BASIC SCIENCE FOR THE CHEST PHYSICIAN

# Obesity and susceptibility to severe outcomes following respiratory viral infection

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Received 21 January 2013
Accepted 1 February 2013
Published Online First 22 February 2013

## 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/m$^2$), 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.

## INTERFERON DEFICIENCY AND RESPIRATORY VIRAL INFECTIONS

Innate and adaptive immune responses protect against respiratory viral infections; however, against novel virus strains not previously encountered, innate responses are particularly vital. Upon recognition of viral-associated pathogen-associated molecular patterns by cellular pattern-recognition receptors, including toll-like receptors (TLRs) and retinoic acid-inducible gene 1-like receptors (RLRs), pro-inflammatory cytokines and antiviral interferons (IFNs) are produced, the latter of which induce IFN-stimulated genes (ISGs) to protect infected and neighbouring uninfected cells (figure 1). With regards to the outcome of influenza A infection, type I (α/β) and type III (λ) IFNs are of paramount importance.

IFN-deficient states, in which antiviral IFN responses are attenuated, have been described; individuals with atopic asthma have been shown to have increased susceptibility to severe outcomes following rhinovirus infection compared with healthy controls, exhibiting more frequent lower respiratory tract infections and suffering from more severe and longer lasting symptoms.[2] Recent studies by Johnston and colleagues have identified deficiencies in IFNα/β and IFNλ induction by rhinovirus infection in primary human bronchial epithelial cells and lung macrophages isolated from asthmatics. Similar deficiencies in rhinovirus-induced IFNs have also been reported by the same group in chronic obstructive pulmonary disease (COPD) and cystic fibrosis. The mechanisms explaining IFN deficiency in these conditions have not yet been elucidated.

## OBESITY AND ATTENUATED IFN RESPONSES FOLLOWING INFLUENZA A INFECTION

Asthma and pregnancy are established risk factors for severe outcomes following influenza infection. Deficient induction of IFNα and IFNλ upon pH1N1/09 or rhinovirus infection of peripheral blood mononuclear cells taken from pregnant women has recently been demonstrated, with deficiency especially prominent in pregnant asthmatics, a group who were particularly susceptible to poor outcomes in the 2009 H1N1 pandemic.[3] Given these data, and combined with corroborative evidence from mouse models of obesity and influenza infection described below, it is clear that IFN deficiency might explain other risk factors for severe outcomes in pandemic influenza infection, such as obesity.

Prior to the 2009 pandemic, Smith *et al* infected diet-induced obese (DIO) and lean C57BL/6J mice intranasally with the mouse-adapted influenza strain A/Puerto Rico/8/34 (A/PR/8/34). Mortality

**To cite:** Almond MH, Edwards MR, Barclay WS, *et al*. *Thorax* 2013;**68**: 684–686.

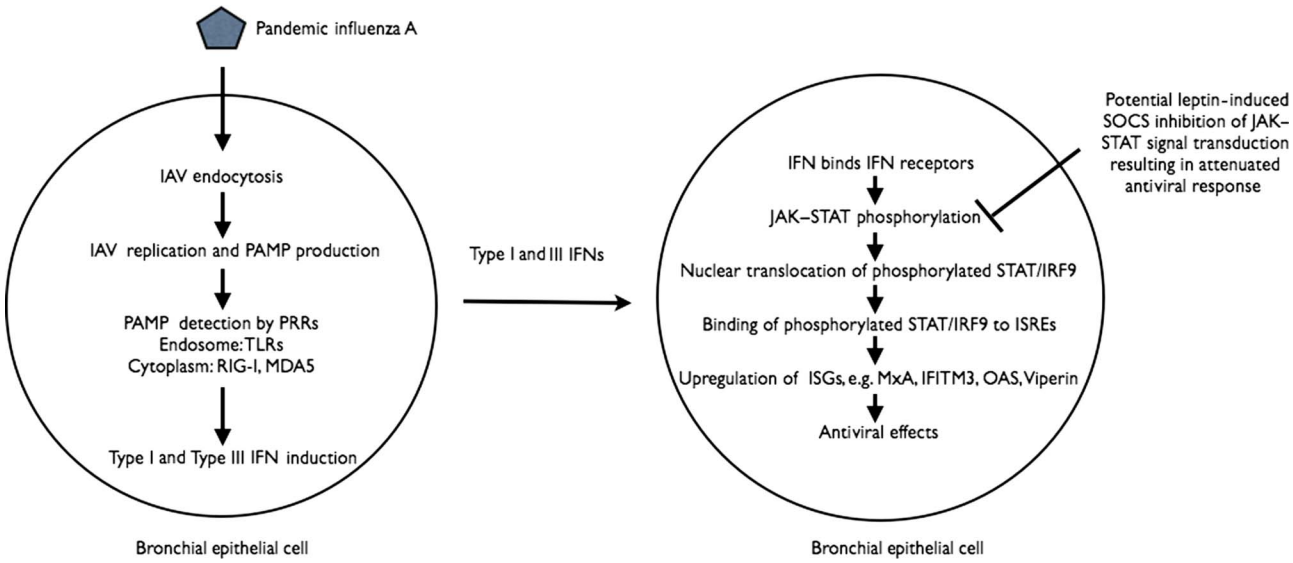


**Figure 1** Overview of influenza A virus (IAV) recognition and interferon (IFN) induction: influenza enters the cell via endocytosis and subsequently replicates, resulting in the generation of pathogen-associated molecular patterns (PAMPs) that are detected by pattern-recognition receptors (PRRs) such as the toll-like receptors (TLRs), retinoic acid-inducible gene I receptors (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), resulting in type I and type III IFN induction. Released IFN subsequently binds IFN receptors, resulting in Janus-activated kinase–signal transducer and activator of transcription (JAK–STAT) phosphorylation and complex formation with IFN regulatory factor 9 (IRF9). This complex translocates to the nucleus resulting in upregulation of antiviral IFN-stimulated genes (ISGs), such as MxA, IFITM3, oligoadenylate synthetase (OAS) and viperin. Obesity may potentially attenuate the antiviral IFN response by leptin-induced upregulation of suppressor of cytokine signalling (SOCS), which inhibits JAK–STAT signal transduction.

was significantly greater in the DIO mice (42%) compared with lean (5.5%), and lung pathology was markedly increased.[4] 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.

## 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', potentially mediated by upregulation of suppressor of cytokine signalling-3 (SOCS-3). Notably, IFN signalling also occurs via the same JAK–STAT pathway and is negatively regulated by SOCS-3, suggesting a potential mechanism by which IFN responses to respiratory viruses in obesity may be attenuated. Although this is still under investigation, Teran-Cabanillas *et al*[5] have recently evaluated the relationship between SOCS expression and type I IFN responses to TLR ligands in obese individuals, showing that basal SOCS-3 mRNA levels are elevated in obesity and associated with diminished type I IFN and pro-inflammatory cytokine responses. This work needs replication and further evaluation with virus infections in primary respiratory cell types but does, however, allude to a potential mechanism for the poor outcomes following virus infection seen in obesity.

## 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.

**Contributors** The literature review and drafting of the manuscript were wholly undertaken by the named authors.

**Competing interests** None.

**Provenance and peer review** Commissioned; internally peer reviewed.

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