Q. "Describe the immune signalling pathways that are activated following an influenza infection. Which evasion methods has the virus developed to prevent elimination from the host?"

Viruses are extremely clever. As humans do, they continue to evolve in an arms race again host evolution of defences. Influenza is a single stranded RNA virus of the family Orthomyxoviridae that has evolved to be able to evade elimination from the host, despite successful recognition of its presence.

Influenza is recognised as a foreign pathogen following the identification of its RNA which is not capped with a methyl group at the 5' end, (like host RNA/DNA is), rather it has a triphosphate group at this 5' end. RIG-I (retinoic acid inducible gene-1), a pattern recognition receptor (PRR) is found within the cytosol and is a cytokine/helicase enzyme responsible for sensing this triphosphate on influenza RNA, binding to it and cleaving it. The enzyme has two CARD domains which interact with transcription factors to stimulate a conformational change allowing CARD to interact with IPS-1, associated with mitochondria. Upon the formation of this complex, IRF3 (interferon response factor 3) is transcribed and can induce the activation of NFkB through downstream signalling. MAP Kinase pathways are also stimulated which result in the translocation of IP1. These responses are sufficient to put the cell in an antiviral state. The distinction of foreign RNA from host RNA (and DNA) is essential to avoiding potentially devastating autoimmune responses.

The recognition of double stranded RNA relies on TLR's (toll-like receptors) present within the endosome membrane, these include TLR3, TLR7, and TLR9, though TLR7 is most commonly associated. RIG-I then initiates the expression of interferon's. Influenza is able to PREVENT the ubiquitination of the CARD domain of RIG-I, (by $TRIM_{25}$), this means that IFN (interferon) is not produced. Influenza has also been associated with the action of $TRIM_{21}$ which is thought to inactivate antibody responses.

Essential to its virulence, is the NS1 gene of Influenza, which has been shown to inhibit the action of RIG-I by binding to TRIM25, compromising its function. The importance of this protein has been revealed by experimental studies which have reported that apathogenic phenotypes occur