Maternal Microchimerism in Human Immunodeficiency Virus and Acquired Immunodeficiency Disease

Yuli McCann, MD
University of Washington
Chief of Medicine Rounds
May 4, 2010
• Background
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Microchimerism (Mc): a small number of cells (or DNA) derived from a genetically disparate individual
Where can you find microchimerism?

- Grafts/Transplantation
- Transfusions
- Twin-Twin
- Maternal-Fetal Microchimerism
  - Bi-directional exchange between mother and fetus during pregnancy
“I contain multitudes”

Walt Whitman

Both fetal and maternal microchimerism are common in healthy individuals.

Can have detrimental, neutral or beneficial effects on the host.

This can be dependent on other factors, eg. HLA genes and HLA relationship of host and non-host cells.
Fetal Microchimerism (FMc)

- Fetal DNA in mothers
- FMc detectable during pregnancy in maternal blood as early as 4-5 weeks gestational age (Thomas et al. 1994)
- Male DNA in woman who had given birth to sons, some decades previously (Bianchi et al. 1996)
• FMc identified within T cells, B cells, monocytes, macrophages, natural killer cells (Evans et al. 1999)
• Found in multiple different types of tissues (Stevens et al. 2004; Koopans et al. 2005, 2008)
FMc: Good or Bad?

- Amelioration of RA during pregnancy
  - Significant inverse correlation of FMc with arthritis activity (Yan et al. 2006)
- Contributes to tissue repair?
- Protective role in breast cancer? (Gadi et al 2007, 2008)
FMc and Systemic sclerosis (SSc)

- Higher levels of FMc in the peripheral blood of women with SSc compared to healthy woman (Nelson et al. 1998)
- FMc found (Artlett et al. 1998) and at higher levels in skin biopsies of SSc patients compared to controls (Ohtsuka et al. 2001)
- FMc was found in multiple organs in women with SSc but infrequently in controls (Johnson et al. 2001)
• Increased FMc in circulation and in renal tissues in lupus nephritis (Mosca et al. 2003; Hovinga et al. 2006)
• Autopsy of a woman with lupus found FMc in all histologically abnormal tissue but not in healthy tissue (Johnson et al. 2001)
• Other autoimmune diseases? Thyroid, liver?
Maternal Microchimerism (MMc)

- Maternal DNA acquired by the fetus in utero
- Found in circulation in multiple cell types
- Found in multiple tissues
- Ability to differentiate into local phenotype in an organ to which it migrates (Stevens et al. 2003; Nelson et al. 2007)
• MMc persists into adult life (Maloney et al. 1999)
  ◦ Up to 4\textsuperscript{th} decade
  ◦ Both in normal subjects and those with systemic sclerosis
Benefits?

- Differentiate into functioning islet beta cells that produce insulin in a child with Type I DM (Nelson et al. 2007)
- Contribute to fetal development?
  - Mold et al. 2008 showed MMc promote development of tolerogenic fetal regulatory T cells that suppress fetal immune responses.
  - Tolerance can be maintained after birth.
- Participate in tissue repair?
• Significantly increased levels in women with SSc than controls (Lambert et al. 2004)
• Increased MMc found in children with autoimmune dermatomyositis (Reed et al. 2000)
• Increased levels in the hearts of patients with neonatal lupus (Stevens et al. 2003)
• MMc known to engraft and persist in childrens with immunodeficiency (Pollack et al. 1982)

• Transfusion Mc increased and prolonged in immune suppressed state (Reed et al 2007)
Role of MMc in immune regulation or dysregulation?

- T lymphocyte plays a key role in immune reactions between autologous and foreign cells
- Unclear what happens in a person who harbors MMc and who becomes immune deficient
- HIV/AIDS characterized by deficiencies in CD4+ T cells
Questions?

1. Can MMc be identified and quantified in HIV/AIDS?
2. Does the prevalence and quantity of MMc increase with HIV infection?
3. Is there a correlation in disease progression and MMc level?
Methods

- Recruitment from Dr. McElrath study cohort and Harborview Madison Clinic for HIV positive subjects.
- Healthy controls locally recruited by Nelson Lab, Fred Hutchinson Cancer Research.
- HIV positive men greater than 16 years old.
- Only those with mothers willing to participate were enrolled.
- Excluded those with history of blood transfusion or twin.
- Excluded those with autoimmune disease
Methods

- Non progressors CD4 > 500
- Progressors CD4 < 300 within two years of infection
- DNA extracted from PBMC from subjects and mouthwash samples from mothers
- HLA genotyped for identification of non-shared allele, using quantitative PCR to identify MMc DNA
# Results

<p>| Table 1. Selected characteristics of the Study Participants, According to disease progression. |
|---|---|---|
| <strong>Control</strong>  | <strong>Non-Progressors</strong>  | <strong>Progressors</strong>  |
| N=17  | N=11  | N=5  |
| Age at study participation  | 28  | 41  | 40  |
| Race: White  | 17  | 11  | 5  |
| Mean CD4 count at study participation (cells/uL)  | N/A  | 832 (1109-602)  | 172 (286-62)  |
| Mean VL at study participation (copies/mL)  | N/A  | 4348 (&lt;50-19,822)  | 101897 (&lt;30-509,000)  |</p>
<table>
<thead>
<tr>
<th>Table 2. HLA Results and MMc levels according to groups</th>
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<tr>
<td>Controls (N=17)</td>
</tr>
<tr>
<td>HLA B57/14</td>
</tr>
<tr>
<td>CCR5</td>
</tr>
<tr>
<td>Mat/CCR 5</td>
</tr>
<tr>
<td>MMc level</td>
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<tr>
<td>Range (3.5-60.7)</td>
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Conclusion

- There was no MMc detected in PBMC of HIV positive patients compared to 24% in normal subjects.
- This was statistically significant (p=0.038).
Discussion

- This pilot study showed no MMc found in HIV subjects. This was found to be significant.
- Significant age difference between study (40) subjects and healthy controls (28).
- Viral tropism for MMc?
- Tissue MMc? In murine models, immune status determines location of MMc (Piotrowski et al 1996)
- MMc protective against HIV?
Thank you!

- Dr. JL Nelson, MD
- Dr. VK Gadi, MD, PhD
- Dr. Zhen Yan, MD, PhD
- Hilary Gammill, MD
- Elisabeth Shaw, DO
- William Chan, PhD
- Nelson Lab
  - Tessa Aydelotte, Natalie Downs, Navkiran Bains, Ara Williams
References

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