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OVERVIEW

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Organ xenografting between rodents: an evolutionary perspective

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Abstract Rejection times of heart xenografts in several donor-recipient combinations including the guinea pig, rat, hamster, and mouse are examined in light of the paleontological history of rodents and the resulting phylogenetic distances between taxa. This multidisciplinary review at the molecular, chromosomal and morphological levels suggests that xenograft rejection time is inversely proportional to the time divergence or phylogenetic distance, and that the binomial terminology concordant/discordant does not reflect the amplitude of phylogenetic distances.

Key words Xenotransplantation, rodents · Rodents, xenotransplantation · Phylogenetic distance, xenotransplantation

Introduction

The use of rodents for research in xenografting can provide valuable information about the mechanism and prevention of organ xenograft rejection and may have implications for xenotransplantation in humans.

The most frequently used rodents are the guinea pig, the rat, the white mouse, and the hamster. According to a recent review of 148 publications [4], the large majority reported the use of rats (86 articles) as recipients of grafts from guinea pigs (20 articles), hamsters (58), or mice (8), or that of mice (50 of the 148 articles) as recipients of grafts predominantly from rats (43 articles). Only 12 of the 148 publications reported the use of guinea pigs (7) or hamsters (5 articles) as recipients.

In five of these donor-recipient combinations – guinea pig-to-rat [1, 14, 33, 59, 63, 81], hamster-[28, 30, 35, 36, 53–55, 57, 61, 71, 72] or mouse-[57]-to-rat, and rat-[9, 10, 57, 71, 72, 74] or hamster-[57]-to-mouse – the fate of heart xenografts was studied. It was found that they are rejected more rapidly in the hamster-to-rat, mouse-to-rat, and hamster-to-mouse donor-recipient combinations than in the rat-to-mouse combination [57] (Table 1). In the guinea pig-to-rat combination [1, 14, 33, 59, 63, 81], rejection is even more rapid, occurring after a few minutes. The survival of kidney [19, 56], liver [59, 71] and lung [67] xenografts has also been studied. As previously observed with liver allografts in hypersensitized rats [31], liver xenografts are less rapidly rejected than heart xenografts [59, 71, 80].

Histological examination of the rejected heart grafts differs between the three main donor-recipient xenogeneic rodent combinations. Vascular lesions are very intense in the guinea pig-to-rat combination [14, 25, 48], with massive interstitial hemorrhage and intravascular platelet aggregates. No interstitial cellular infiltration is seen. Immunofluorescence shows rat IgM [52] and C3 [59] deposits. In the hamster-to-rat combination, severe endothelial damage is seen with irregular accumulation of neutrophils around blood vessels, but with little interstitial

Table 1 Rejection time of heart xenografts in five donor-recipient combinations of rodents

Donor-recipient combinations	Heart xenograft rejection time	Reference
Guinea pig-to-rat	15.8 ± 8 min	[59]
Hamster-to-rat	4.0 ± 1.0 days	[30]
Mouse-to-rat	4.2 ± 1.1 days	[30]
Hamster-to-mouse	4.9 ± 1.1 days	[30]
Rat-to-mouse	7.5 ± 1.1 days	[30]

hemorrhage and without lymphocytic infiltration [45]. Immunofluorescence shows no deposits of immunoglobulin, C3, or fibrinogen [64]. In the rat-to-mouse combination, moderate endothelial damage is seen and lymphocytic interstitial infiltration is prominent [65]. In the guinea pig-to-rat combination, the mechanism of rejection is clearly humoral and involves primarily natural IgM antibodies directed against guinea pig xenoantigens [1, 14, 24, 33, 56, 57, 68] and complement activation. Through the classical or alternate pathway [24, 57, 69], the prominent role of complement is suggested by the prevention of rejection using complement depletion by cobra venom factor [1] or the use of soluble complement receptor type 1 [52]. In the hamster-to-rat combination, the absence of natural rat cytotoxic anti-hamster antibodies [28, 30, 36, 49, 55] is challenged by the recent demonstration of a low level of natural anti-hamster xenoantibodies in the rat using flow cytometric cross-matching [64]. The relative efficacy of the inhibition of antibody production [28, 36, 45], the failure to obtain long-term heart graft acceptance using anti-CD4 and anti-CD8 monoclonal antibodies and cyclosporin [6], and the ability of nude rats to reject heart grafts as rapidly as normal rats [41, 70] also suggest a prominent role of humoral factors. In the rat-to-mouse combination, the role of cell-mediated rejection is supported by the efficacy of anti-thymocyte globulins [63] or cyclosporin [65] and the absence of rejection of rat skin grafts by nude mice [47]. However, some recent data also suggest a possible role for very low level natural antibodies [2].

Such differences between animals that all belong to the order of Rodentia [2, 12, 17, 18, 21, 26, 44, 62] are better understood from an evolutionary perspective.

Systematic position of the animals within the order of Rodentia

The domestic guinea pig *(Cavia porcellus)* belongs to the superfamily of the Cavioidae, where it is grouped together with capybara. All of these rodents, which are exclusive to South America, are grouped with many others under the more general term of Caviomorpha. Caviomorphs, along with Phiomorphs (African spiny and mole rats; Old World porcupines), belong to the great morphological suborder Hystricognathi and have a so-called hystricomorphic skull structure.

The rat *(Rattus rattus)*, mouse *(M. musculus)*, and hamster *(Mesocricetus auratus)* belong to another suborder, the Sciurognathi, and are sciuromorph rodents (superfamily Muroidea). The rat and mouse belong to the Murinae subfamily which, with ten or so other subfamilies, make up the Muridae family. The hamster belongs to another subfamily, the Cricetinae.

Phylogenetic relationships

Relationships between rodents were originally based on anatomy and tooth features [12, 17, 18, 21, 26, 37–39, 44, 51, 75, 76] by trying to establish step-by-step ancestor-descendant ties within a geological framework. New studies along cladistic lines were first undertaken in the 1970s [42, 46, 66] and these led to a multidisciplinary review of phylogenetic relations in rodents [44] (Fig. 1). Studies involving morphology [32], molecular biology [15, 27, 79], and cytogenetics [73] have since provided new data and sometimes challenged what was thought to be a well-established classification, in particular with regard to the place of Caviomorphs within rodents and mammals [15, 27, 29, 73].

Fossil record

Caviomorphs are found in paleontological records from the lower Oligocene in Patagonia, 33 million years ago (Myr). Two hypotheses have been put forward to explain the origin of South American Caviomorphs [43, 50]. On the basis of anatomical features, the structure of the inner ear [40] and the relationship between parasites of the African and South American forms, Lavocat [38] suggests that the group originated in Africa and emigrated to South America before the Oligocene, at a time when the Atlantic Ocean was narrower, drifting on tree trunks torn from the banks of great African rivers, or along the land bridges that may have remained in place until the Oligocene. In contrast, Wood [77] claims that Hystricognath rodents originated in Asia and emigrated first to North America and then to South America, a view that can be debated.

Thus, the great divide between Caviomorphs and Muroidea goes back much further on the time scale, to well over 33 Myr. All of the molecular, chromosomal and morphological data confirm the great divergence between Caviomorphs and African Hystricognaths resulting from over 33 million years of independent evolution from a common ancestor that passed down many characteristics.

The dichotomy between rats-mice (Muridae) and hamsters (Cricetidae) is put between 35 and 16 Myr by paleontology and between 19.1 and 16.5 Myr by molecular biology. If the mouse is taken as a reference, the closest species is undeniably the rat, for which the divergence

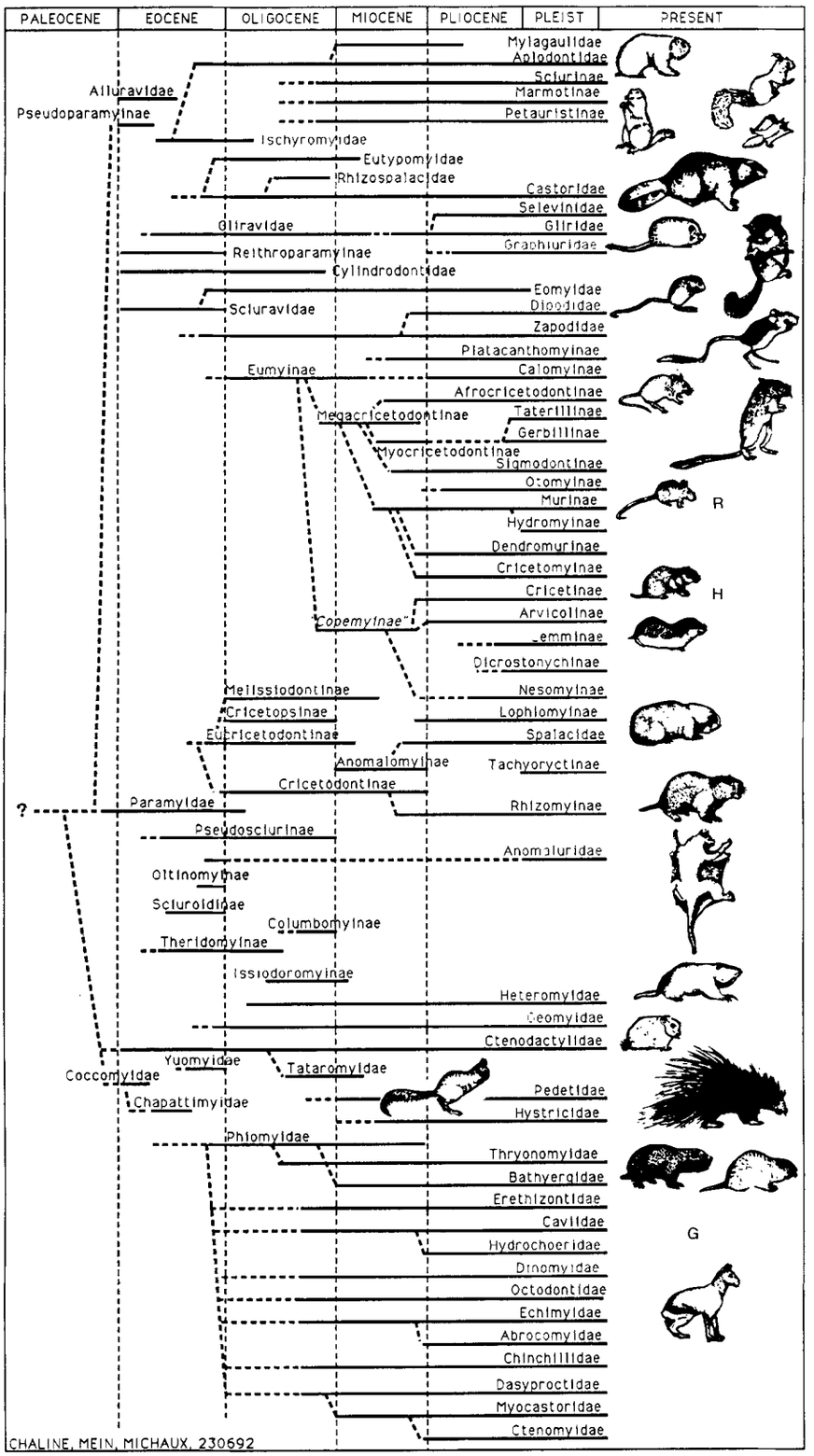

Fig. 1 Provisional scenario of the diversification of the rodents, including stratigraphic record and possible phylogenetic relationships [13, 17, 44, P. Mein and J. Michaux, personal communications] (*R* Rat and mouse, *H* hamster, *G* guinea pig)

evaluated by paleontological data lies at between 12 and 8 Myr and around 10 Myr by molecular data.

Distances between rodent species used for research in xenografting: a discussion

In addition to inner ear structure and in spite of important chromosomal differences [25, 73], numerous features shared by African and South American Hystricognaths support monophyly of the group and, thus, point to a clear grouping of *Cavia*, *Rattus* and *Cricetus* in the same monophyletic group. These features include: (1) anatomical features of the skull [22, 23, 32, 50, 78] and carotid artery branching [8], (2) amino acid sequences of α and β hemoglobin chains [60], (3) immunological data [58] and ribonuclease [5], and (4) eye lens protein α-crystallin A [34].

However, analysis of protein sequences recently led Graur et al. [27] to the conclusion that the guinea pig may be genetically closer to humans than to the reference myomorph (rat, mouse, or hamster). This conclusion was based upon the notion that the rates of evolution of various molecules are highly uneven and often particularly rapid in rodents [16, 34]. In fact, among mammals, the greatest differences in nonrepetitive DNA rates of change are those occurring between hominoid primates and murid rodents. Taking a base of 10 Myr for the separation between *Rattus* and *Mus*, mitochondrial DNA evolution rates of 4.8%–9.7% per Myr are observed, which is at least three times more than those in primates (2% per Myr) or other mammal groups [15]. Using the same analytical method described by Graur et al. [27], which is based upon the comparison between two rodent suborders, a reference order (primate or artiodactyl) and an outgroup (e.g., chicken), a comparison of RNA nucleotide sequences of the 12S mitochondrial ribosome was made that also challenged the traditional monophyletic conception with the suborders of Sciurognaths and Hystricognaths separated from other orders of mammals [3]. However, the choice of very remote out-groups, such as the chicken, which contain information on very different hierarchical levels (class, order, family, species, individual), may strongly bias the interpretation of divergences among closely related species. Divergences observed at one level cannot suitably be used for handling problems of divergence at another level as undue weight is given to convergence, that is, similarities which, as in the area of isoenzymes [7], do not stem from inheritance from a common ancestor. It is, therefore, indispensable to use an out-group that is phylogenetically far closer to the groups tested.

The important point is that evolution does not occur identically across various levels of organization of life [20]. Evolution of the middle ear is virtually nil in Hystricognaths while chromosomal formulae evolve vastly. On the molecular level, the eye lens protein α-crystallin A shows a slow cytochrome c type evolution that is far slower than that of hemoglobin, myoglobin, and pancreatic ribonuclease. The study of crossreactions of antialbumin precipitins reveals that the guinea pig and the rat have not acquired great divergences in terms of albumin [58]. On the contrary, the divergence is perhaps important for molecules such as proteins of the complement system, transferases, membrane glycoproteins or glycolipids, which are particularly involved in xenograft rejection.

From morphology and particularly molecular biology studies, it is obvious that the guinea pig, rat, white mouse, and hamster differ by unequal genetic distances.

It can be seen from a comparison of graft rejection time with the time divergences of the four types of rodents studied here that phylogenetic distance seems inversely proportional to graft rejection time, at least in muroids (Table 1). This observation adds to that made by Calne [11] that rejection of an organ xenograft is probably related to immunological divergence, the reflection of phylogenetic divergence. It led to the concept of concordant or discordant xenogenic donor-recipient combinations, depending on whether rejection time was close to that of an allograft or, on the contrary, very rapid.

The extreme rapidity of the rejection time of a guinea pig-to-rat heart xenograft reflects the divergence observed at the genetic and morphological levels.

Perspectives for xenotransplantation in humans

Beginning with the shortest distance and going on to the longest one, global relative phylogenetic distances between humans and other mammals create the following ranking order: (1) chimpanzee, (2) baboon, (3) pig, rat, and guinea pig. However, in order to determine their genetic distances appropriately, comparative molecular analyses of the six taxa taken as a whole should be done.

Understanding that divergence between humans and other mammals depends upon each type of molecule and its evolutionary rate, it is interesting to observe that for α and β hemoglobin chains [60], humans are at an equal distance from rodents and pigs, but that for amino acid sequences of eye lens protein α-crystallin A [34], humans are closer to rodents than to pigs. From the perspective of xenotransplantation in humans, this provocative observation could raise some interest in the largest caviomorph of South America, the cabiai or capybara *(Hydrochoerus hydrochoerus)*, an animal the size of a pig and presently farm-raised for food requirements. Recent experiments (J. Cardoso, unpublished data) have shown that human natural hemagglutinating antibodies react less strongly to capybara red blood cells than to pig red blood cells.

Conclusion

Comparison suggests that between rodents the heart xenograft rejection time is inversely proportional to the time divergence, also called phylogenetic distance, between the four types studied (guinea pig, hamster, rat, mouse). This overall coherence should not conceal the fact that divergence can vary considerably from one level of organization to another. On the other hand, it suggests that the binomial terminology concordant/discordant, which is useful for practical reasons to classify organ xenograft rejection, does not properly reflect the variety and amplitude of the phylogenetic distances between species.

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