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Naturally occurring, physiologically normal, primate chimeras

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Callitrichids, South American primates including marmosets and tamarins, have evolved a unique physiology. Twins share a placenta during gestation and exchange stem cells, resulting in naturally occurring chimeric adults. Our study used a quantitative PCR-based assay to address whether this chimerism was restricted to blood and other cells of the hematopoietic lineage or whether it extended to other somatic tissues. These studies help to characterize species that have adapted evolutionarily to pervasive chimerism, with every individual healthy and unperturbed. This experiment of evolution offers insight into transplantation and histocompatibility, reproductive biology and behavior, and innate and adaptive immunity.

Keywords: *Saguinus oedipus*, *Callithrix jacchus*, hematopoiesis, quantitative pcr, animal models, transplantation, MHC

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When the first rhesus macaques made from whole embryo aggregation were published,[1] science journalists blared, "First monkey chimera created." Unnoticed and ignored was the fact that evolution itself has been creating chimeric New World monkeys for the last 15 million years. Marmosets and tamarins, members of the family Callitrichidae, have been well established as hematopoietic chimeras since the 1960s[2] and reports of their unique placental development date back to over 80 years ago.[3,4] Callitrichid pregnancies typically result in the birth of fraternal twins, while instances of triplets and quadruplets are also quite common in captivity. Early in gestation, placental fusion and anastomosis arise, allowing an exchange of genetically distinct precursor stem cells and resulting in naturally occurring chimeric animals.

While hematopoietic chimerism is not in doubt, the presence or absence of chimerism in tissues that are not of the hematopoietic lineage is of considerable debate.[5-7] In our recent publication, we were not only able to detect chimerism, but, using a quantitative PCR based methodology, we were able to find variances in levels of chimerism both between individuals and across multiple tissue types within single individuals.[8] Chimerism levels were significantly higher in tissues primarily derived from the hematopoetic lineage, while they were lower, though still detectable, in tissues with other origins. Noteworthy, fibroblast cell lines from chimeric individuals were not found to be chimeric themselves. The levels of chimerism in callitrichid tissues of different origins coupled with other lines of evidence suggest that only hematopoietic cell lineages are chimeric. We believe that the chimerism detected in other tissues is likely the result of blood or lymphocytic infiltration.

Looking forward, however, is the unresolved issue of germ cell chimerism. Ross et al.[7] found evidence for germ cell chimerism as did others previously.[9,10] Though these studies focused on sperm, a lack of distortion in sex ratios in captive breeding colonies suggests that ova must also be chimeric.[11] Indirect evidence of this was found in the form of maternal sibling-derived alleles and extrapolated out to associations with parental behavior.[7] The distinct ontogenic origins and relative motility of the primordial germ cells make this possibility feasible and increasingly intriguing.

So why should we be interested in these small primates? The science of chimerism extends into multiple fields including transplantation, genetics, maternal-fetal care and immunology and the marmoset can easily serve as a putative animal model

for any of these areas. The marmoset model possesses the benefits of New World primates: small body mass allowing for more tractable husbandry needs than the larger Old World primates, relatively short adolescence before reaching sexual maturity and multiple offspring at each birth without reproductive seasonality. In addition, captive marmosets have relatively short life spans, an advantage of particular importance to aging research.

Several years ago, the common marmoset (*Callithrix jacchus*) genome was selected to be sequenced, and with it has come the molecular tools of other animal models. Marmosets were the first transgenic primates to demonstrate germline transmission[12] and their amenability to stem cell technologies is notable among primates.[13-15] They have also been suggested as particularly suitable models for gene therapy studies.[16,17] Part of the reason for this may be their limited MHC diversity, unique among primates.[18-20] This same paucity of immunogenetic variability may play a role in the facility of callitrichids in the study of transplantation.[6,21] While the evolutionary forces responsible for the restricted repertoire are still unknown, it is likely that the natural chimerism in the species is effectively selecting for allotolerance.[22]

These factors can make marmosets and tamarins useful for biomedical studies and also present factors that complicate research and must be taken into consideration. The underlying and unspoken question remains. Why? Why has evolution undertaken this experiment in natural chimerism and why have the callitrichids persisted and flourished? If indeed the restriction in MHC alleles has come as a consequence to pervasive hematopoietic chimerism, then there must be advantages to overcoming an increased susceptibility to infectious disease.[23] Understanding chimerism in Callitrichidae not only helps us better understand our model organisms, but it also may further our understandings of the ecological, environmental and physiological pressures that have molded genomes and organisms.

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