"Interspecific Chimeras in Mammals: Successful Production of Live Chimeras Between Mus musculus and Mus caroli" (1980), by Janet Rossant and William I. Frels [1]

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In 1980 Janet Rossant [2] and William I. Frels [3] published their paper, "Interspecific Chimeras in Mammals: Successful Production of Live Chimeras Between Mus musculus and Mus caroli," in Science. Their experiment involved the first successful creation of interspecific mammalian chimeras [4]. Mammalian chimeras [5] are valuable for studying early embryonic development. However, in earlier studies, clonal analysis [6] was restricted by the lack of a cell marker, present at all times, that makes a distinction between the two parental cell types in situ. To battle this limitation, Rossant and Frels decided to make chimeras [7] from embryos of two different species in order to have sufficient genetic differences so that, in any tissue type, the two cell types could be clearly identified. In their paper Rossant and Frels describe the successful creation of live chimeras [8] between Mus musculus and Mus caroli. These two species of mice are more closely related than chimeras produced previously. The chimeras [9] created in the experiment showed no sign of selection against one cell type or the other. Therefore, they are valuable for clonal analysis [10] of development. Rossant and Frels were the first to successfully produce an interspecific mammalian chimera that experienced normal development.


In their experiment, Rossant and Frels worked with M. musculus, a laboratory mouse [11], and M. caroli, a wild species originating from Southeast Asia. These two species show multiple genetic differences and do not usually interbreed in nature. The two species differ in pre-implantation [13] development with M. caroli being complete sixteen to twenty hours earlier than M. musculus. M. caroli also has a shorter gestation [15] period. The two species share similar morphological changes in relation to embryogenesis [16]. Rossant and Frels created chimeras [17] by injecting the inner cell masses of M. caroli into M. musculus blastocysts. They used M. musculus blastocysts retrieved on the afternoon of the fourth day after the mating of albinos, non-agouti mice that were homozygous for the b allele of the glucose phosphate isomerase (GPI) gene (Gpi-1b-Gpi-1b). M. musculus females were super-ovulated and bred with males. Seventy-six hours after a human chorionic gonadotropin [17] (hCG) injection, Rossant and Frels removed the fetuses from pregnant females and then injected them into M. musculus blastocysts.

On the third day of artificial pregnancy [18] these embryos were transferred into uterine horns of albinos, non-agouti mice homozygous for the b allele of the GPI gene. Right before the birth of the fetuses, nine were dissected to study fetal tissues and extra-embryonic structures. Six out of the nine were determined, by GPI analysis and eye pigmentation, to be chimeric. Each chimera showed M. musculus and M. caroli GPI enzymes in every tissue that was analyzed. Rossant and Frels noted that the proportions of the enzymes varied from tissue to tissue, similar to that observed in M. musculus-M. musculus chimeras [11].

During the experiment Rossant and Frels found a hybrid GPI enzyme present in the skeletal muscles of the chimeras [5]. From this they concluded that normal interaction between M. musculus and M. caroli cells had occurred. The myoblasts from both M. musculus and M. caroli fused to create myotubes with normal function. Five other females were allowed to give birth. Out of forty-eight offspring, thirty-eight were determined to be chimeric by hair and eye pigmentation and GPI analysis. Coat and eye pigmentation, as well as the percentage of M. caroli GPI enzyme in the blood, varied in each chimera. Of those chimeras [5] brought to term, twenty-seven were male and nine were female. Similar to previous findings with M. musculus-M. musculus chimeras [11], there were more phenotypic males. Rossant and Frels found that M. musculus-M. caroli chimeras [11] and M. musculus-M. musculus chimeras [5] showed striking similarities in their somatic tissue organization [19]. They concluded that there was no evidence to suggest that M. caroli cells were selected against.

Rossant and Frels were the first to successfully create an interspecific mammalian chimera. Unlike in previous experiments, the M. musculus-M. caroli chimera survived after birth and developed normally. Such chimeras [11] may be valuable for studying early embryonic development. Rossant and Frels indicate that the creation of species-specific antisera, or the identification of genetic differences between the two species in order to provide an in situ cell marker, would make interspecific chimeras [8] more valuable for further studies of mammalian development. Rossant and Frels state that interspecific chimeras [8] may also be beneficial for studying interactions between mother and fetus [20] and the genetic control of mating behavior.

Sources


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