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Neuroscience Reviews: Male Microchimerism in the Female Brain

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Introduction

The human brain is a relatively immune privileged site and the blood-brain barrier (BBB) prevents most molecules and foreign cells from entering and disrupting neurotransmitter release. Thus, it is most surprising to learn that foreign cells and/or DNA strands transverse the BBB and integrate into the brain without activating peripheral mechanisms of autoimmunity and tolerance. The presence of foreign molecules and cells in the brain inspires numerous questions and offers new perspectives on the biology of self-immunity. This brief essay provides a basic overview of the phenomenon known as microchimerism, particularly as it relates to the trafficking of cells between the male fetus and the adult female brain.

What is Microchimerism?

Microchimerism is the migration of fetal genetic material and cells into the mother (Fig. 1). Microchimerism can also occur between the mother and the fetus (Dawe et al., 2007). This phenomenon occurs in placental vertebrates and despite its prevalence, the functional significance of this exchange remains unclear. Nevertheless, male fetal cells migrate through the placenta during pregnancy and engraft maternal tissues, including bone marrow, spleen and liver (Tanaka et al., 1999; Invernizzi et al., 2000; Johnson et al., 2001). The broad anatomical distribution of male genetic material in human females is of

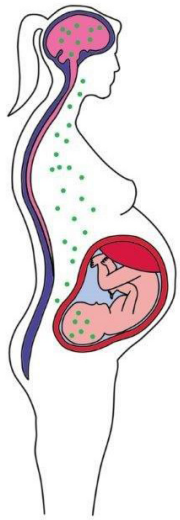

Fig. 1. During the course of pregnancy there is a trans-placental migration of cells from the male fetus to the mother. This phenomenon is referred to as fetal microchimerism. Male fetal microchimerism is detected in healthy women after pregnancy and appears to be not recognized by the maternal immune system. Male fetal cells integrate and differentiate into maternal tissues, including the brain.

particular interest as it may have implications for graft survival, autoimmunity and tissue repair.

Timing and Onset of Microchimerism

In mice, male fetal cells are seen in the mother immediately after the establishment of the utero-placental circulation (i.e., second week of pregnancy; Khosrotehrani et al., 2005). In humans, fetal DNA is seen in maternal blood as early as four weeks post-conception, when fetal organogenesis and circulation to the placenta is nearly completed (Thomas et al., 1995; Pertl and Bianchi, 1999). Thus, migration of fetal material to the mother occurs as soon as placental blood channels become functional to allow passage of fetal cells into the maternal circulation (Dawe et al., 2007). It is not clear, however, how cells are exchanged across the placental barrier. Also, it is not clear why a mother's immune system does not recognize male fetal cells, which have unfamiliar DNA, as foreign. It is thought that fetal cells escape maternal immune surveillance because immunological tolerance is relatively low during pregnancy (Lissauer et al., 2007; Gammill and Nelson, 2010). Regardless, once fetal cells (e.g., lymphocytes, erythroblasts or mesenchymal progenitor stem cells) infiltrate host tissues, they differentiate, replicate and proliferate in the mother (Liegeois et al., 1981). Interestingly, fetal cells can be detected decades in women previously pregnant with males, including one woman who was last pregnant 51 years earlier (O'Donoghue et al., 2004). Taken together, these data suggest that the prevalence, diversity and durability of male fetal cells acquired during pregnancy may contribute to women's health, longevity and risk of disease.

Source and Origin of Microchimerism

In most cases, the source and origin of male fetal cells is from normal pregnancies. However, women without sons can still derive fetal cells from spontaneous abortions, unrecognized miscarriages, from an unrecognized (vanished) male twin or from an older brother (Gammill and Nelson, 2010). Other potential sources of male fetal cells in women without sons include iatrogenic sources such as blood transfusions and tissue transplantation (Lissauer et al., 2007). Alternatively, women could still be peppered with male fetal cells during routine sexual intercourse or from pre-existing fetal material of matrilineal generations (e.g., grand-mothers with histories of blood transfusions, tissue transplantation or pregnancies with male fetuses; Dawe et al., 2007). While some of the aforementioned sources of microchimerism may be relatively rare, the possibility of Y chromosome material entering females is certainly sporadic and highly variable.

Microchimerism in Health and Disease

As discussed earlier, the functional significance of microchimerism is unclear. Some studies speculate that microchimerism may improve rheumatoid arthritis, which is a relatively common autoimmune disorder whose symptoms often subside during pregnancy (Nelson et al., 1993; Yan et al., 2006). A similar beneficial effect may be operative in two other autoimmune diseases, multiple sclerosis and Graves' thyroiditis (Gammill and Nelson, 2010). Conversely, other studies suggest that genetically distinct male fetal cells in the mother may precipitate pathology including, systemic sclerosis (Artlett, 2005) and lupus erythematosus (Samura, 2010). Thus, it is conceivable that male fetal material could bring resistant or risk effects to some autoimmune diseases that show predilection for women in

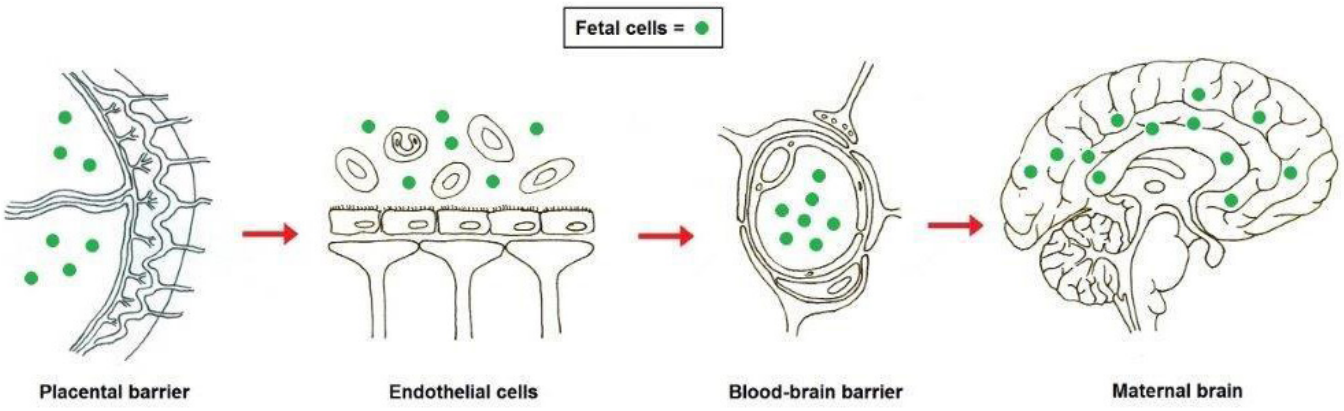

Fig. 2. Male fetal cells readily cross the placental barrier, multiple layers of epithelial cells and the blood-brain barrier to enter the maternal brain during pregnancy and differentiate into neural cells. Male fetal cells in the maternal brain can be detected decades after pregnancy suggesting a continuous cycle of cell growth and cell division. Male fetal microchimerism in the adult female brain may contribute to women's health, longevity and risk of disease.

their child-bearing years and beyond. Nevertheless, what is certain is that women, men and children are constitutively chimeric. Furthering our understanding of microchimerism may provide new insights into fundamental mechanisms of immune tolerance.

Male Fetal Microchimerism in the Brain

In human females, fetal cell microchimerism is observed in peripheral tissues and organs where they survive and differentiate into epithelial and hematopoietic cells. The brain, although isolated and protected by the BBB, is also peppered by foreign, male fetal material. Indeed, mouse fetal cells are found in maternal brain as confirmed by quantitative real-time PCR analysis (Tan et al., 2005). Interestingly, these fetal cells have the ability to adapt to the host circuitry and express immunocytochemical markers of neuron-astrocyte and oligodendrocyte-like cells (Fig. 2). Furthermore, these newly differentiated neurons, can be detected in maternal brains up to seven months postpartum (Tan et al., 2005; Tan et al., 2011). More recently, microchimerism was also observed in the human female brain (Chan et al., 2011). In this particular study, fetal DNA was measured in brains of deceased women targeting the Y-chromosome-specific DYS_{14} gene. Male microchimerism was detected in specific brain regions: the frontal lobe, putamen and medulla. Similar to the mouse data, male microchimerism showed considerable variability with some female brains showing little or no trace of fetal DNA (Chan et al., 2011). In this regard, the same study also measured male microchimerism in female brains diagnosed with Alzheimer's disease (AD) as this disease is more prevalent in women than men. AD is a neurodegenerative disease characterized by the abnormal formation of β-amyloid plaques and neurofibrillary tangles leading to deterioration of cognition, physical functioning and behavior (Walker et al., 2013). Interestingly, AD brains showed a lower concentration of male microchimerism than non-diseased brains (Chan et al., 2011). At present, there is no meaningful explanation for the differential expression of fetal DNA in AD as further studies are needed to replicate the above findings. Nevertheless, these preliminary findings suggest that DNA material of male fetal origin may have important beneficial relevance to female brains.

Conclusion

The demonstration that male fetal cells and DNA material persist in the brain and have engraftment capabilities, potentially for the life of the mother, is remarkable. Unfortunately, the integration of foreign cells into preexisting brain circuitries and its relevance to function and disease still is fraught with controversies and mysteries. Male microchimerism in the female brain still requires further research.

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Editor's Column

2014 already! It seems like we just rushed through 2103. We had a very successful Society for Neuroscience meeting in November, with good weather in San Diego. Next year, the meeting will be in Washington, DC, where it will probably be colder than it was in San Diego, but where, I fear, the Congress will be getting nothing done again for another year. It could be, however, that it could be better than them doing a lot of things that make life even more difficult.

As I look back over 2013, I realize that I have been retired for 5.5 years now. However, it seems like I am almost as busy as ever. Besides editing the Kopf *Carrier*, I am an Associate Editor for the *Journal of the American Osteopathic Association* and serve on the board of directors of our condominium association in Dublin, OH (where we spend about 4 months of the year, visiting grandchildren), and travel, usually giving lectures. Jan and I came back to Florida from the condo on Jan. 16 in time to host brother Jeff and partner Mary before their annual blues cruise in the Caribbean.

In February, we went to Madrid, Spain where Mike lectured at the Wernham Osteopathic Conference. In March, we went on a cruise with son Shad's family and another family sailing out of Port Canaveral. It was a fun trip especially for the kids. In April, we went to Lisbon, Portugal where I lectured again, and our host took us to Coimbra, home to Portugal's oldest university. We toured their beautiful library that had a student prison in the subbasement where unruly students served time.

In May, we went to Montreal for a Science Editors Conference and a tour of the Montreal Osteopathic School's new facilities. In June, Mike went to Los Angeles to keynote the Chiropractic Kinesthesiology Conference and came back to have cataract surgery on both eyes. The surgery went quite well and brought Mike a new world-view. We then went to our Dublin condo in late June.

In early July, we drove with son Shad and family to the Outer Banks for a week in a huge house on the seashore. Many of Shad's wife, Adele's family were there and we had a great time. Mike facilitated the Osteopathic Heritage Foundation's annual conclave of Fellows in late July in Columbus, OH. In September, son Shane and his two kids came to Orlando for a week with us in a timeshare. Lots of fun in the theme parks, visiting the Space Center, etc. They stayed a couple days at our Florida home; very enjoyable.

Later that month, we went to Las Vegas for OMED, the annual osteopathic convention. In November, we traveled to Iguazu Falls, Brazil where Mike again lectured, coming back directly to San Diego for the Society for Neuroscience annual meetings. A long trip coming back; 24 straight hours of travel. We had a very quiet hurricane season, so did not have to worry about being blown away. So, retirement is fun, but still busy. I do highly recommend it.

This issue of the *Carrier* was written by Goretti Chiang, Jaskiran Ghuman, Brian H. Hallas and German Torres of the New York Institute of Technology College of Osteopathic Medicine and is another in our "Neuroscience Reviews" series. As usual, they have done a wonderful job and I think you will find the article both interesting and enlightening. Many thanks to them. If any of our readers would like to write an article for the Carrier, please contact me about your interest.

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