Introduction to Microchimerism

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BLOOD SERVICE

Chimera

"a thing of immortal make, not human, lion-fronted and snake behind, a goat in the

middle, and snorting out the breath of the terrible flame of bright fire".

Homer- Iliad

Apulian plate 350BC Musee Louvre

Chimerism and Microchimerism

- *Chimerism –The fusion of either two fertilized ova or two sperm fertilizing an ova producing a mixed genetic individual or chimera. Occurs in animals but is rare in humans.*

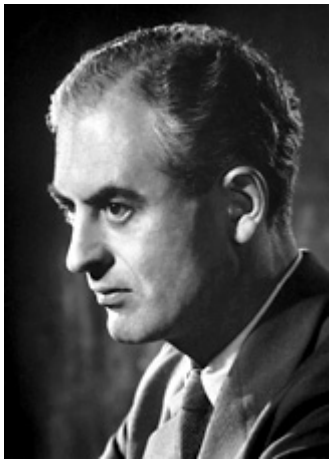
- *Macrochimerism refers to the situation where large numbers of introduced cells exist e.g. bone marrow transplantation.*

- *Microchimerism refers to the presence in an individual of a relatively small population of cells derived from another individual. Can be described as peripheral blood or tissue microchimerism.*

- *In microchimerism cells of the recipient and donor live in a state of mutual tolerance. However in some instances tolerance may be in one direction only.*

Microchimerism and the discovery of immunological tolerance

- *Discovery in 1948 of blood group chimerism in twin cattle by Ray Owen*
- *This led to experiments in 1953 by Medawar and Billingham demonstrating successful skin grafting between twin cattle*



Peter Medawar
1915-1987

Rupert Billingham
1921-2003

When does microchimerism occur?

- *Induced -blood transfusion*
  -transplantation
- *Naturally -pregnancy*

Foetal microchimerism (FMc)
foetal to maternal bleed during pregnancy or parturition

Maternal microchimerism (MMc)
mother to foetus bleed

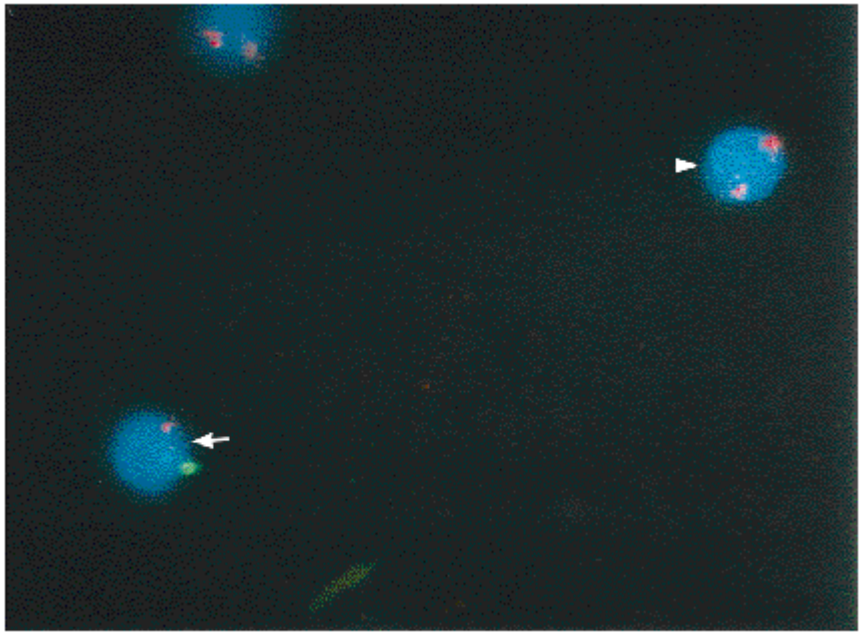
Methods for detecting microchimerism

- *Direct observation of cells using molecular probes i.e X and Y chromosome probes using FISH*

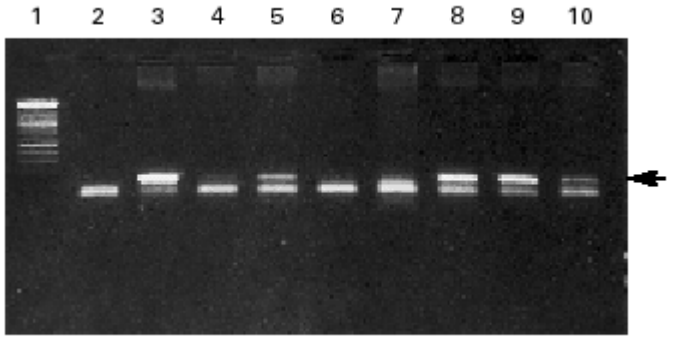
- *DNA analysis- using PCR primers to polymorphic genes mixtures of DNA can be demonstrated in either genomic DNA samples, plasma or serum samples.*

Methods for detecting microchimerism

Direct observation of cells using molecular probes



DNA analysis of cells or serum.



Artlett et al NEJM 338(17): 1186,1998

Microchimerism in Clinical Transplantation

Hematopoietic stem cell transplantation

- *Infusion of donor marrow or HSCT into recipient creates a state of chimerism.*

Advantages: *Immune status of recipient is restored. After a period immunosuppression can be stopped.*

Disadvantages:

- *Lack of engraftment results in relapse.*
- *Because infused immune cells are competent they can recognize the host (recipient) as foreign and mount a rejection process called graft versus host disease (GVHD)*

Microchimerism in organ transplantation

- *Donor microchimerism in transplantation can be measured by detection of donor cells in the recipient circulation.*

- *Donor microchimerism is associated with long term graft survival particularly in liver and renal transplantation. Cause or effect?*
- *Case reports of non compliant patients suggest cause.*

- *Recipient tissue microchimerism also occurs e.g recipient endothelial cells lining the donor vessel wall.*

Donor microchimerism actively promotes unresponsiveness

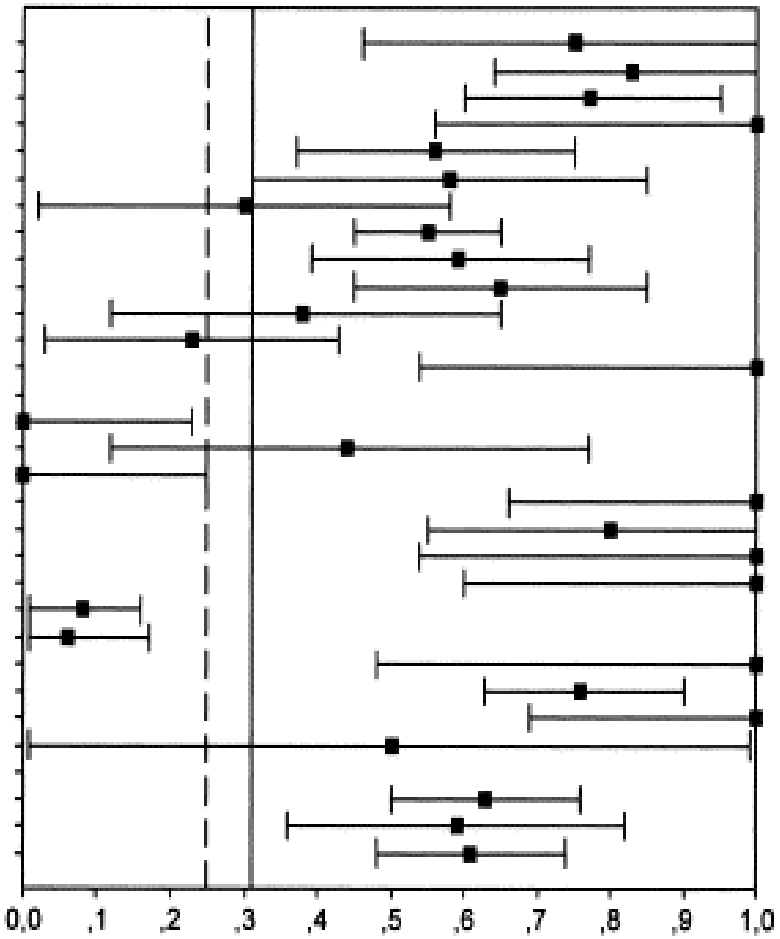
Bonilla W, Geuking M, Aichele P, Ludewig B, Hengartner H, Zinkernagel R. Microchimerism maintains deletion of the donor cell specific CD8+ T cell repertoire. Journal of Clinical Investigation January 2006;116(1):156.

Bonilla et al showed in a mouse model that donor microchimerism maintains cytotoxic T cell unresponsiveness by specific deletion.

Meta-analysis of microchimerism in organ transplantation

Transplanted Organ	Site Examined	Number of Patients	Chimeric Patients	Prevalence
Liver (58)	Blood	8	6/8	,75
Liver (54)	Blood	6	5/6	,83
Liver (57)	Blood	22	17/22	,77
Liver (49)	Blood	7	7/7	1
Heart (56)	Blood	25	14/25	,56
Kidney (49)	Blood	12	7/12	,58
Kidney (56)	Blood	10	3/10	,30
Kidney (59)	Blood	89	49/89	,55
Kidney (31)	Blood	22	13/22	,59
Kidney (32)	Blood	20	13/20	,65
Kidney (55)	Blood	13	5/13	,38
Kidney (54)	Blood	17	4/17	,23
Kidney + Pancreas (49)	Blood	6	6/6	1
Lung (48)	Tissue	12	0/12	,00
Liver (45)	Tissue	9	4/9	,44
Liver (50)	Tissue	13	0/13	,00
Liver (46)	Tissue	9	9/9	1
Heart (52)	Tissue	10	8/10	,80
Heart (47)	Tissue	6	6/6	1
Heart (2)	Tissue	8	8/8	1
Kidney (43)	Tissue	40	3/40	,08
Kidney (42)	Tissue	17	1/17	,06
Kidney (35)	Tissue	5	5/5	1
Kidney (53)	Tissue	38	29/38	,76
Kidney (51)	Tissue	10	10/10	1
Kidney (44)	Tissue	4	2/4	,50
Mean, blood chimerism				,63
Mean, tissue chimerism				,59
Mean, blood and tissue chimerism				,61

P<0.001

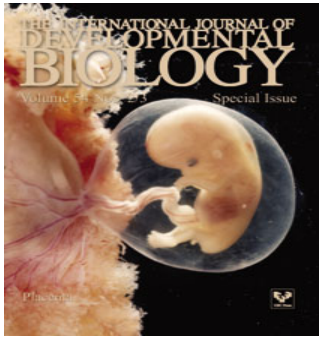


Poelgeest et al Transplantation Reviews 18(3);2004

Microchimerism in Pregnancy

Naturally acquired microchimerism

- ***Foetal microchimerism (MMc)***



Transplacental traffic from foetus to mother has been well known for over 50 years eg Rh sensitization.

Cells can stay in circulation for up to 30 years.

Benefits *– introduction of stem cells into maternal circulation. Helps repair tissue*

Complications- *?Causes auto-immune disease in mother e.g systemic sclerosis*

Evidence for foetal stem cells in parous females

- *In apheresis products from females with GCSF mobilization male DNA (Y chromosome marker) was detected in 34% of cases.*
- *When enriched for CD34+ cells 48% were positive*.

Adams KM et al Blood 102:3845,2003

- *A mean of 11.8% of CD34+ cells in maternal blood taken prior to delivery are of foetal origin*

Mikhail MA et al Human Reproduction 23:928,2008

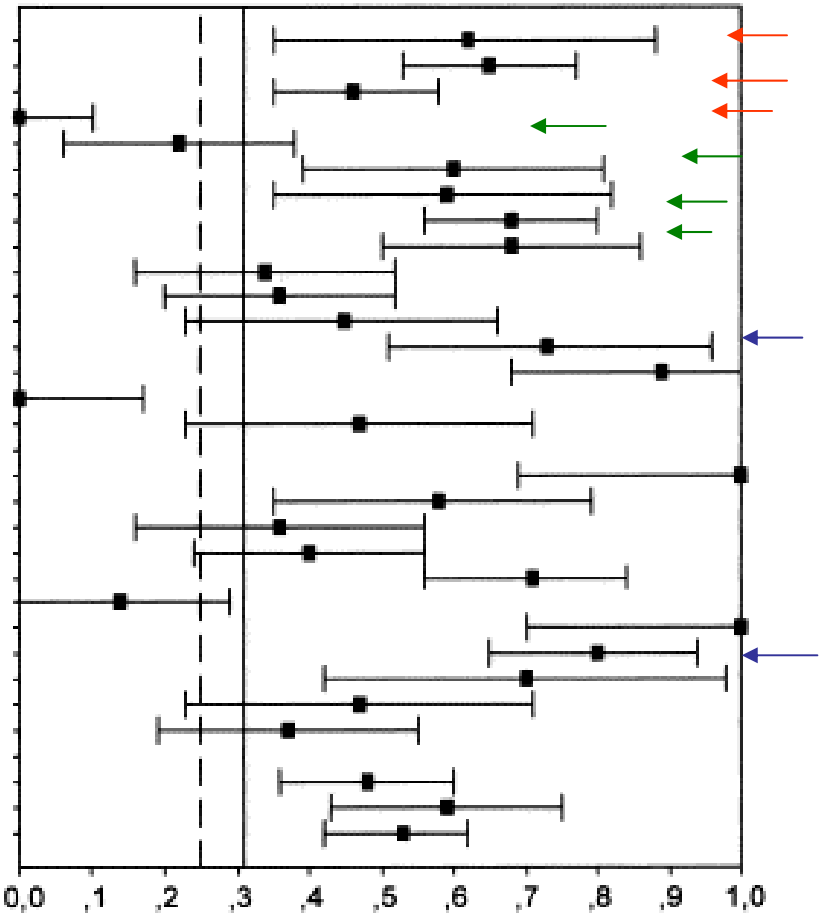
What are the implications for HSCT?

Evidence for link between FMc and SSC

- *SSC has clinical similarities to GVHD.*
- *Higher levels of FMc are found in female SSC patients.*
- *FMc found in PBMC subsets including T cells, B cells, monocytes, and natural killer cells.*

Meta - analysis of microchimerism association with autoimmune disease

Auto-immune Disease	Site Examined	Number of Patients	Chimeric Patients	Prevalence
Systemic Sclerosis (27)	Blood	13	8/13	,62
Systemic Sclerosis (20)	Blood	63	41/63	,65
Systemic Sclerosis (18)	Blood	69	32/69	,46
Sjögren's Syndrome (25)	Blood	22	0/22	,00
Scleroderma (22)	Blood	23	5/23	,22
Scleroderma (10)	Blood	20	12/20	,60
Scleroderma (28)	Blood	17	10/17	,59
Scleroderma (26)	Blood	57	39/57	,68
Systemic Lupus Erythematosus (12)	Blood	28	19/28	,68
Systemic Lupus Erythematosus (22)	Blood	27	9/27	,34
Primary Biliary Cirrhosis (23)	Blood	36	13/36	,36
Primary Biliary Cirrhosis (21)	Blood	20	9/20	,45
Juvenile Dermatomyositis (15)	Blood	15	11/15	,73
Juvenile Ideopathic Inflammatory Myopathies (14)	Blood	9	8/9	,89
Inflammatory myopathies (22)	Blood	8	0/8	,00
Graves' Disease (19)	Blood	17	8/17	,47
Systemic Sclerosis (17)	Tissue	5	5/5	1
Systemic Sclerosis (18)	Tissue	19	11/19	,58
Sjögren's Syndrome (25)	Tissue	28	10/28	,36
Primary Biliary Cirrhosis (21)	Tissue	15	5/15	,40
Primary Biliary Cirrhosis (30)	Tissue	37	26/37	,71
Primary Biliary Cirrhosis (29)	Tissue	28	5/28	,14
Juvenile Ideopathic Inflammatory Myopathies (14)	Tissue	10	10/10	1
Juvenile Dermatomyositis (15)	Tissue	15	12/15	,80
Auto-immune Thyroid Disease (16)	Tissue	10	7/10	,70
Hashimoto's Thyroiditis (24)	Tissue	17	8/17	,47
Graves' Disease (19)	Tissue	27	10/27	,37
Mean, blood chimerism				,48
Mean, tissue chimerism				,59
Mean, blood and tissue chimerism				,53



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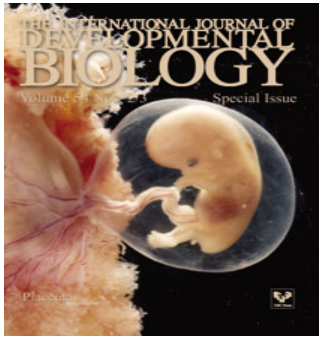
Naturally acquired microchimerism

- **Maternal microchimerism (MMc)**

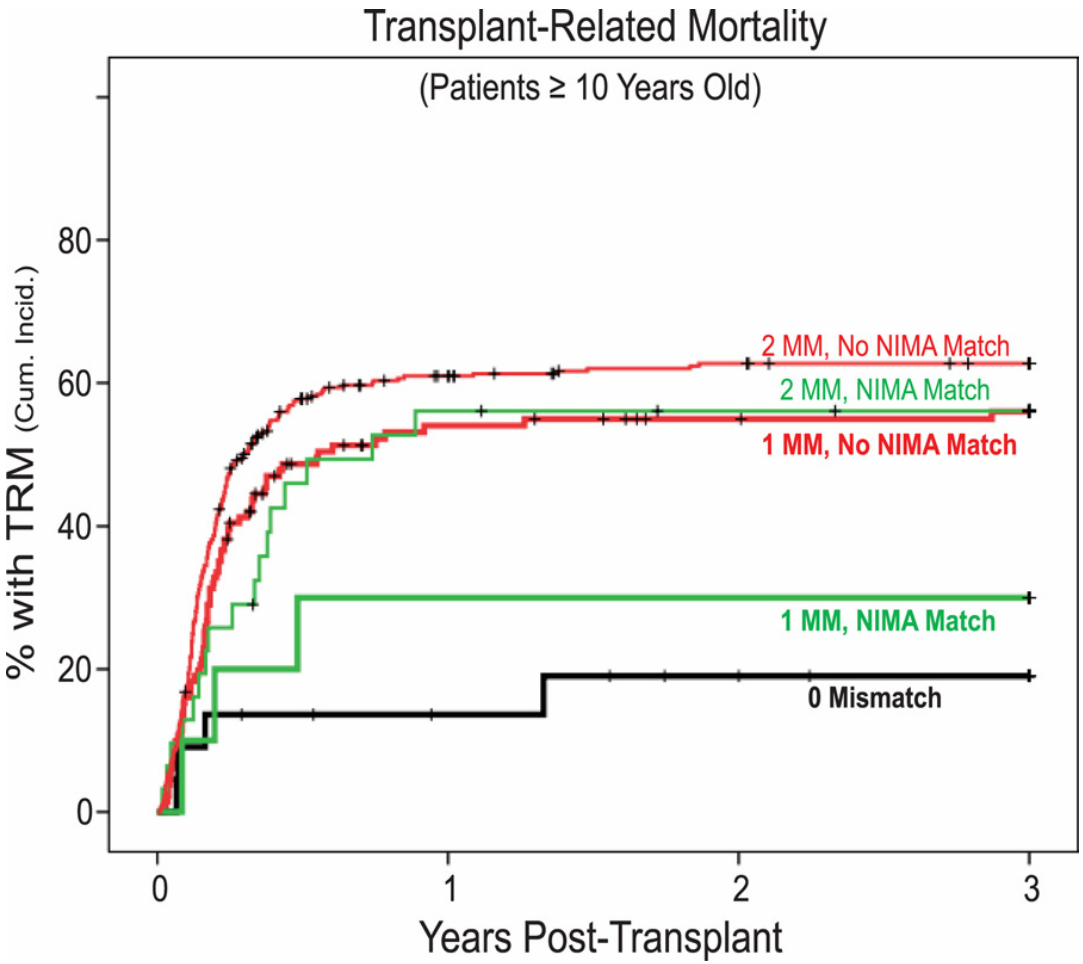


Essential difference is that foetus is not immunologically mature
-more likely to promote foetal tolerance to maternal antigens.

Complications – *Does this play a role in some auto- immune diseases?*
e.g Dermatomyositis,SCID

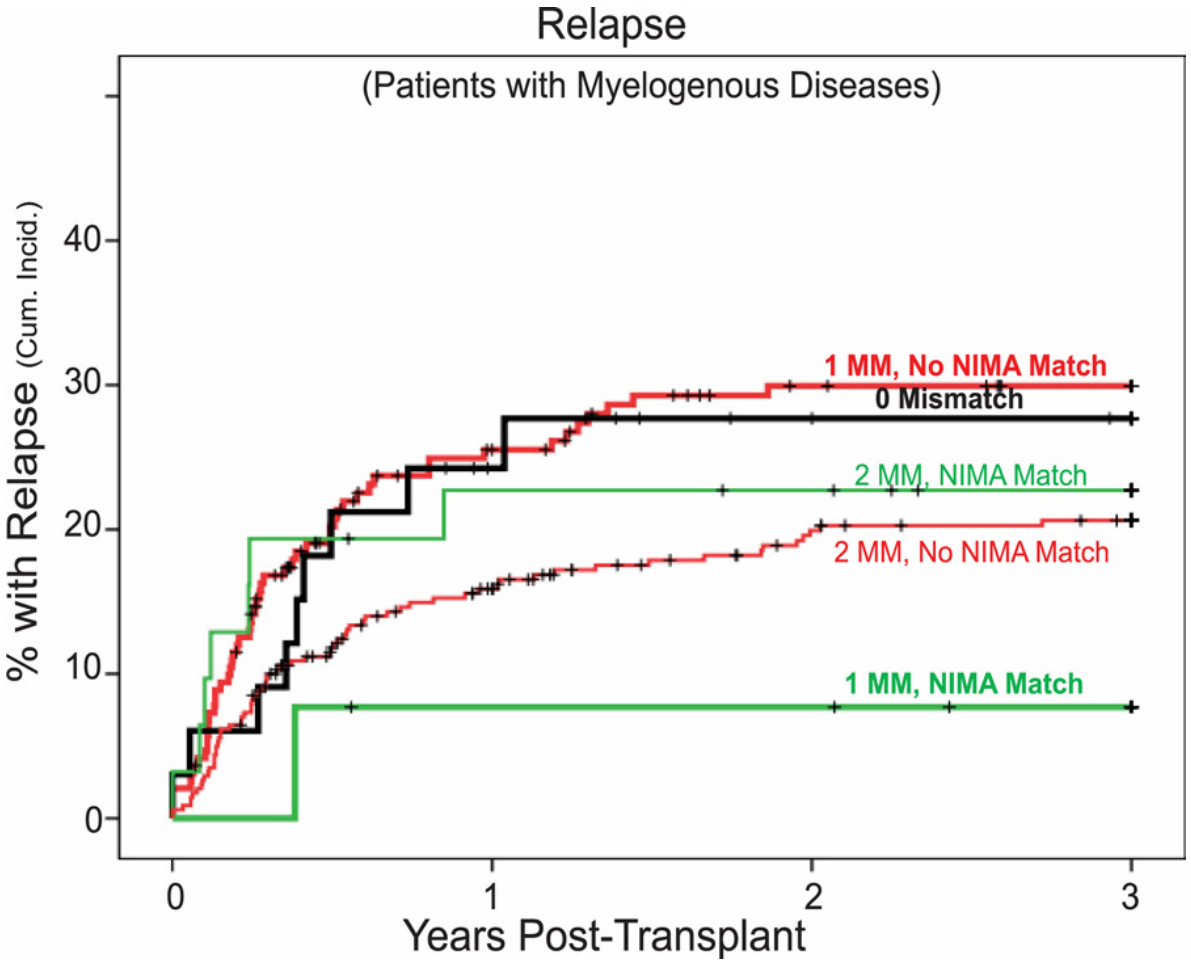
Benefits – *Unexpected benefits in transplantation. Children appear to be tolerant to the HLA antigens of the mother (so called NIMA effect)?*

Re-exposure of cord blood to non inherited maternal HLA antigens in the recipient reduces mortality



Van Rood et al PNAS 106(47):19952,2009

Re-exposure of cord blood to non inherited maternal HLA antigens in the recipient reduces relapse rate



Van Rood et al PNAS 106(47):19952,2009

Summary

- *Microchimerism occurs commonly in pregnancy and transplantation and has been shown to be associated with:*

- *long term graft survival*
- *some auto-immune diseases e.g systemic sclerosis (FMc) and dermatomyositis (MMc).*

Mechanisms are not understood.

- *Microchimeric stem cells may assist in tissue repair in pregnancy and transplantation.*