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Cell mediated immunity to meet the avian influenza A (H5N1) challenge

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Summary Avian influenza A subtype H5N1 virus with its recombination potential with the human influenza viruses presents a threat of producing a pandemic. The consensus is that the occurrence of such a pandemic is only a matter of time. This is of great concern, since no effective vaccine is available or can be made before the occurrence of the event. We present arguments for the use of cell mediated immunity for the prevention of the infection as well as for the treatment of infected patients.

Transfer factor (TF), an immunomodulator of low molecular weight capable of transferring antigen-specific cell mediated immune information to T-lymphocytes, has been used successfully over the past quarter of a century for treating viral, parasitic, and fungal infections, as well as immunodeficiencies, neoplasias, allergies and autoimmune diseases. Moreover, several observations suggest that it can be utilised for prevention, transferring immunity prior to infection. Because it is derived from lymphocytes of immune donors, it has the potential to answer the challenge of unknown or ill-defined pathogens. Indeed, it is possible to obtain an antigen-specific TF preparation to a new pathogen before its identification. Thus, a specific TF to a new influenza virus can be made swiftly and used for prevention as well as for the treatment of infected patients.

Introduction

An avian influenza A virus (H5N1) has recently appeared in Asia [1,2]. It has crossed the species barrier infecting patients, and often lethally so [3–5]. Its pathogenicity is high and increasing [6–8]. Usually a respiratory failure is caused by diffuse, ground-glass infiltrates and manifestations of the

Abbreviations: ADRS, Acute Respiratory Distress Syndrome; CBO, Congressional Budget Office; CMI, Cell-Mediated Immunity; CMV, Cytomegalovirus; EBV, Epstein Barr Virus; HHV-6, Human Herpes Virus 6; HSV, Herpes Simplex Virus; LMI, Leukocyte Migration Inhibition; SIV, Simian Immunodeficiency Virus; TF, Transfer Factor; VZV; Varicella Zoster Virus.

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acute respiratory distress syndrome or ARDS. Its potential of generating a pandemic is extremely high, especially by recombination in infected patients with the seasonal human influenza virus rendering the new viral entity highly contagious, and making human to human transmission possible.

The strategy to avert this threat is use of antivirals for treatment, and vaccination for prevention. Regrettably, the number of effective antivirals available is limited, and the preparation of a vaccine at the experimental stage. However, another approach is worth considering: the use of cell mediated immunity (CMI), viz. an influenza-virus-specific Transfer Factor (TF) for the prevention and the treatment of the infection.

The concept of TF was first reported in 1954 [9—11]. Over fifteen hundred publications have since been established that lymphocyte-dialyzable-extracts from immune donors can transfer antigen-specific CMI information in vitro to naïve lymphocytes or in vivo to patients and experimental animals. Since CMI plays a crucial role in the control of infectious, parasitic, autoimmune diseases, and cancer, TF has been used over the past 30 years for treating such conditions and sometimes with dramatic success. Because it was believed to be species-specific, for many years TF was prepared from the lymphocytes of immune blood donors, viz. patients' household contacts. In 1974, it was shown that human TF with known specificities could be replicated in tissue culture, using a lymphoblastoid cell line [12,13], and in the late 1970s, evidence was presented that antigen-specific TF obtained from mammals after immunisation with a given antigen was active in humans [14,15].

If an active-household TF can be used for patients' treatment, or replicated in tissue culture, it is obvious that the immune cells recognize epitopes of interest, even if the physician has not identified the pathogen. This '*black box*' effect can also be used for TF production in animals, i.e., by injecting laboratory animals with a TF from household contacts, thus solving the availability problem especially for non-identified pathogens. Moreover, animal immunisation with partially identified microorganisms may also be utilised for production of a TF with a new specificity.

The rationale for the in vitro replication stems from the original Lawrence observations. He had shown that a TF of the donor's specificity can be retrieved from a naïve recipient whose lymphocytes apparently act as a photocopier multiplying the injected TF and thus becoming a subsequent effective donor. Biochemical data suggest that the activity is carried by a ribonucleopeptide of ca. 5000 Da. Yet, at the molecular level, the mechanism of action remains largely unknown, and because of the presence of a blocked amino terminus, attempts to sequence the peptide have failed. Recent work has partially identified the amino acid sequence, thus giving partial biochemical identity to a still elusive moiety [16]. However, in order to grasp the mode of action, unravelling the rest of the peptide sequence and identifying the ribonucleotides remains of the essence.

Although the transfer of antigen-specific CMI information by this extract is thought-provoking and has been challenged on theoretical grounds, the experimental evidence, albeit readily reproducible has never been contested [17]. Various explanations for understanding the mechanism have been proposed, but so far none has been proven entirely satisfactory. For instance, studies with such rare antigens as coccidioidin [18] or keyhole limpet haemocyanin (KLH) [19] preclude non-specific enhancement of lapsed pre-existing immunological memory.

At least three types of antigen-specific activities are present in lymphocyte dialysates: inducer or helper, suppressor and cytotoxic [20]. Data suggest that antigen-specific inducer and antigen-specific suppressor and cytotoxic transfer factors may be derived respectively from CD4 and CD8 lymphocyte sub-populations (Viza, unpublished data). This accounts for the immunomodulating activity of the extract, boosting the immune response via the CD4 lymphocytes, and decreasing the immune over-reactivity by stimulating the suppressor cells.

TF has been proven to be an effective treatment for a variety of pathologies. In favour of its clinical use, one should stress its lack of toxicity and the absence of side effects. Indeed, for over three decades, several hundreds of patients have received large amounts of TF and none has ever reported signs of acute or chronic toxicity when TF was prepared by expert physicians.

Clinical observations

Since the 1970s seminal work of Fudenberg's group on the use of TF for treating neoplasias, viz. osteosarcoma [21—23], numerous publications have produced evidence that TF can be used as an adjuvant treatment for cancer, e.g. Burkitt's lymphoma [24], nasopharyngeal carcinoma [25], urological neoplasias [26,27]. Several parasitic diseases are known to respond to TF therapy, e.g. cutaneous leishmaniasis [28—30], schistosomiasis and cryptosporidiosis [31], whereas rare syndromes such as Behçet's, probably of viral origin, and Wiskott—Aldrich's genetic immunodeficiency are both