Common marmoset (*Callithrix jacchus*) in biomedical research

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Overview

Common marmosets, or white-tufted-ear marmosets (*Callithrix jacchus*), have been subjects in biomedical research since the 1960's[1]. In recent years, their popularity as a research model has increased dramatically, prompted to a large degree by their realized utility for neuroscience and aging research[2,3] as well as their potential as a nonhuman primate transgenic model[4,5]. Many factors make the marmoset an attractive model system including their genetic and physiological similarity to humans, relatively short lifespan, high fertility, rapid development, small size and human-like social structure.

Natural biology

Common marmosets are diurnal, arboreal Neotropical primates within the family Cebidae and subfamily Callithrichinae which is comprised of over 40 species including marmosets, tamarins and Goeldi's monkey[6]. They are endemic to northeastern Brazil where they live in environments ranging from the humid Atlantic Forest to the dry scrub forest of the Caatinga[7]. They remain abundant in Northeastern Brazil and are classified as "Least Concern" by the IUCN Red List of Threatened Species[8].

Common marmosets are small-bodied and lack sexual dimorphism. The marmosets small body size (~300-500 grams in captivity) is a derived trait of declining body size and is therefore considered a case of phyletic dwarfism[9]. Common marmosets are considered infants until 3-4 months of age, juveniles from 4-5 months to 10 months of age, sub-adults from 11 months of age until they reach sexual maturity and are considered adults at approximately 13-15 months of age. Common marmosets are considered aged by approximately 8 years, and in captivity they have a median lifespan of approximately 10 years and a maximum lifespan of approximately 16-20 years[10]. Little is known about marmoset lifespan in the wild given the inherent difficulties in acquiring such data. Common marmosets become reproductively competent by 1.5 years of age and then go on to regularly produce fraternal twins or triplets (and occasionally quadruplets) every five to six months making them among the most fecund of the anthropoid primates. Their small body size along with routine twining results in an overall high litter weight compared to the dam's weight. Marmosets have been known to be hematopoietic chimeras since the 1960's[11]. Early in gestation, the placentas fuse allowing for exchange of genetically distinct stem cells which results in naturally occurring chimeric animals[12]. Whether chimerism in marmosets extends beyond hematopoietic cells in still a matter of debate[12–14].

Marmosets have several adaptations specific for their diet and arboreal habitat. Their long tail helps them maintain balance while moving along tree branches and they have claw-like nails (tegulae) on all but their big toe that allow them to effectively cling vertically to trees, run quadrupedally across branches and leap between trees. Their claws, along with their enlarged chisel-shaped incisors, also allow marmosets to gouge trees in search of the exudates that form the basis of their diet[15]. To digest these exudates, marmosets have a large and complex cecum[16]. In addition to tree exudates, common marmosets consume an omnivorous diet including fruit (preferred when available), insects, seeds, flowers, and small amphibians, reptiles and mammals[17].

Common marmosets live in cooperative breeding groups of approximately 3-17 individuals generally consisting of a breeding pair, other adults, sub-adults juveniles and infants[6]. Generally, only the dominant male and female breed, while other group members assist in raising offspring forming a cooperative breeding system comparable to that of humans[18]. To facilitate this arrangement, subordinate females in the group are reproductively suppressed[19]. In the wild, breeding strategies may be more flexible[20,21].

Research Contributions/Biomedical models

Though similar in size to rodents, marmosets share physiological, behavioral, and cognitive characteristics that distinguish primates from all other animals. This along with their small body size, rapid development, high fecundity and 93% sequence identity with the human genome[22,23] represents a unique opportunity to study biomedical processes that are not feasible to model in other nonhuman primates. Tools that further enhance the value of this species include complete sequencing, assembly, and annotation of the marmoset genome[24], generation of induced pluripotent stem cells, and production of transgenic marmosets – the first successful production of a transgenic nonhuman primate with germline transmission[25]. Common marmosets are particularly interesting for longitudinal and lifespan studies and provide advantages for studies involving modern molecular gene-editing technologies. They have been particularly useful in neuroscience studies given similarities between marmosets and humans in behavior, cognition, and communication as well as shared brain architecture and a smooth cortex that facilities certain types of experiments. The small body size of marmosets is particularly attractive for early-stage pharmaceutical testing where smaller amounts of the substance would need to be produced than if using a larger bodied model.

1. Aging

Given their rapid aging course, common marmosets are perhaps an ideal animal model for aging studies as the dynamics of the aging process can be studied longitudinally potentially throughout the entire lifespan. Importantly, their rapid life history means that within a 5-year period, three generations of offspring can be produced and during this time the founding animals will progress through old age. Furthering their utility as an aging model, common marmosets develop similar age-related conditions as humans. For example, they exhibit age-related declines in lean muscle mass, motor function, hearing, and cognition[26,27] and changes in microbiome[28] and the immune system[29]. Marmosets show a marked age-related increase in diabetes, cardiovascular disease, inflammatory conditions, cancers, amyloidosis, pathogenic tau accumulation, and renal diseases, as do humans[4,30]. Obesity along with dyslipidemia and altered glucose metabolism leading to hepatomegaly, hepatic steatosis, diabetes, atherosclerosis, cardiomyopathies, and stroke is becoming a more frequent finding in captive marmosets[31,32]. Age-related increases in insulin resistance have been detected[33] and potential biomarkers of aging have been identified in the plasma metabolome[34]. These facts have led to interest in a marmoset aging model of obesity and metabolic syndrome.

2. Neuroscience

Marmosets have a small brain with a smooth cortex, expanded temporal lobe and a highly developed prefrontal cortex. This, along with notable similarities in their social behavior, cognition, sensory perception, and communication with humans, make common marmosets uniquely suited to explore neuroscience questions and to model neuropsychological and neurodegenerative disorders that affect humans. At the central nervous system level, efforts are ongoing to characterize age-related changes in the marmoset brain[27,35] and associated changes in perception, cognition and motor function[36,37]. Marmosets are a popular model for neurodegenerative diseases including Parkinson's, Alzheimer's, Huntington's and multiple sclerosis, due to the existence of validated behavioral, surgical and imaging techniques[38] and their similarities with humans, including evidence of age-related decreases in neurogenesis that occur prior to old age[39]. Marmosets have been particularly useful as a neurotoxin induced model of Parkinson's disease[40] and genetic models of Parkinson's disease have been developed[5]. Of particular interest, aged marmosets spontaneously develop β-amyloid deposition and tauopathies[41], both implicated in the pathogenesis of Alzheimer's disease. Because the high rate of failure in

Alzheimer's disease clinical trials has been ascribed, in part, to the inadequacy of rodent models that recapitulate only limited aspects of Alzheimer's disease pathology, these features of marmoset biology position them as an excellent primate model for advancing our understanding of Alzheimer's disease.

3. Transgenics

Genetically modified rodent models have contributed significantly to our understanding of a myriad of diseases, however extrapolation from rodents to humans is challenging due to physiological and anatomical differences between the species. Genetically modified nonhuman primates could mitigate this translation issue. For transgenic production, the small size, fast maturation, and high fecundity of the marmoset provide logistical advantages, as does the marmosets amenability to modern molecular gene-editing technologies. Dr. Sasaki and colleagues first reported successful germline transmission of a transgene in marmosets in 2009[25]. Since then, efforts to implement modern gene-editing technologies in marmosets have accelerated. These have included development of CRISPR[42] and viral based approaches[43] including techniques with high potential for translation to humans such as intravenous delivery of viral capsids designed to cross the blood-brain barrier[44]. Research has focused on developing genetically modified marmosets to model Alzheimer's disease[45], Parkinson's disease[42] and other age-related brain disorders. In addition, techniques such as optogenetics, chemogenetics, and calcium-imaging have been developed in marmosets to selectively manipulate brain circuits[46,47] and better understand large populations of neurons[48]. As this critical line of research and technical development continues to evolve, the promise of marmosets as a primate model that can leverage genetic technologies is beginning to be realized.

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