BASIC SCIENCE FOR THE CHEST PHYSICIAN

Obesity and susceptibility to severe outcomes following respiratory viral infection

Mark H Almond,1,2 Michael R Edwards,1 Wendy S Barclay,2 Sebastian L Johnston1

ABSTRACT

During the 2009 H1N1 influenza pandemic, obesity was convincingly identified as a novel, independent risk factor for multiple markers of disease severity. Associations between numerous nosocomial and community-acquired clinical infections have previously been established; yet, little is known about the mechanisms underpinning the increased susceptibility to severe outcomes following pandemic H1N1/09 infection in obesity. Here, we present a brief synthesis of the recent advances in our understanding of the immunomodulatory effects of obesity on outcomes following respiratory viral infection, with a particular focus on pandemic influenza.

INTRODUCTION

We live in an ‘obesogenic environment’ in which overconsumption of affordable, energy-dense processed foods has resulted in the prevalence of obesity more than doubling since 1980, such that it is now the commonest nutritional disorder worldwide. In 2008, 502 million adults were classified as obese (body mass index ≥ 30 kg/m2), and it is estimated that by 2030, this number will have increased by 65 million in the USA and 11 million in the UK, adding £1.9–2 billion per year to National Health Service medical costs.1

In March 2009, a novel strain of influenza A virus (pH1N1/09) emerged in Mexico, rapidly spreading around the world to cause the first influenza pandemic of the 21st century. Obesity was convincingly identified as a novel, independent risk factor for multiple markers of disease severity, including hospitalisation, intensive care unit admission and death following infection. Associations between obesity and numerous nosocomial and community-acquired clinical infections have previously been established, and concurrent studies have demonstrated immunomodulatory effects of obesity; yet, little is known about the mechanisms underpinning the increased susceptibility to severe outcomes following pH1N1/09 infection in obesity. It has long been known that obesity negatively affects pulmonary mechanics; however, recent evidence suggests that the immunomodulatory effects of obesity may play a significant contributory role to outcome following respiratory viral infection.

Here, we present a brief synthesis of the recent advances in our understanding of these immunomodulatory effects, with a particular focus on pandemic influenza.
ADIPOKINES, IFNS AND POTENTIAL MECHANISMS  

Obesity is a state of chronic low-grade inflammation; in addition to serving as an energy-storage depot, adipose tissue has endocrine functions, producing ‘adipokines’ that exert immunomodulatory effects. The most extensively studied adipokine expressed in the lung is leptin. Leptin, identified in 1994, is a 16 kDa pro-inflammatory adipokine produced predominantly by white adipose tissue that increases (in serum and bronchoalveolar lavage fluid) in proportion to the body adiposity and whose primary function is appetite control via the hypothalamus. It binds the Ob-Rb receptor, stimulating the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway, resulting in translocation of phosphorylated STAT proteins to the nucleus and subsequent gene transcription. Leptin has been implicated in physiological (lung maturation, respiratory control) and pathological states (asthma, COPD, obstructive sleep apnoea) within the respiratory system. Obese individuals exhibit high circulating levels of leptin, implying a situation of leptin resistance.

Inhibits JAK – STAT signal transduction.

Obesity may potentially attenuate the antiviral IFN response by leptin-induced upregulation of suppressor of cytokine signalling (SOCS), which inhibits JAK–STAT signal transduction.

Concurrently, despite similar viral titres in the lung, DIO mice exhibited diminished lung type I IFNα/β mRNA expression, reduced natural killer cell cytotoxicity and diminished lung pro-inflammatory cytokine (IL-6, TNFα and IL-1β) and chemokine (MCP-1 and RANTES) mRNA expression. Subsequent studies by other groups, using more clinically relevant influenza strains, including pH1N1/09, have similarly demonstrated increased mortality and attenuated IFN responses in DIO mice. Adaptive immune responses are also altered by obesity, with changes in T-cell number and function and diminished influenza vaccine responses.

CONCLUSIONS

Given that 1.46 billion adults worldwide are currently overweight and that pH1N1/09 resulted in approximately 59 million cases of severe illness in the USA alone, disturbingly little is known about the mechanisms underpinning the susceptibility to severe outcomes following respiratory viral infection in obesity. Here, we suggest that obesity may result in attenuated antiviral IFN responses; however, further studies in human tissues from obese individuals without confounding comorbidities are warranted. Additionally, research focus should broaden to include other potentially relevant adipokines aside from leptin as very little is known about their role in respiratory viral infection.

REFERENCES


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