Transfer Factor Therapy Revisited

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CONTENT.
Ilya Metchnikoff

Phagocytosis theory

“eating to eat”
Ilya Metchnikoff

Phagocytosis theory

“eating to defend”
Hans Ernst Buchner

Humoral theory of immunity
Karl Landsteiner & Merrill Chase

Cell-mediated immunity
Transfer of delayed cutaneous hypersensitivity

A. Picryl chloride + MTb
B. DCH – to DCH +
C. Peritoneal exudates out
D. Washed peritoneal exudates in
E. DCH – to DCH +
Sherwood Lawrence

Transfer factor

Lymphocytes or their lysates
DCH transfer specific to donor
Rapid in onset
Long duration
Not inactivated by trypsin, DNase or RNase
Low molecular weight “informational” or “activator” molecule
Gene de-repressor?
Others

Colostrum & cloned lymphocytes
DCH transfer both specific & nonspecific
>200 highly polarized, hydrophilic, low molecular weight peptides
Functions across species
Well tolerated & stable

Non-immunogenic
No viruses > 10,000 mw
Mild pain at site of injection
Readily sterilized
Can store in lyophilized state > 5 years
Occasional flare of illness
Similarities to thymosins

Thymosin-α
- Pleiotrophic peptide
- Activates moDC and pDC subsets
- Promotes T & NK cell maturation
- Stimulates cytokine production and CTL-mediated cytotoxicity
Similarities to thymosins

Prothymosin-α

- A histone H1-binding polypeptide
- Synergizes with CREB binding protein to stimulate AP1- and NF-κB-dependent transcription by chromatin remodeling
- Immune stimulation is mediated primarily by induction of monocyte-derived dendritic cell maturation and by monocyte activation
Dendritic cells

Immature  Mature
Dendritic cells

- Premier antigen-presenting cells (MHC I & II)
- Activate self-replicating (IL-2 +) cytotoxic T cells
- Activate thymocytes
- Activate T helper cells
- Activate macrophages
- Promote TH1 differentiation
- Kill viruses (plasmacytoid DCs)
- Detect PAMPs (TLRs)
Macrophages

- Antigen presentation (MHC II)
- Immune response amplification
- Inflammation
- Pathogen ingestion/killing
- Apoptotic T cell clearance
- Chronic graft rejection
Clinical Studies
Patients

Candidiasis & congenital thymic disorders
Congenital CMV infection
Prosthetic valve candida endocarditis
Chronic active hepatitis
Disseminated molluscum contagiosum
Recalcitrant malignancies
My first medical record (circa 28,000 years b.c.)
Methods

TF prepared from leukocyte dialysates (DLE) (<10,000 molecular weight)
DCH testing with candida, SK-SD, trichophyton, mumps antigens +/- DNBC
Standard assays were used to measure T & B cells, immunoglobulins, ABO isoagglutinins, HMP shunt activity, complement, leukocyte chemotaxis, migration inhibition factor (MIF), mitogenic responses, and FcyRs.
Methods

T rosette assay: an early marker for CD3+ T cell activation

- Both CD4+ & CD8+ T cells & thymocytes
- Correlates with DCH to specific antigen, allogeneic cell cytotoxicity, and B cell activation
- Rosetting populations increase with mitogenic stimulation (PHA, ConA)
Methods

Migration Inhibition Factor (MIF)

- Multifunction pro-inflammatory cytokine produced by T-lymphocytes & macrophages
- Suppresses anti-inflammatory effects of glucocorticoids
- Increases endothelial leukocyte recruitment and adhesion
- Direct chemokine effects
- Induces DC maturation and IL-12 production
Congenital thymic disorders

Autoimmune polyendocrinopathy syndrome type 1
APS-type 1

Mutations in transcriptional regulator and proapoptotic factor AIRE in the thymus & in monocyte-derived dendritic cells (moDCs)

- Impaired clonal deletion of self-reactive thymocytes.
- Autoimmune destruction of adrenal & parathyroid glands
- Tolerance to candida infection
APS-type 1

Positive selection
MHC–self peptide recognition = promoted

Thymic epithelial cells

Negative selection
MHC-self peptide recognition = fail (98%)
APS-1 = graduate

Thymic dendritic cells
K. F.

CMC at 3 months of age
No response to mycostatin, amphotericin, 5-fluorocytosine
Addison’s disease & hypoparathyroidism
Anergic
Monocytopenic (including FCyR+ cells)
High levels of IgG anticandida antibody
K. F. - pretreatment

Positive cultures for *C. albicans*
K. F. - pretreatment

- DCH to candida antigen
K. F. - pretreatment
Response to treatment

![Graph showing the relationship between mean monocyte count (cells/μm^3) and transfer factor dose (LEU x 10^9).]
Response to treatment

![Graph showing the relationship between TF dose and peak monocyte count. The graph includes a trend line with a slope, indicating a positive correlation. The x-axis represents TF dose (LEU x 10^9), and the y-axis represents peak monocyte count (cells/cumm). The equation of the line is P = <0.001.]
Response to Treatment

FCyR+ monocytes

Migration inhibition

Control
Pre-Rx
Post-Rx

2.9 x 10^9 LEU TF
K. F. – post-treatment

+ DCH to candida antigen
K. F. – post-treatment
Dendritic cells

Activate self-replicating (IL-2 +) cytotoxic T cells
Activate thymocytes
Activate T helper cells
Activate macrophages
Promote TH1 differentiation
Kill viruses (plasmacytoid DCs)
Detect PAMPs (TLRs)
Happier times
Congenital thymic disorders

DiGeorge syndrome
DiGeorge syndrome

Immune deficiency due to single copy deletion of TBX1

Encodes transcription factor T-box-1 which is required development of thymic epithelium
DiGeorge syndrome
L. H.

23-day-old baby girl
Low calcium, parathyroid hormone
Absent thymic shadow
Truncus arteriosus Type IV
Characteristic phenotype
Candidiasis
Immune assessment

Hypoergic
Marked T cell lymphopenia
Diminished mitogenic responses to PHA
Dendritic cells

- Activate self-replicating (IL-2 +) cytotoxic T cells
- Activate Thymocytes
- Activate T helper cells
- Activate macrophages
- Promote TH1 differentiation
- Kill viruses (plasmacytoid DCs)
- Detect PAMPs (TLRs)
Congenital CMV
Positive urine & sputum cultures
L. S.
Immune assessment

Absent MIF production by CMV-stimulated PBMC

Patient

Control
## Response to treatment

<table>
<thead>
<tr>
<th>Dose (L&lt;sub&gt;U&lt;/sub&gt;)</th>
<th>0.3</th>
<th>1.0</th>
<th>2.0</th>
<th>1.5</th>
<th>1.0</th>
<th>1.5</th>
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<tr>
<td>IV Titer</td>
<td>16</td>
<td>32</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>16</td>
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<tr>
<td>F Response</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>IV culture</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<table>
<thead>
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<th>Time post treatment</th>
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<tr>
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<td>7</td>
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<tr>
<td>11</td>
</tr>
<tr>
<td>17</td>
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<tr>
<td>34</td>
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</table>
Post-treatment

MIF production in response to CMV

- CMV

+ CMV
Post-treatment

Negative urine & sputum cultures
Dendritic cells

- Activate self-replicating (IL-2 +) cytotoxic T cells
- Activate thymocytes
- Activate T helper cells
- Activate macrophages
- Promote TH1 differentiation
- Kill viruses
- Detect PAMPs (TLRs)
Happier times
A Medical First

Baby Cured of Virus That Causes Mental Retardation

...New Technique Could Help 1,000 Babies a Year

A team of researchers at the Children's Hospital of Philadelphia has successfully cured a child of a viral infection that caused severe mental retardation. This is the first time such a cure has been achieved.

The virus, which is called CMV (Cytomegalovirus), is a common infection that can cause serious damage to the brain and other organs in newborns. In some cases, it can lead to permanent disabilities such as hearing loss, vision problems, and mental retardation.

The researchers used a combination of antiviral drugs and a new treatment method to eliminate the virus from the child's body. The child, who is now 18 months old, is developing normally and is expected to have a normal lifespan.

The success of this treatment opens the door to new possibilities for treating similar conditions in the future. The researchers are now working on developing a vaccine to prevent CMV infections in the first place.

Source: Children's Hospital of Philadelphia
Candida prosthetic valve endocarditis
Failed on two years of parenteral antimicrobial therapy (amphotericin B, 5-fluorocytosine)

Reinfected two aortic valve prostheses

Febrile, toxic, semicomatose, petechial rash

Positive urine, blood cultures for *C. krusei*
Immune assessment

Absent DCH to candida antigen
Leukopenia with 0% monocytes
Diminished MIF production with candida antigen
High levels of IgG anticandida antibody
Response to treatment

Blood cultures:
- Day 0: +
- Day 3: -
- Day 10: -

DCH to candida:
- Day 0: 0
- Day 3: +
- Day 10: +

Graph:
- Y-axis: leu TF
- X-axis: day of treatment
- Red bar: monocytes (%)
- Green bar: migration inhibition (%)
- Blue bar: WBC (per cumm)

2.48 x 10^9 LEU TF
Response to treatment

+ *C. krusei* culture at 3 months
Dendritic cells

- Activate self-replicating (IL-2 +) cytotoxic T cells
- Activate thymocytes
- Activate T helper cells
- Activate macrophages
- Promote TH1 differentiation
- Kill viruses (plasmacytoid DCs)
- Detect PAMPs (TLRs)
Chronic active hepatitis
B. J.

8 year-old girl with biopsy-proven chronic active hepatitis
### B. J.

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>6 weeks</th>
<th>3 months</th>
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<tr>
<td>OT</td>
<td>330</td>
<td>850</td>
<td>320</td>
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<td>PT</td>
<td>370</td>
<td>600</td>
<td>360</td>
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<tr>
<td>Anorexia</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Two closely spaced doses of TF totaling 4.8 billion LIU given at baseline
Disseminated molluscum contagiosum

Atopic dermatitis
Severe generalized eczema
Serum IgE >1,000 IU/mL
+ RAST to inhalants, foods
Recalcitrant disseminated molluscum
No response to high dose TF
Dendritic cells

- Activate self-replicating (IL-2 +) cytotoxic T cells
- Activate thymocytes
- Activate T helper cells
- Activate macrophages
- Promote TH1/Th2 differentiation
- \(\times\) Kill viruses (plasmacytoid DCs)
- Detect PAMPs (TLRs)
# Transfer Factor in Malignancies

<table>
<thead>
<tr>
<th>Tumor</th>
<th>TF dose (LEU)</th>
<th>TF source</th>
<th>MIF*</th>
<th>Tumor response</th>
<th>Immunosuppression</th>
<th>Outcome &amp; survival**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma, metastatic</td>
<td>11 billion</td>
<td>non-specific</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>death, 3 months</td>
</tr>
<tr>
<td>Adenocarcinoma colon, metastatic</td>
<td>19 billion</td>
<td>specific &amp; non-specific</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>death, 5 months</td>
</tr>
<tr>
<td>Squamous cell carcinoma skull</td>
<td>9.3 billion</td>
<td>non-specific</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>death, 2 months</td>
</tr>
<tr>
<td>Melanoma, metastatic</td>
<td>6 billion</td>
<td>specific</td>
<td>nd</td>
<td>transient ↓ skin nodules</td>
<td>+</td>
<td>death, 5 months</td>
</tr>
<tr>
<td>Carcinoma pancreas</td>
<td>24 billion</td>
<td>non-specific</td>
<td>nd</td>
<td>?</td>
<td>+</td>
<td>alive, 12 months</td>
</tr>
</tbody>
</table>

* Response to tuberculin & candida antigens. **From onset of transfer factor therapy.

8 Denotes survived similar tumor.
Conclusions

TF therapy shows promise as a treatment for congenital thymic disorders, and as an adjuvant in the treatment of certain recalcitrant viral and fungal infections in selected patients.

Further studies of its molecular contents, modus operandus & clinical efficacy are warranted.
Low molecular weight “informational” or “activator” molecule
Gene de-repressor?