Using Transfer Factor to Strengthen Cell-Mediated Immunity

Presented by
Aaron White, PhD
Introduction

- 1949 – NYU immunologist Dr. H. Sherwood Lawrence transferred immunity to tuberculosis (TB)

- Injected filtered leukocyte extract from TB+ patient into TB- patient

- TB- patient developed positive delayed skin test reaction to tuberculin

- He called the mystery component of leukocyte extract, “Transfer Factor”
Definition of transfer factor

- Borkowsky and Lawrence (1979):
  
  “‘Transfer Factor’ was originally coined as a convenient shorthand to describe the material or materials present in leukocyte extracts or dialysates of skin test-positive donors that had the capacity to transfer cutaneous delayed type hypersensitivity responses to skin test-negative human subjects.”

- Now commonly used in the plural – “transfer factors”
What are transfer factors?

- Peptides of low molecular weight (approximately 5 kDa) and perhaps RNA
- Made by Th1 CD4+ Helper T-cells
- Present in colostrum
- Three components - Antigen specific region, region that binds to Th1 Helper T-cells, and a connector
- Can strengthen cell-mediated immunity against specific pathogens
- Can be used to immunize against specific pathogens

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Cell-mediated (Th1) and Humoral (Th2) Immunity

1. Innate immune response
   - Unlearned
   - Natural Killer cells, phagocytes

2. Adaptive immune response
   - Learning and memory (immunity) for specific pathogens

   - Humoral response
     - Extracellular infections
     - T-helper 2 (Th2)
     - B-cells
     - Antibodies
     - Complement system
     - IL10 (-)

   - Cell-mediated response
     - Intracellular infections and cancers
     - T-Helper 1 (Th1)
     - Cytotoxic T-cells
     - Transfer factors
     - IL10 (-)

   - Regulatory T-cells, Th3 cells
     - Calm the immune response down

   (+) IL4
   (-) IL10
   (+) IL12
   (+) TNF-β
   (+) IFN-γ
   (+) IL4
   (-) IL4
   (-) IFN-γ
   (-) IL12
Basic model of antibody-mediated (Th2) immunity with a virus as the pathogen

- Virus
- Phagocytosis
- Th2 CD4+
- B-cells
- Antibodies
- Disabled virus

Phagocytes show antigens (different forms) to T-cells and B-cells, which then interact via cytokines. B-cells are given the green light to crank out antibodies.

If the pathogen is familiar it is engulfed by phagocytes called macrophages. Dendritic cells are in charge of dealing with new threats. These cells kick off the immune response.

Antibodies tag and sometimes disable viruses and other pathogens and help provide immunity against re-infection.

Basic model of cellular-mediated (Th1) immunity with a virus as the pathogen

Phagocytes present antigens and cytokines to Th1 CD4+ cells, which release transfer factors to tag antigens. Th1 cytokines give CD8+ Killer T-cells the green light to seek and destroy tagged body cells. Transfer factors help protect against re-infection.

To summarize thus far

- In essence, transfer factors appear to be the smaller siblings of antibodies but are used to label self-cells infected with pathogens (cell-mediated immunity) rather than labeling free-floating pathogens with antibodies (humoral immunity).

- They are so named because, when extracted from exposed patients and given to non-exposed patients, they appear to transfer cell-mediated immunity.
Research on transfer factors

**In vitro studies**

- Direct antibacterial effect against *Staph, Strep, E. coli* and other pathogens (Franco-Molina et al, 2006).

- Inhibited the growth of breast cancer cells (Mendoza-Gamboa et al., 2008) and increased the death of breast cancer cells (Franco-Molina et al., 2006).

Research on transfer factors

In vivo immunological effects

- Increased Th1 cytokines e.g. INFγ (Kirkpatrick et al., 2000).
- Reduced size of glioma in rat brains and increased number of dying tumor cells (Pineda et al., 2005).
- Transfer of cell-mediated immunity as evidenced by delayed-type hypersensitivity (Borkowsky and Lawrence, 1979).
- Increased levels of Th1 Helper T-cells, Cytotoxic T-cells and Natural Killer cells (Pineda et al., 2005; Estrada-Parra et al., 1995; Granitov et al., 2002).

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Example observation of effects of transfer factor on Natural Killer (NK) cell levels*

**Subjects**
- 20 patients with NK cells levels no more than 110% of the lower end of the normal range

**Methods**
- 10 patients given 2 capsules TF Multi-Immune per day for 30 days
- 10 patients given 4 capsules TF Multi-Immune per day for 30 days

**Outcomes**
- 2 capsules per day increased NK cell levels 235%
- 4 capsules per day increased NK cell levels 620%

*Unpublished results provided by Researched Nutritionals

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Research on transfer factors

*In vivo clinical effects*

- Diminished frequency and duration of herpes outbreaks (Khan et al., 1981; Estrad-Parra et al., 1995; Pizza et al., 1996; Meduri et al., 1996).

- Increased survival times for those with cancer of the prostate (Pizza et al., 1996) and lung (Pilotti et al., 1996; Franco-Melina et al., 2008).

- Improved cognitive function in patients with Alzheimer’s disease (Leszek et al., 2002; Bilikiewicz and Gaus, 2004; Stewart, 2008; Szaniszlo et al., 2009).

- Improved clinical markers in HIV/AIDS patients (Raise et al., 1996; Granitov et al., 2002).
Comment by authors of a study on transfer factors and HIV

“We conclude that transfer factors therapy considerably improves the immune status of HIV-infected patients and can be recommended in combating the pathogenesis of the disease. Further studies are needed to determine optimal therapy, the necessity to repeat courses of the treatment and the frequency of therapy needed.”

- Granitov et al. (2002)
How do they work?

- The existing research suggests transfer factors provide antigen-specific immune information that helps the body defeat and avoid infections best dealt with through cell-mediated immunity – but how?
  - Thought to have antigen binding section and section that binds to Th1 Helper T-cells and perhaps CD8+ Cytotoxic T-cells
  - Thought to facilitate binding of Th1 cells to antigen and change gene expression and cytokine release in Th1 cells
  - They stimulate the production of a variety of cell types involved in the Th1 response – Cytotoxic T-cells, Helper T-cells, macrophages and Natural Killer cells – helping the body fight existing infections harder and avoid new ones
Potential future uses of transfer factors

- List of known pathogens growing and includes a variety of intracellular agents (mycoplasma; cell-wall deficient bacteria; XMRV, HHV6 and other viruses).
  - Transfer factors can be (and are) custom made for pathogens.
- Many pathogens suppress Th1 immunity (HIV, Lyme) and require cell-mediated immunity to be beaten.
  - Transfer factors strengthen cell-mediated immunity.
- Could be helpful for autoimmune conditions involving too much Th2 (e.g., lupus) but seem less likely to be effective against those involving too much Th1 (e.g., multiple sclerosis).
- Cancer treatment
- Could be used to support or even replace many vaccines, which skew the immune system in the Th2 direction.
“Vaccines often elicit an immune response that does not actually protect against the disease. Most vaccines preferentially induce the formation of antibodies rather than cell-mediated immunity. This is fine for those diseases caused by toxins (diphtheria, tetanus), extracellular bacteria (pneumococci), even viruses that must pass through the blood to reach the tissues where they do their damage (polio, rabies). But viruses are intracellular parasites, out of the reach of antibodies while they reside within their target cells. They must be attacked by the cell-mediated branch of the immune system, such as by cytotoxic T lymphocytes (CTLs). Most vaccines do a poor job of eliciting cell-mediated immunity.”

- John Kimball, PhD (2008)
Transfer factors might be able to convey protection against infections via Th1 immunity

“Sixty-one patients with leukemia and no immunity to chickenpox were given dialyzable transfer factor or placebo and followed for 12 to 30 months in a double-blind trial designed to examine the clinical efficacy of transfer factor. Sixteen patients in the transfer-factor group and 15 in the placebo group were exposed to varicella zoster, and most of them had a rise in antibody titer. Chickenpox developed in 13 of 15 exposed patients in the placebo group but in only one of 16 in the transfer-factor group.”

- Steele et al. (1980)
Transfer factors might be able to convey protection against infections via Th1 immunity

“Avian influenza…presents a threat of producing a pandemic. 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)…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 utilized for prevention, transferring immunity prior to infection…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.”

- Pizza et al. (2006)
Protocol considerations

Properly prepared oral transfer factor preparations have powerful effects on the immune system

- Start low go slow – perhaps $\frac{1}{4}$ to $\frac{1}{2}$ dose for the first few weeks

To pulse or not to pulse?

Why it might be a good idea

- Many successful clinical studies used weekly or monthly injections or pulsed oral treatment (staggered dosing, periodic breaks)
- Activates the immune system then allows time for it to work and then calm down before the next round of signals
- Potential for immune tolerance to a constant signal

Why it might not be a good idea

- When fighting pathogens with rapid antigenic drift or pleomorphic bacteria (e.g., Borrelia) it might be best to keep the pressure on
From research to practice

- Broad-spectrum and targeted transfer factors
  - Broad spectrum include a wide mix of transfer factors from colostrum and/or egg yolk
    - Produce a robust boost in measures of Th1 immune activity (e.g., NK cell levels)
      - Logical for conditions that involve Th2 hyperactivity (e.g., asthma, allergies) and in cases where cell-mediated immune activity is beneficial (e.g., pneumonia, herpes, Candida, TBD)
  - Targeted transfer factors are those created against specific antigens associated with specific pathogens
    - Boost Th1 immune responses in general but also aim the immune system toward the pathogen of interest
      - Logical when a specific pathogen is documented or suspected and to help protect the body from infection with a specific pathogen down the road
From research to practice

- **Patient education**
  - Jarisch-Herxheimer *type* reactions
    - Toxic reaction to rapid bacterial die-off
    - Term now used for all toxicity related to bacterial die-off, die-off of infected self-cells, etc.
    - Temporary exacerbation of existing symptoms
    - Common early in antibiotic treatment
    - Can occur with transfer factors at any time, often first few weeks
  - Cytokine reactions
    - Increased cytokine levels contribute to physical symptoms of illness (e.g., inflammation, fatigue) and also psychological symptoms (e.g., depression, anxiety)
    - Contributes to symptom flare

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In honor of Dr. Lawrence

April 8, 2004

H. Sherwood Lawrence, 87, Immunology Pioneer

By LAWRENCE K. ALTMAN

Dr. H. Sherwood Lawrence, a pioneering immunologist who helped found the branch of biology that explores the function of lymphocytes, a type of white cell in blood and lymph nodes, died on Monday in Manhattan. He was 87.