Commentary

Skeletal Muscle in Influenza Virus Infection- a Key Player or a Bystander?

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Abstract | Skeletal muscle constitutes the largest soft tissue mass in the body whose principal roles are postural maintenance and locomotion. Comprising heterogeneous multi-nucleated fibres, skeletal muscle is one of more astounding and unusual tissues in the body in its ability to undergo dramatic phenotypic changes in response to physical demands, age and disease. The contributions of skeletal muscle to immune response and virus pathogenesis are increasingly recognized. Recent evidence strongly indicated that skeletal muscle cells fully support productive replication of influenza A virus (IAV) and could play an important role in disease outcome. We are of the opinion that skeletal muscle could be a key innate immune tissue/organ in the pathogenesis of influenza and other systemic viral infections which warrants further in-depth investigations.

Editor | Muhammad Munir, The Pirbright Institute, Compton Laboratory, UK
Received | March 04, 2015; **Accepted** | March 15, 2015; **Published** | March 16, 2015
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Citation | Kuchipudi, S.V and K. Chang. 2015. Skeletal muscle in influenza virus infection- a key player or a bystander? *British Journal of Virology*, 2(2): 19-21.

Influenza A virus (IAV) infection is arguably the most important global zoonotic disease that can seriously threaten human and animal lives on a massive scale. Influenza virus infection results in varying outcomes ranging from mild to severe fatal disease depending on the virus subtype and host species involved. Avian influenza viruses are significant zoonotic pathogens (Gibbs et al., 2009), in particular, Eurasian lineage highly pathogenic avian influenza (HPAI) H5N1 viruses that are panzootic in domestic poultry and wild birds (Peiris et al., 2007; Guan et al., 2009; I.H.Brown, 2008) could cause severe disease in humans with a fatality rate of about 60% (Thitithanyanont et al., 2010).

IAV is primarily a respiratory pathogen and respiratory epithelial cells are the primary early targets of IAVs. Hence, both primary and transformed respiratory epithelial cells have been the choice of cell type to study influenza virus host interactions in vitro (Seng et al., 2014). However, IAVs are known to cause systemic infections in humans with detectable viral antigen in a number of tissues in addition to the lung and the upper respiratory tract (Zhang et al., 2009).

Skeletal muscle is the most abundant soft tissue in the body comprising about 40-50% of body mass in the pig (Wolfe, 2006) and 35% and 16% of the total live weight of adult broiler chickens and ducks, respectively (Baquero-Perez et al., 2015). The importance of muscle in movement, posture bearing and metabolic functions is widely recognized (Wolfe, 2006). However, studies exploring the role of skeletal muscle in immune response and virus pathogenesis have emerged only recently. Muscle is increasingly being recognized as a major target innate immune tissue/organ with a capacity to produce cytokines and chemokines (De Rossi et al., 2000, Tournadre and Miossec,

2007), collectively termed myokines and respond to pro-inflammatory cytokines (Nagaraju et al., 1998).

Skeletal muscle appears to play a significant role in IAV infection in humans and birds. Human skeletal muscle cells support productive infection of IAVs in vitro (Desdouits et al., 2013) and there is a strong evidence to support the involvement of skeletal muscle in influenza illness in humans. Influenza-associated myositis (IAM) is one of the complications of influenza (Izurieta et al., 2000) and a substantial increase in pediatric IAM cases was recorded during the 2009 influenza pandemic (Buss et al., 2009; Davis, 2010). Highly pathogenic avian influenza (HPAI) viruses are known to cause systemic infections in birds (Kuchipudi et al., 2014) and live HPAI H5N1 viruses have been recovered from muscle of experimentally infected chickens (Das et al., 2008; Swayne and Beck, 2005; Tumpey et al., 2002) and naturally and experimentally infected ducks (Antarasena et al., 2006; Mase et al., 2005; Londt et al., 2008). We recently showed that chicken and duck skeletal muscle cells support productive replication of a range of IAVs (Baquero-Perez et al., 2015). Given the ability of chicken and duck skeletal muscle to support productive replication of HPAI H5N1viruses and survival of these viruses in exported meat for extended periods of time, highlights the importance of enforcing rigorous meat testing procedures to prevent trans- boundary spread of these deadly viruses.

Unlike most cell types used in virus studies, skeletal myofibres (myotubes) are post-mitotic multi-nucleated syncytia. The rich concentration of nuclei within a fibre could conceivably facilitate higher replication of viruses, especially those that replicate in host cell nucleus. There is also evidence that skeletal muscle could be a key target of other important human viruses. For example Dengue virus targets heart and skeletal muscles (Salgado et al., 2010) and human immunodeficiency virus (HIV) causes polymyositis (Sangle et al., 2010).

Skeletal muscle could be a key tissue in the pathogenesis of systemic viral infections. While the role of skeletal muscle in virus pathogenesis has largely been under-appreciated, with the recent advances in in-vitro skeletal muscle cell culture methods (Baquero-Perez et al., 2012; Desdouits et al., 2013), studies into this aspect could shed more light into the pathogenesis and epidemiology of systemic virus infections.

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