

Differential Biphasic Transcriptional Host Response Associated with Coevolution of Hemagglutinin Quasispecies of Influenza A Virus

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Abstract

Severe influenza associated with strong symptoms and lung inflammation can be caused by intra-host evolution of quasispecies with aspartic acid or glycine in hemagglutinin position 222 (HA-222D/G; H1 numbering). To gain insights into the dynamics of host response to this coevolution and to identify key mechanisms contributing to copathogenesis, the lung transcriptional response of BALB/c mice infected with an A(H1N1)pdm09 isolate consisting HA-222D/G quasispecies was analyzed from day 1 to 12 post infection (p.i). At day 2 p.i. 968 differentially expressed genes (DEGs) were detected. The DEG number declined to 359 at day 4 and reached 1001 at day 7 p.i. prior to recovery. Interestingly, a biphasic expression profile was shown for the majority of these genes. Cytokine assays confirmed these results on protein level exemplarily for two key inflammatory cytokines, interferon gamma and interleukin 6. Using a reverse engineering strategy, a regulatory network was inferred to hypothetically explain the biphasic pattern for selected DEGs. Known regulatory interactions were extracted by Pathway

Studio 9.0 and integrated during network inference. The hypothetical gene regulatory network revealed a positive feedback loop of Ifng, Stat1, and Tlr3 gene signaling that was triggered by the HA-G222 variant and correlated with a clinical symptom score indicating disease severity.

Beteiligte Forschungseinheiten

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