Influenza 2009 pandemic: Cellular immunemediated surveillance modulated by TH17 & Tregs.
Influenza 2009 pandemic: Cellular immune-mediated surveillance modulated by TH17 & Tregs

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Abstract:
Influenza A virus is a serious public health threat. Most recently the 2009/H1N1 pandemic virus had an inherent ability to evade the host’s immune surveillance through genetic drift, shift, and genomic reassortment. Increased age may have provided some degree of immunity, but vaccines against seasonal influenza viruses seldom yield cross-reactive immunity, exemplified by 2009/H1N1. Nonetheless, about 33% of individuals, over the age of 60, had cross-reactive neutralizing antibodies against 2009/H1N1, whereas only 6-9% young adults had these antibodies. Children characteristically had no detectable immunity against 2009/H1N1. Taken together, these observations suggest some degree of immune transference with at least certain strains of virus that have afflicted the human population in past decades. Because internal influenza proteins may exhibit less antigenic variation, it is possible that prior exposure to diverse strains of influenza virus provide some immunity to novel strains, including the recent pandemic strain (swine-avian A/H1N1). Current trends in immunological studies – specifically the modulation of cellular immune surveillance provided by TH17 and Tregs – also support the need for additional proteomic research for characterizing novel translational evidence-based treatment interventions based on cytokine function to help defeat the virus. Timely and critical research must characterize the impact of genetics and epigenetics of oral and systemic host immune surveillance responses to influenza A virus. The continued development and application of proteomics and gene expression across viral strains and human tissues increases our ability to combat the spread of influenza epidemics and pandemics.

Key words: A/H1N1 2009, cytokines, TH17, Tregs, cellular immunity, epigenetics, comparative effectiveness and efficacy research

Background & Description:
The inherent ability of the 2009/H1N1 pandemic influenza virus to evade immune surveillance through genetic drift, shift, and genomic reassortment is a serious public health threat [1]. Reactivity studies demonstrate species-specific antigenic differences in virulence as well as immune surveillance. The ‘avian-like’ swine viruses, including the recent pandemic strain (swine-avian A/H1N1) are characteristically most similar to avian viruses, and antigenic drift is more marked in ‘avian-like’ swine viruses than in classical swine strains [1].

Humoral Immunity:
Phage expression library molecular methods serve to characterize influenza antigens and antibodies. Immune characterization methods used whole-genome-fragment phage display libraries expressing fragments of 15-350 amino acids traversing all the proteins of influenza A/Vietnam/1203/2004 (H5N1). These oligopeptides induced B cell responses using neutralizing sera and monoclonal antibodies following full recovery from H5N1 infection. This approach yielded two broadly neutralizing human monoclonal antibodies with conformation-dependent epitopes. Sera of patients convalescing from H5N1 infection yielded potentially protective H5N1-specific antibody epitopes in the H5 HA, without any cross-reactivity with sera from H5N1-naïve or H1N1-/H3N2-seropositive controls. Additional promising epitopes include the neuraminidase catalytic site M2 ectodomain, and the PB1-F2 virulence factor. The germline gene VHH-69 yields a common neutralizing mechanism specific for the HA fusion domain. This region exhibits less neutralization escape, and could be a promising strategy for broad-spectrum therapeutic protection against pandemic influenza threats [2].

Cellular Immune Surveillance:
A wider use of influenza vaccines could control the severity of influenza pandemics. Moreover, comparative effectiveness and efficacy research increasingly indicates that humoral immunity alone may be insufficient to defeat influenza virus. Cellular immune events, mediated by sub-populations of both CD4+ and CD8+ T lymphocytes, contribute important surveillance against influenza virus, via cytokine modulation and the cross-reactivity that exists with virus-specific cytotoxic T lymphocytes (CTL, CD8+CD38+). For epitopes on NP and M1, CTL-based assays cross-reacted with viral strains from
patient infections that were up to 9 years apart [3]. The 1977/8 influenza A/H1N1 infections occurred in otherwise healthy children and young adults in up to 50% of the cases. In fact, actuarial inferences from epidemiological data suggest that people infected with the 1945-55 influenza A/H1N1 developed immune surveillance against that later strain, which persisted as immune memory [4].

Incidences for H5N1 infection and fatality rates are lower for the older than 40-year age group (10.9% and 32%, respectively) than less than 40-year age group (89.1% and 59%, respectively). While these differences may be due to exposure to seasonal infection or vaccination, and the higher fatality rate may be due to differences in virus replication rates, the persistence of antigen-specific CD8+ T cells confers the ability of CTL to clear infection and assists in reducing viral pathogenesis [5]. Greater than 97% of US H1N1 recovered isolates are from patients who are younger than 26 years old. For people over the age of 35, the recovery rate of H1N1 viruses drops to 4-5%. In the elderly, T-cell responses correlate better with vaccine protection than humoral immunity [6].

Impact of Immunology on Clinical Outcome:
In most cases, patients with H1N1 influenza have self-limited illness. However, some patients, especially those with co-morbidities, are more susceptible to influenza complications. In addition, the fine regulation of cellular immunity requires both vigorous effector responses and the maintenance of regulatory T subsets, such as TH17 and Tregs. Any disturbances in the balance between these two opposite activities of immune system, including tumor microenvironment, pregnancy or immune senescence, can seriously jeopardize this balance, and profoundly affects epigenetic regulatory controls of cellular immune surveillance [10-12]. The latter actually provides a suggestive rationale to account for the anomaly of the 2009 influenza pandemic that exhibited higher lethality in younger patients than in the elderly, as noted above, because it is conceivable that the Tregs/TH17 ratio may be biased toward Tregs with age, thus yielding to a suppression and inhibition of TH17-mediated responses during senescence [10].

In conclusion, current trends suggest that immunological studies support the need for additional proteomic research for characterizing novel treatment interventions based on chemokine and cytokine functions to help defeat the influenza virus. Timely and critical research must characterize the impact of genetics and epigenetics of oral and systemic host immune surveillance responses to H1N1. The continued development and application of proteomics and gene expression to diagnosis and characterization of influenza viruses and host responses across viral strains and human tissues ensure our ability to combat the spread of influenza epidemics and pandemics by means of carefully articulated research synthesis designs for developing and testing Translational Comparative Effectiveness and Efficacy Research and Analysis for Practice (T-CEERAP) interventions.

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