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Gelatinase B deficiency impairs reproduction

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Letter to the Editor

Gelatinase B has been suggested to intervene at different stages of the cyclical changes in female reproduction (1–3): in the menstrual cycle, ovulation, implantation, parturition, and involution of the mammary glands after lactation. Gelatinase B has also been implicated in the process of growth and development of the embryo (4, 5). So far, the only reported spontaneous phenotype of gelatinase B deficiency is a delayed ossification of the growth plate in long bones (6). Most other phenotypes of gelatinase B are induced tissue reactions of the skin (7), the lung (8), the central nervous system or bone (9), and the aortic wall (10). Is there any spontaneous effect of gelatinase B ablation on reproductive capacity? Gelatinase B–deficient mice were generated by a functional knockout of the active and zinc-binding domain of MMP-9 as previously described (9). In the three reports published to date (6, 9, 11), which described structurally distinct null alleles in the gene, gelatinase B–deficient mice were found to reproduce. However, in the course of studying the induction of autoimmune diseases in these animals, we noted a significantly diminished breeding efficiency of the gelatinase B–deficient mice as compared with wild-type controls. During a test period of 3 months, the number of mice born per breeding pair is significantly lower in the gelatinase B–deficient than in the wild-type mice. […]

Gelatinase B deficiency impairs reproduction

Letter
TO THE EDITOR

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Gelatinase B has been suggested to intervene at different stages of the cyclical changes in female reproduction (1–3): in the menstrual cycle, ovulation, implantation, parturition, and involution of the mammary glands after lactation. Gelatinase B has also been implicated in the process of growth and development of the embryo (4, 5). So far, the only reported spontaneous phenotype of gelatinase B deficiency is a delayed ossification of the growth plate in long bones (6). Most other phenotypes of gelatinase B are induced tissue reactions of the skin (7), the lung (8), the central nervous system or bone (9), and the aortic wall (10). Is there any spontaneous effect of gelatinase B ablation on reproductive capacity?

Gelatinase B–deficient mice were generated by a functional knockout of the active and zinc-binding domain of MMP-9 as previously described (9). In the three reports published to date (6, 9, 11), which described structurally distinct null alleles in the gene, gelatinase B–deficient mice were found to reproduce. However, in the course of studying the induction of autoimmune diseases in these animals, we noted a significantly diminished breeding efficiency of the gelatinase B–deficient mice as compared with wild-type controls.

During a test period of 3 months, the number of mice born per breeding pair is significantly lower in the gelatinase B–deficient than in the wild-type mice. In addition, the individual litters in knockout mice are smaller, and the percentage of infertile breeding pairs is elevated in the gelatinase B–deficient mice, whereas maximal litter numbers were observed in the wild-type mice (Table 1). The percentages of breeding pairs with 0, 1, 2, or 3 litters were respectively 18, 5, 18, and 59 for the wild-type mice (n = 39), versus 36, 20, 17, and 27 for the gelatinase B–deficient mice (n = 89) (P = 0.007, χ^2 with Yates's correction = 12.10, 4 × 2 contingency table, 3 degrees of freedom). Control and knockout mice were bred on C57BL/6 background. We observed a quantitatively similar suppression of fertility in gelatinase B–deficient mating pairs whether we compared *MMP-9*$^{-/-}$ animals with their wild-type littermates or with wild-type breeding pairs that carried the pure C57BL/6 background genotype. Hence, the differences seen in fertility are not caused by genetic background effects but, indeed, by gelatinase B deficiency. Further studies are required to elucidate whether this spontaneous phenotype may be attributed to male or to female fertility.

Matings of heterozygous mice resulted in the expected mendelian frequency of *MMP-9*$^{+/+}$ (101/359, 28.1%), *MMP-9*$^{-/-}$ (81/359, 22.6%) and *MMP-9*$^{+/-}$ (177/359, 49.3%) mice (9), suggesting that embryonic and fetal development of homozygous mutant mice were not impaired, as also observed by Vu et al. (6).

Based on the combination of a reduced breeding efficiency of homozygous gelatinase B–deficient mice and the occurrence of the expected mendelian frequency of *MMP-9*$^{+/+}$, *MMP-9*$^{-/-}$, and *MMP-9*$^{+/-}$ mice in heterozygous matings, we conclude that decreased fertility is a spontaneous phenotype of gelatinase B deficiency. This finding reinforces the role of gelatinase B in the establishment and maintenance of a normal pregnancy and suggests that influencing gelatinase B activity may be a target in birth control. In addition, decreased fertility is anticipated in the treatment with nonselective and selective MMP-inhibitory drugs that are currently used in clinical trials for inflammatory and neoplastic diseases.

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Table 1
Gelatinase B deficiency impairs fertility in mice

	KO	WT	P
Mean number of newborn mice per breeding pair	8.18 (n = 89)	14.05 (n = 39)	< 0.001
Mean number of mice per litter	6.03 (n = 120)	7.64 (n = 72)	< 0.001
Percent of breeding pairs without litters	36 (32/89)	18 (7/39)	0.064
Percent of breeding pairs with three litters	27 (24/89)	59 (23/39)	0.0013

Pairs of gelatinase B–deficient (KO) or wild-type controls (WT) of C57BL/6 background were left together during an observation period of 3 months, and the mean number of newborns as well as the numbers of mice per litter were calculated. Statistical analysis was performed using the Wilcoxon and the χ^2 method with Yates's correction.

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