EDITORIAL

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Obesity and influenza infection severity

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“Identifying the biological factors that potentiate influenza severity in the obese could help limit morbidity and mortality in this at-risk population by improving vaccination and clinical management.”

Globally, more than 500 million individuals are obese. Excess adiposity increases risk for a number of adverse health effects, including cancer, diabetes and cardiovascular disease [1]. Obesity also increases susceptibility to bacterial and viral infections [2]. In 2009, the CDC identified obesity as a risk factor for hospitalization and death from pandemic H1N1 influenza virus infection [3]. An association between obesity and severe influenza outcomes, including seasonal influenza, has since been corroborated in other epidemiological studies [4–6]. Influenza outbreaks cause 250,000–500,000 deaths annually [7], and mortality can be even higher in pandemic years. Identifying the biological factors that potentiate influenza severity in the obese could help limit morbidity and mortality in this at-risk population by improving vaccination and clinical management. The scope of this Editorial will highlight current evidence and future approaches regarding influenza severity in the obese. This public health threat is especially pertinent given the global prevalence of obesity and the consistent threat of influenza outbreaks.

Influenza vaccination is the best available measure for preventing influenza

infection and limiting infection severity [8]. We have reported that obese adults immunized with trivalent influenza vaccine (TIV) show impaired influenza-specific antibody and T-cell responses [9]. One month after TIV immunization, antibody responses were similar in obese and healthy weight individuals; however, 1 year postvaccination, obese adults had significantly lower levels of protective antibodies than did healthy weight adults [9]. In addition to a decline in humoral immunity over time, memory T-cell responses in vaccinated obese adults were also impaired [9,10]. Memory CD4⁺ and CD8⁺ T cells from obese adults stimulated *ex vivo* with influenza virus expressed lower activation and functional markers compared with stimulated T cells from healthy weight individuals [9,10]. Impaired responsiveness to vaccination could increase influenza infection severity in the obese; therefore, further investigation of the mechanisms of impaired vaccine responses is necessary.

Obesity also affects immune defenses to influenza virus infection in mice. Obese mice exhibit greater influenza morbidity and mortality than do lean control mice [11–13]. Indeed, a number of immune cells

KEYWORDS

• H1N1 • infection • influenza
• leptin • obesity • pandemic

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(natural killer cells, dendritic cells, epithelial cells, macrophages, effector T cells, regulatory T cells, memory T cells and B cells) are altered by obesity during influenza infection in mice [11–16]. Although obesity affects the function of a variety of immune cells that limit virus replication, greater viral burden in the lung is not a consistent outcome in obesity and influenza infection mouse models [11–16]. However, one common finding in studies investigating the impact of obesity on influenza infection is greater lung inflammation or pathology during infection [11–16]. This response suggests that obese mice do not adequately regulate antiviral and inflammatory immune responses in the lung during influenza infection. This loss of regulation exacerbates lung injury during influenza infection in obese mice, likely contributing to greater morbidity and mortality.

The cellular and molecular mechanisms by which obesity increases influenza severity are complex. Obesity causes a variety of metabolic changes that alter the concentration of circulating nutrients and hormones [2]. For example, serum leptin and insulin concentrations are elevated and adiponectin levels are lowered in obese humans and mice [2]. These hormones can affect immune cell function, thus alterations in their plasma concentration could contribute to impaired immunity [2]. Furthermore, obesity induces alterations in circulating levels of nutrients and metabolites, which can modulate immune cell function through a variety of pathways, such as regulating metabolic and inflammatory cell signaling pathways and influencing metabolic programming [2]. The metabolism of immune cells is closely linked to functionality; therefore, the complex milieu of altered hormones and nutrients in an obese state provides a number of mechanisms for impaired immune responses.

In addition to perturbations in circulating levels of nutrients and hormones, there are a variety of other pathophysiological complications of obesity that may contribute to excessive antiviral responses and lung damage during influenza infection. Obesity induces a state of oxidative stress [17], which has been shown to increase influenza severity in mice [18]. Furthermore, a hallmark of obesity is a state of chronic, low-grade inflammation [2], which may compromise the immune response to influenza infection or vaccination. Finally, obesity is associated with distinct changes in the intestinal

microbiome [19], which may potentially impact antiviral responses given that manipulation of the intestinal microbiota in mice can influence influenza infection outcome [20].

In summary, there are a variety of mechanisms by which obesity may alter immune responses, including changes in the levels of circulating hormones and nutrients, oxidative stress, chronic inflammation and gut bacteria composition. To further complicate this picture, each type of immune cell (and each subtype) likely responds differently to these stimuli. For example, leptin can enhance inflammatory CD4⁺ effector T-cell proliferation, and reciprocally, inhibits regulatory T-cell proliferation [2]. Ideally, the best approach to investigate the impact of these different immunomodulatory mechanisms in an obese mouse model would be to systematically normalize each parameter that may contribute to impaired immunity. However, the major limitation of such an approach is that all of the pathophysiological complications associated with obesity (i.e., altered levels of hormones and nutrients, oxidative stress, inflammation, and so on) are intimately linked. For example, experimental normalization of leptin levels in obese mice during influenza infection would address the impact of hyperleptinemia on immune defenses. In fact, anti-leptin monoclonal antibody treatment limited influenza mortality in obese mice [14]. However, hyperleptinemia may be affecting other potentially immunomodulatory factors associated with obesity such as oxidative stress, inflammation and regulation (or dysregulation) of food intake. Therefore, it would be all but impossible to separate the contribution that hyperleptinemia has on immune cell function versus the secondary consequences of manipulating leptin levels. One immunological technique used to identify how changes in immune cell activity or the immune cell environment impacts infection responses *in vivo* is an adoptive transfer approach. However, transferring immune cells from an obese animal into a lean animal (and *vice versa*) would subject the transferred cells to the obese (or lean) environment, which could alter their phenotype, therefore limiting the ability to interpret the outcome. Currently, there is little understanding of the stability of the altered phenotypes of the immune cells from the obese host.

Given the large number of potential mechanisms altering immune processes during influenza infection in the obese, narrowing the focus

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to one particular mechanism, cell type or molecular pathway may not be the best approach to addressing this problem. Obesity is inherently a metabolic disease, and therefore we believe that metabolic profiling could be a useful tool in identifying perturbations in lung-specific and systemic metabolites altered by obesity during influenza infection. Uncovering metabolic biomarkers and patterns of altered metabolites would provide a global view of the impact of obesity on dynamic infection responses and simultaneously address the complicated interactions of the molecular underpinnings driving obesity-induced influenza mortality. Furthermore, identification of biomarkers or predictive metabolic signatures could be used in clinical settings to enhance influenza diagnosis and/or treatment of severely infected obese individuals.

Perhaps, given the complexity of obesity, a systems biology approach may be useful in

identifying the complicated interactions driving greater infection severity. Although it is well-established that obesity results in greater influenza severity in mice and humans, the mechanisms responsible for this outcome have not been clearly defined. Future applications of metabolic profiling together with immunological and physiological approaches may offer a superior means of addressing this global public health issue.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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