Moseley, J Virol Antivir Res 2012, 1:1
http://dx.doi.org/10.4172/2324-8955.1000e103

Journal of Virology & Antiviral Research

Editorial

A SCITECHNOL JOURNAL

Viral Interferon Antagonism: Making the Leap from the Bench to the Clinic

Gregory W. Moseley[1*]

Since the discovery of the type-I interferon (IFN) antiviral cytokines more than 55 years ago, and the subsequent identification of viral products able to inhibit IFN-mediated antiviral responses during the 1960s, it has become increasingly clear that viral interactions with the IFN system form a central host-pathogen interface in determining the outcome of infection. Recent years have seen an explosion in data regarding the mechanisms employed by viruses to subvert the IFN-dependent innate immune response, including the identification and detailed molecular characterisation of the mediators of viral immune evasion, collectively termed IFN antagonist proteins [1,2].

IFN antagonists are often multifunctional proteins that appear to mediate highly diverse mechanisms to target the IFN response; in some cases IFN antagonists also have additional, apparently concurrent roles in essential viral life cycle processes such as genome replication. The variety of mechanisms of viral IFN antagonism identified is remarkable, suggesting that viruses have evolved a great number of intricate strategies to block the response at many stages including IFN induction, IFN signalling, and the functions of antiviral IFN-stimulated gene products. Specific mechanisms include the expression of extracellular IFN receptor analogues as decoys for IFN, the binding and degradation or mislocalization of factors of the IFN system, inhibition of phosphorylation cascades, and general shut-down of cellular transcription [1,2]. Importantly, the fact that individual viruses/IFN antagonists appear to employ several distinct targeting strategies has led to the hypothesis that IFN antagonism involves a cumulative, coordinated strategy to comprehensively shut down the potent IFN system. However, a major caveat regarding this data has been its reliance on *in vitro* cell-culture based experiments with much of the mechanistic data relying on protein-based transfection studies [1,2]. Although this has proven invaluable in dissecting the molecular mechanisms by which IFN antagonists can impair antiviral responses, there has been a dearth of data relating to the genuine importance of viral IFN antagonism to virulence *in vivo*, and in particular to the contribution of specific antagonistic mechanisms. Thus, while the targeting of IFN antagonism/antagonists appears to have great promise for the development of new vaccines and antivirals, the real potential of this approach has remained largely unresolved.

***Corresponding author:** Dr. Gregory W. Moseley, Viral Immune Evasion and Pathogenicity Laboratory, Monash University, Australia, E-mail: greg.moseley@monash.edu

Received: June 20, 2012 **Accepted:** June 21, 2012 **Published:** June 23, 2012

Recent years have seen acceleration in research aimed at understanding the importance of IFN antagonists in *in vivo* infection, which combine *in vitro* observations with reverse genetics approaches and animal pathogenicity systems. Clear data has emerged from studies of viruses such as influenza, RSV and coronaviruses, with *in vivo* infection studies revealing that the IFN antagonists of these viruses are essential to virulence, and that engineered viruses defective in IFN antagonist expression or function may represent the progenitors of new live vaccine strains [2-4].

In a number of viruses the IFN antagonists are non-essential accessory proteins such that they can readily be deleted/ truncated without rendering virus non-viable. In the case of viruses such as Ebola, rabies and measles viruses, the situation is more complex as the IFN antagonists also play essential roles in genome replication/ transcription. Recent studies have begun to address this issue by targeting specific, discrete functional regions/ residues identified as important to particular mechanisms of IFN-antagonism in *in vitro* molecular studies. The characterisation of mutations of IFN-antagonists which can impair processes such as targeting of essential IFN-activated transcription factors and of IFN-induction pathways without significantly impairing replication has enabled the study of viable recombinant viruses defective in particular IFN-antagonistic processes [5,6]. The analyses of these viral strains in rodents and primates have begun to confirm the importance of these mechanisms in virulence.

Through these approaches, researchers have started to bridge essential studies of viral immune evasion at the molecular, viral, cellular and whole-animal levels, and are beginning to fully appreciate the importance of specific mechanisms of IFN antagonism in pathogenic virus infection. Future studies should further elucidate the quantitative contributions and interrelationships of individual antagonistic mechanisms in pathogenic infection, to build clearer models of the virus: IFN interface *in vivo*. Vitally, such studies are showing us that, even for complex multifunctional IFN-antagonists, it is possible to dissect out specific pathogenic mechanisms such that the targeting of IFN antagonism for a new generation of therapeutics and vaccines against highly pathogenic viruses is an exciting and very real possibility.

References

1. Randall RE, Goodbourn S (2008) Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. J Gen Virol 89: 1-47.
2. Versteeg GA, García-Sastre A (2010) Viral tricks to grid-lock the type I interferon system. Curr Opin Microbiol 13: 508-516.
3. Hai R, Martinez-Sobrido L, Fraser KA, Ayllon J, Garcia-Sastre A, et al. (2008) Influenza B virus NS1-truncated mutants: live-attenuated vaccine approach. J Virol 82: 10580-10590.
4. Zust R, Cervantes-Barragan L, Kuri T, Blakqori G, Weber F, et al. (2007) Coronavirus non-structural protein 1 is a major pathogenicity factor: implications for the rational design of coronavirus vaccines. PLoS Pathog 3: e109.

doi:http://dx.doi.org/10.4172/2324-8955.1000e103

5. Hartman AL, Dover JE, Towner JS, Nichol ST (2006) Reverse genetic generation of recombinant Zaire Ebola viruses containing disrupted IRF-3 inhibitory domains results in attenuated virus growth in vitro and higher levels of IRF-3 activation without inhibiting viral transcription or replication. J Virol 80: 6430-6440.

6. Ito N, Moseley GW, Blondel D, Shimizu K, Rowe CL, et al. (2010) Role of interferon antagonist activity of rabies virus phosphoprotein in viral pathogenicity. J Virol 84: 6699-6710.

Author Affiliation

Top

[1]*Viral Immune Evasion and Pathogenicity Laboratory, Monash University, Australia*