immune response to infection. Several reports indicate that the percentages, numbers, and functions of both innate and adaptive immune cells are sensitive to nutritional modulation. This suggests that any modification in nutritional status that affects the activation of NK cells, DCs, and T cells may affect the coordinated regulation and interaction between the innate and adaptive immune response to influenza infection. Thus, the focus of this review is to illustrate the importance of understanding how energy extremes, ER and DIO, positively or negatively affect the immune response to influenza.

SYMPTOMS OF INFLUENZA INFECTION

The most characteristic symptoms for influenza infection in humans are fever, cough, and myalgia (63) but can also include headache, sore throat, nasal congestion, weakness, and loss of appetite (24). Similar to humans, mice infected with influenza exhibit overt signs of illness, including chills, listlessness, and lack of grooming. Recent studies in mouse models show primary influenza infection is associated with weight loss, which can be observed as early as one day after infection (71). The degree and severity of weight loss correlates with the dose of influenza (15, 85). Thus, weight loss in mice is often used to monitor the severity of infection during the early stages of the primary response.

Characterization of the degree of weight loss and its correlation with survival during influenza infection has been performed using ER and ad libitum (AL) fed mice. It is typical for AL mice to lose up to ~30% of initial body weight within the first 4–6 days after infection and still recover, whereas ER mice can only lose ~15% of initial body weight and survive (71). Interestingly, studies have clearly demonstrated that AL mice refuse food and begin to lose weight on the first day of infection. In contrast, ER mice, despite showing the same physical signs of illness, continue to consume food and maintain body weight until day 2 postinfection (71). This may reflect an adaptation to ER in an attempt to meet increased metabolic demand during the early stages of infection (71). However, recovery from influenza infection in both ER and AL mice correlates with regaining appetite and body weight beginning at 4–6 days postinfection. Once stable weight is achieved, mice generate a CTL response and recover from infection.

Weight loss has not been reported as a method to assess the severity of primary influenza infection of DIO mice. However, studies have shown that DIO mice demonstrate increased lung pathology, enhanced mortality rates, and severity to primary influenza infection (77). Additional studies also report that DIO mice were more susceptible to a secondary infection with a heterologous strain of virus, evidenced by significant weight loss, increased virus titers, and mortality at virus doses that did not result in mortality of lean mice (43). Thus, it appears that there is a fundamental difference in the susceptibility of ER and DIO mice to influenza: Whereas ER increases the severity of primary influenza infection, DIO negatively affects both the primary and secondary responses to influenza. Thus, future studies should address whether milder infections have the same impact on the secondary response of ER mice to influenza infection. However, this may not be possible because even subclinical doses of virus produce at least 50% mortality during the primary response of ER mice (32).

CYTOKINE PRODUCTION IN RESPONSE TO INFECTION

Cytokines in Response to Inflammation

Disease parameters of mouse models of chronic inflammation and autoimmunity are improved when mice consume an ER diet. In NZBxNZW mice, ER has also been shown to delay the onset of renal disease produced by autoimmune reactions (83). In models of lung injury from acute infection, ER has been shown to reduce the production of key proinflammatory cytokines, TNF-α, and IL-6, by alveolar macrophages, which lessens the severity of lung pathology (22). However, the inhibition of monocyte-derived proinflammatory cytokine has also been recognized to contribute to enhanced mortality in other experimental models (84). Thus, although in most cases ER has distinct beneficial anti-inflammatory effects, there are instances when it is detrimental to the host response.

Although influenza in particular induces a proinflammatory cytokine response in the lung, the overall effects of ER on influenza infection have not yet been characterized extensively. In one report, ER mice infected with influenza demonstrated reduced IFN-α or IFN-β mRNA transcription compared with

AL mice two days postinfection, although there were no reported differences in plasma IL-12 (71), TNF-α, and IL-6 production (E.M. Gardner, unpublished observations). These limited data suggest that ER may actually dampen the early proinflammatory response and contribute to exacerbation of disease.

Chronic caloric excess induces changes in metabolic programming and dysregulation of inflammatory processes that are characteristic of the obese phenotype. Obesity causes a dramatic expansion of adipose tissue and can contribute to upwards of 40% of the total body mass (26). This enlarged adipose tissue contributes to the inflammatory cytokine milieu by producing and subsequently releasing proinflammatory cytokines, such as IL-1b, IL-6, and TNF-α (50, 87). This increase in proinflammatory cytokines has also been attributed to influencing the enhanced frequency of pulmonary diseases occurring in the obese (56).

Similar to ER mice, DIO mice also demonstrate delayed mRNA transcription of proinflammatory cytokines and increased lung pathology during primary infection with influenza virus. In DIO mice, IFN-α, IFN-β, TNF-α, IL-6, and IL-10 were significantly lower compared with lean mice three days postinfection (77). At later time points, however, IL-6 and TNF-α expression remained elevated in DIO mice but not in lean mice (77). After a second challenge with a heterologous strain of influenza, DIO mice demonstrated increased mortality (43) and lower expression of IFN-α, IFN-β, IL-6, and TNF-α in lung two to three days postinfection. These data suggest that the observed state of chronic inflammation impairs the induction of a coordinated proinflammatory cytokine response to influenza infection.

Importantly, these data indicate that there is dysregulation in the proinflammatory responses of both ER and DIO mice during influenza infection. However, future research is required to elucidate how these energy extremes that result in the same overall exacerbation of disease are influenced by the inflammatory cytokine milieu prior to and during influenza infection.

Leptin in Response to Infection

Although leptin is well known as a satiety hormone, it structurally resembles cytokines of the long chain helical family and is often described as a proinflammatory cytokine. Immune cells including T cells, B cells, NK cells, monocytes, and macrophages express the long form of the leptin receptor, OBRb. Leptin signaling has been shown to be critical for the survival and function of these cells (12, 52, 53).

During an acute infection, leptin is produced in combination with IL-1, IL-6, and TNF-α, induces the acute-phase response during inflammation, and is accompanied by hypoglycemia and anorexia (31, 82). Studies by Mancuso et al. (41, 57) have shown that acute starvation reduces circulating leptin concentrations prior to a respiratory infection and results in a blunted immune response. Importantly, however, administration of exogenous leptin corrected starvation-induced innate immune suppression, increased killing of bacteria, restored cytokine production, and improved survival (41, 57). This critical observation identified a key role for leptin in regulating the innate immune response to respiratory infection. The effects of leptin on immune cells are numerous; extensive reviews have been devoted to this subject, which is beyond the purview of this review.

Body fat is directly correlated with circulating leptin levels, independent of acute anorexia (9, 30). Investigation of the relationship between body fat and leptin levels prior to and during influenza infection of ER and AL mice indicated that ER mice had decreased body fat stores (8% to 12%) compared with AL (18% to 20%) (13). Importantly, we and others have shown baseline leptin levels in ER mice are significantly reduced, accounting for only ~20% of that observed in AL mice (13, 70). However, during influenza infection, circulating leptin concentrations increased in AL one day

postinfection, but not in ER or DIO mice (13, 77). The observed increase in serum leptin concentrations of AL mice is consistent with findings in other respiratory infections and suggests that leptin plays a role in providing signals to the immune system during an acute infection, such as influenza.

Increased adiposity in DIO mice results in the release of high concentrations of leptin in the systemic circulation (31). However, immune cells from these animals exhibit impaired responsiveness to leptin (69). It has been proposed that chronic leptin signaling in DIO results in upregulation of suppressor of cytokine signaling proteins (SOCS) expression, resulting in a state of leptin insensitivity (40). Furthermore, SOCS upregulation may result in poor responsiveness to inflammatory stimulus in DIO mice by dampening the signaling of cytokines such as IL-2, IL-6, IFN-α/β, IFN-γ, and leptin (2, 17, 80).

A critical role for leptin in maintenance of immune function has been reported previously. Leptin administration can enhance cytotoxicity and stimulate both innate and adaptive immune cell proliferation (12, 59, 60, 79). The low levels of leptin in ER mice and leptin insensitivity of DIO mice suggest that altered leptin signaling may be a common factor for increased susceptibility of ER and DIO mice to influenza infection.

NATURAL KILLER CELL FUNCTION DURING PRIMARY INFLUENZA INFECTION

The higher lung virus titers observed early in the course of infection of ER mice suggest an impaired ability to limit viral replication prior to the induction of an adaptive immune response (32, 71). Histological examination confirmed this observation, as influenza infection of young ER mice results in increased lung pathology scores and epithelial cell damage (71). Thus, the combination of increased early mortality and virus load of ER mice suggests that ER may lead to a defect in NK cell function during the critical first few days of infection. In accord with this hypothesis, ER mice demonstrated reduced influenza-induced cytotoxicity compared with AL mice controls between one and two days post-influenza infection (71). More detailed mechanistic studies revealed that ER impaired pulmonary influenza-induced NK cell cytotoxicity, even after restimulation with IFN-α/β in vitro (71). This ER-related impaired NK cell cytotoxicity was further characterized by a concomitant decrease in the number and percentage of NK cells and in the total lymphocyte population in the lungs two days postinfection. Interestingly, a reduction in NK cells, but not effector CD8 T cells, has been also observed in cases of lethal H1N1 influenza in humans, further supporting the role of these cells in the host response to influenza (18).

There is a paucity of data regarding the effects of DIO on NK cells and related cytokine production before and after influenza infection. Obese mice have approximately the same percentages of NK cells in lungs and spleens as control mice before influenza infection, similar to what is observed in ER mice (71, 77). However, after influenza infection, DIO mice demonstrate significantly reduced NK cells, and most important, reduced NK cell cytotoxicity in lungs (77).

A possible explanation for the decrease in NK cell cytotoxicity observed in both of these energy extremes could be related to reduced production of immunostimulatory cytokines, such as leptin and IFN-α/β. Signal transduction through signal transducer and activator of transcription 1 (STAT1) and STAT4 or STAT3 increases NK cytotoxicity from IFN-α/β and leptin, respectively (1, 65, 67, 92). Interestingly, mouse models of ER and DIO have also revealed alterations in IFN-α/β transcription and leptin production in response to influenza infection. Thus, it is possible that alterations in leptin concentrations along with the inability to maintain IFN-α/β production result in decreased NK cell cytotoxicity in both models during influenza infection.

ENERGY EXTREMES DURING THE ADAPTIVE IMMUNE RESPONSE TO INFLUENZA

Little is known regarding the effects of ER on the primary adaptive response to influenza infection in mouse models. As stated above, this is because long-term survival of ER mice is not possible even using subclinical doses of the PR8 strain of influenza A. Effros et al. (25) generated the majority of data regarding influenza-specific responses during ER. However, it should be noted that the experimental design of these studies focused more on the effects of ER on age-related changes in immune function, using intraperitoneal *immunization* with influenza virus. The studies highlighted in this review have focused on the effects of ER *alone* on the immune response to influenza *infection*. Regardless of this discrepancy in study design, these studies were the first to identify key effects of ER in attenuating the age-related changes in the adaptive immune response to influenza immunization. In this study, adaptive immune parameters were assessed 21 days after immunization and revealed increased memory T cell proliferation, higher anti-influenza antibody production, and improved antigen presentation in aged ER mice compared with aged control mice. Interestingly, both young AL and aged ER mice had similar adaptive immune responses to immunization, providing the first evidence for ER delaying age-related changes in immune function not only to mitogens but also to influenza virus (25, 90). Importantly, studies by Gardner (32) revealed that aged ER mice were more susceptible to intranasal influenza infection, as evidenced by increased mortality, such that the development of an antigen-specific adaptive immune response was not possible.

The differences in outcomes on the effects of ER on primary immunization and infection suggest that the benefits of ER are dependent on the immunologic challenge. The principal reason for immunization is to develop memory T and B cells over a period ranging from weeks to years (25). Once generated, the maintenance of these cells is a relatively inexpensive metabolic process. In contrast, an initial exposure to a new virus, to which vaccines are unavailable or ineffective, may be detrimental during ER. In our recent studies, we have shown that initial infection with influenza induces acute weight loss and is an energetically costly event, as assessed by changes in body composition. During the first five days of infection, both ER and AL mice become anorexic and lose equal amounts of body fat (J.F. Clinthorne and E.M. Gardner, unpublished observations). Presumably, this mobilization of energy from body fat reflects a much smaller pool of the total body fat in AL compared with ER mice. Thus, these data suggest that increased metabolic and immunologic demands during acute infection are more detrimental to the energy-restricted host.

Much more information is available regarding the effects of DIO on the primary adaptive response to influenza infection. Given the importance of DCs in activating NK cells and in bridging the late innate and early adaptive responses, Smith et al. (78) assessed the contribution of DCs and their subsets, pDCs and cDCs, during primary influenza infection of DIO mice. Although others have shown impaired DC and phagocytic cell function with obesity (55, 57), these were the first studies to indicate that influenza-specific DC cell function was impaired in DIO mice. Obese mice had lower numbers of total DCs and cDCs in lung but increased numbers of cDCs in lymph nodes, related to those of lean mice. This suggests that obesity does not affect the migration of these cells to lymph nodes but may impair the homeostatic levels of these cells in the lung (78). Influenza-primed CD8 T cells from lean mice cultured with DCs from DIO mice demonstrated impaired IFN-γ production in vitro. The authors suggested that this reduced DC function in DIO mice is related to decreased IL-12 production in lymph nodes (78).

Smith et al. (78) showed that the absolute number of pDCs in the lungs of DIO mice was significantly reduced compared with that of lean mice after infection. Importantly, our

laboratory has also recently found that pDCs were reduced in ER mice compared with AL mice during the first four days of influenza infection (D.M. Duriancik and E.M. Gardner, manuscript in preparation). This impaired pDC function in both DIO and ER mice suggests that this subset of DCs may be particularly sensitive to energy extremes. In addition, the observed reduction in IFN-α/β in the lungs of DIO and ER mice may reflect altered pDC function and partially account for increased susceptibility to influenza infection in both models.

To our knowledge, no studies have examined the memory T cell response to influenza infection in ER mice. However, Beck's laboratory (43, 44, 77) studied both the primary and secondary responses to influenza infection in DIO mice. For these studies, DIO mice were first infected with the X31 strain of influenza A to assess the primary immune response. The secondary (memory response) was assessed at one month using PR8 because it is a heterologous strain of influenza A. The rationale for this design was that X31 is a milder strain of influenza A but can still generate influenza-specific memory T cells against PR8. Although lean mice did not succumb to primary or secondary infection, DIO mice exhibited increased mortality after secondary infection with PR8. In addition, DIO impaired the ability of memory T cells to control viral replication, resulting in increased mortality. This was reported to be due to reduced survival of memory CD8 cells in the lungs between first and second infections (44).

Further analysis revealed that there were alterations in the expression of IL-7 and IL-15 mRNA after primary infection of DIO mice. Since both of these cytokines are necessary to support the maintenance and survival of effector memory CD8 T cells, this suggests that DIO may reduce the number of effector memory cells available to respond during secondary infection (43, 44). In support of this observation, DIO mice had only half the number of influenza-specific CD8 T cells producing IFN-γ postinfection (44, 78). Additional studies by Karlsson et al. (43, 44) also showed that individual influenza-specific CD8 cells from DIO mice did not produce IFN-γ during the secondary response as robustly as did CD8 T cells from lean mice. Taken together, these data suggest that the number and function of memory influenza-specific CD8 T cells in the lungs of DIO mice may account for a preferential increased susceptibility to secondary, rather than primary, influenza infection (43).

In summary, there is strong evidence that both ER and DIO have distinct deleterious effects on the immune response to influenza infection. In many instances, the result is the same: Both ER and DIO increase susceptibility to influenza infection. However, in ER mice, these effects are principally observed during the innate immune response to influenza and may reflect a combination of dampened and poorly coordinated inflammatory responses, an impaired early NK cell response, and acute anorexia in the face of increased metabolic demand. In contrast, DIO affects both the innate and adaptive immune responses to influenza. During the innate response, DIO is characterized by dysregulated inflammatory responses and reduced NK cell cytotoxicity. During the adaptive response, DIO impairs antigen presentation by DCs, reduces interferon production of IFN-γ by CD8 T cells, and more importantly, decreases the generation of effector memory influenza-specific CD8 T cells. Clearly, studies are required to establish further the effects of energy extremes on the immune response not only to influenza but also perhaps to other infectious diseases in nutritionally compromised individuals.

DIETARY INTERVENTIONS

Refeeding to Improve the Response During Energy Restriction

The studies reviewed indicate the need for the development of dietary interventions that may correct the deleterious effects of energy extremes during acute influenza infection. A recent study by Clinthorne et al. (13) examined the effects of refeeding previously ER mice with

AL diet for 14 days to determine whether this nutritional paradigm could improve outcome from influenza infection. This study was designed to determine whether increased energy could offset the deleterious effects of ER during acute infection. We showed that during the first five days of refeeding, refed mice demonstrated a hyperphagic response to food until about seven days postinfection, when their body composition and weight were restored. After this time, food intake in RF mice was comparable to AL controls (13). These observations are in accord with previous observations (79) indicating that ER mice overcompensate when exposed to AL food, thus hunger is maintained despite the length of ER.

Interestingly, in refeeding studies (13), despite restoration of body fat, serum leptin concentrations in RF mice were not restored to AL levels but were higher than ER mice (13). However, after influenza infection, RF mice demonstrated an increased percentage and number of pulmonary NK cells, including activated NK cells, compared to ER mice (13). Although RF mice had improved survival, they did show increased weight loss compared with infected AL mice (E.M. Gardner, unpublished observations). Despite enhanced influenza-induced weight loss, NK cell function was partially restored with refeeding, contributing to protection from mortality.

These results (13) suggest increased energy intake prior to infection may offset the detrimental effects of catabolism induced by an anorexic respiratory infection, such as influenza. However, these studies used a relatively short refeeding period of two weeks, which did not completely restore the NK cell response to that seen in AL mice. Therefore, it is imperative for additional studies to identify the metabolic mechanisms that are positively impacted by increased caloric intake to improve this response to infection in vulnerable populations. It is equally important to define specific, realistic nutritional refeeding paradigms, using various dietary protocols, that provide the best outcomes, leading to overall improved health and survival from infection.

Based on the review of studies examining the effects of DIO on influenza, an additional consideration would be to determine whether ER in obese mice would produce positive effects on the outcome of influenza disease. Future studies should explore this possibility in terms of determining the extent of ER necessary to improve metabolism and immune parameters prior to and during infection.

In conclusion, these feeding paradigms are realistic approaches for under- or overweight populations at risk for an infection such as influenza, which is seasonal and can be predicted in advance. However, it is imperative to attain a better understanding of the effects of energy extremes on the immune response not only to acute infection, but also during chronic disease states. Once these parameters are identified, nutritional therapeutic targets can be defined to maintain an appropriate response to stresses, including influenza, in nutritionally compromised individuals.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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