INTRODUCTION

The development of a senescence-accelerated mouse (SAM) strain has been under way at Kyoto University since 1970. At present, 12 lines of inbred strains have been maintained as original colonies of the SAM model: 9 senescence-prone (SAMP) and 3 senescence-resistant (SAMR). In addition, several lines of SAM have been developed at Takeda Chemical Ind., Ltd., using original mice from Kyoto University. Based on data obtained from Kyoto University and elsewhere, this review describes (1) the circumstances related to the development of SAM mice and their genetic background, (2) the pathobiological phenotypes of SAM, and (3) the significance of SAM development.

DEVELOPMENT AND GENETIC BACKGROUND OF SAM MICE

In 1968, several pairs of AKR/J mice were donated by Jackson Laboratory (Bar Harbor, Maine) to the Department of Pathology (currently the Department of Senescence Biology), Chest Disease Research Institute, Kyoto University, Japan. While continuing brother-sister mating to maintain this inbred strain under conventional conditions, we became aware that in certain litters most of the mice showed a moderate to severe degree of decreased activity, hair loss and dull hair, coarse skin, periophthalmic lesions, and increased lordokyphosis. Additionally, the life span for most mice was shortened. We also noted the inheritance of these phenotypes.

In 1975, 5 litters of mice with severe exhaustion were selected as the progenitors of the senescence-prone (P) series. Litters in which the aging process was normal were selected as progenitors of the senescence-resistant (R) series. Thereafter, selective breeding based on senescence, life span, and pathological phenotypes was carried out in addition to the routine brother-sister mating (Hosokawa and others 1997; Takeda and others 1981, 1991).

From each of the selected litters of mice with severe exhaustion, 5 different series were obtained and designated

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Senescence-accelerated Mouse (SAM): With Special Reference to Development and Pathobiological Phenotypes

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characteristic of a senescence-resistant strain, compared with cell neoplasms and histiocytic sarcoma, an advantageous SAMR1 and SAMR4. SAMPl has the shortest life span of SAMP strains at 8 months is 7.97, about twice that of SAMR strains (16.3 months). The senescence grading score SAMP and the SAMR strains (Takeda and others 1991, and SAMR5. SAM has become a general term for both the Mechanisms of Ageing and Development common to all the P series—“accelerated senescence.” After a brief period of normal development, accelerated senescence is an irreversible advance of senescence manifested by gross lesions and such signs as abnormal behavior, various skin lesions, and increased lordokyphosis. The P series was named SAM, and our first paper on the SAM model appeared in 1981 (Takeda and others 1981). At that time, the mean life span in the P series was 9.7 months, 27% shorter than that of the R series (13.3 months). The senescence grading score of the P series at 8 months of age was 3.67, about 3 times that of the R series (1.26). The Gompertz coefficient for the P series was 0.133, significantly greater than that for the R series (0.083). Necropsy findings in both series showed prominent amyloid deposition, abscess, thymic and nonthymic lymphoma, and pneumonia. A low incidence of thymic and nonthymic lymphoma in both the R (16.3%) and the P (8.3%) series in comparison with that reported in the authentic AKR/J strain (Festing 1992) suggested a genetic deviation from the original AKR/J in this model of accelerated senescence. A high incidence of amyloidosis in the P (77.9%) and the R (32.0%) series compared with the reported incidence in the AKR/J strain (Ebbeisen 1974) also seemed to support this (Takeda and others 1981).

Breeding among P-4, P-5, and R-3 mice has been unsuccessful; however, it has been possible to establish several new strains that fulfill the criteria of inbred strains: successful brother-sister mating over 20 generations with a stable homozygosity and stable expression of pathological phenotypes (Hosokawa and others 1984; Takeda and others 1991). After 1984, the established strain was denoted SAM-R/1 instead of R-1 (Hosokawa and others 1984). In 1991, SAM-R/1 changed to SAMR1, following the rules for international nomenclature of inbred strains of mice (Festing 1992, 1993). In 1994, we established 2 new inbred strains, SAMR5 and SAMP11, from the P-4 and P-3 series, respectively.

At present, there are 12 lines, all of which originated from the P and R series. Senescence-prone (SAM) inbred strains include SAMP1, SAMP2, SAMP3, SAMP6, SAMP7, SAMP8, SAMP9, SAMP10, and SAMP11, while the senescence-resistant (SAMR) inbred strains are SAMR1, SAMR4, and SAMR5. SAM has become a general term for both the SAM and the SAMR strains (Takeda and others 1991, 1994). Recent data show that the median survival time of SAM mice is 9.7 months, 40% shorter than that of the SAMR strains (16.3 months). The senescence grading score of SAMR strains at 8 months is 7.97, about twice that of SAMR (3.94) (Takeda and others 1994).

SAMP5 demonstrated a lower incidence of lymphoid cell neoplasms and histiocytic sarcoma, an advantageous characteristic of a senescence-resistant strain, compared with SAMR1 and SAMR4. SAMP11 has the shortest life span among all the SAM strains. The incidence of hyperplasia of the bile duct increased and the life span shortened in each succeeding generation of SAMR2, a resistant strain that is no longer being bred (Takeda and others, 1994).

To establish a specific-pathogen-free SAM strain, breeding pairs of the P and R series (P-1, P-2, R-1) and SAMP strains (SAMP6, SAMP10) were sent from Kyoto University to Takeda Chemical Ind., Osaka, Japan. From these series and strains, SAMP1TA, SAMP6/Ta, SAMP8/Ta, SAMPI0/Ta, and SAMR1TA have been developed and maintained. The lineage of each strain of SAM from the original AKR strains is presented in Figure 1. At present, breeding pairs of most of the strains reared at Takeda Chemical Ind. as well as Kyoto University are available for investigators if application is approved by the Council for SAM Research.

Necropsy findings on the P and R series suggested genetic deviations in the SAM model from the original AKR/J strain as noted above (Takeda and others 1981). Data on 17 biochemical and 10 immunogenetic markers revealed that at least 1 genotype in each SAM strain differed from the authentic AKR/J strain (Takeda and others 1994). These results, along with information gathered from genome mapping using oligonucleotide probes designed to recognize endogenous mouse retrovirus sequences, show that each SAM strain is genetically distinct and contains certain amounts of genetic information derived from strains other than AKR/J (Kitado and others 1994). Therefore, it is reasonable to assume that the original AKR/J strain was unintentionally outbred with other strains before 1975, when the progenitors of the P and R series were selected and selective breeding began (Finch 1994; Kitado and others 1994; Takeda and others 1991). At present, it is not clear what strains were mated with the AKR/J mice.

**PATHobiological PHenotypes in SAM**

Routine postmortem examinations and a series of systematically designed studies conducted on living as well as dead SAM mice revealed that in addition to accelerated senescence, which is common to all the SAMP strains, SAMP strains manifest various pathobiological phenotypes that are often characteristic enough to differentiate the strains (Table 1) (Takeda and others 1997). Some of these phenotypes are briefly presented below.

**Senile Amyloidosis**

Severe age-associated systemic amyloidosis was first reported in the P series (Higuchi and others 1983b; Takeda and others 1981; Takeshita and others 1982). A unique senile amyloid fibril protein (AAp0AII, formerly called ASSAM), which is distinguishable from murine protein AA in secondary amyloidosis, was isolated from the liver of SAMP1 mice (Matsumura and others 1982) and was later found to be present universally in such aged mice, regardless of strain
The protein consists of a single polypeptide chain of 78 amino acid residues, and its amino terminus is blocked with pyrrolidone carboxylic acid. Additional biochemical and immunochemical studies revealed that the primary structure of apolipoprotein A-II (apoA-II) is identical to that of the amyloid fibril protein (Higuchi and others 1983a, 1986; Yonezu and others 1986). This finding proves conclusively that apoA-II, one of the major protein constituents of plasma high density lipoprotein, deposits in tissues without degradation.

Next, apoA-II cDNA of SAMP1 and SAMR1 were characterized. Nucleotide sequencing confirmed the amino acid substitution (Pro5-Gln) in SAMP1—a result of the substitution of 2 nucleotides (CCA to CAG) (Kunisada and others 1991b).

TABLE 1 Pathobiological phenotypes

<table>
<thead>
<tr>
<th>Strains</th>
<th>Phenotypes</th>
</tr>
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<tbody>
<tr>
<td>SAMP</td>
<td>Senile amyloidosis, contracted kidney, impaired immune response, hyperinflation of lungs, hearing impairment</td>
</tr>
<tr>
<td>SAMP1TA</td>
<td>Deficits in learning and memory</td>
</tr>
<tr>
<td>SAMP2</td>
<td>Senile and secondary amyloidosis, contracted kidney, impaired immune response</td>
</tr>
<tr>
<td>SAMP3</td>
<td>Degenerative temporomandibular joint disease</td>
</tr>
<tr>
<td>SAMP6</td>
<td>Senile osteoporosis, secondary amyloidosis</td>
</tr>
<tr>
<td>SAMP6/Ta</td>
<td>Senile osteoporosis</td>
</tr>
<tr>
<td>SAMP7</td>
<td>Thymic lymphoblastic lymphoma, senile amyloidosis</td>
</tr>
<tr>
<td>SAMP8</td>
<td>Deficits in learning and memory, impaired immune response</td>
</tr>
<tr>
<td>SAMP8/Ta</td>
<td>Deficits in learning and memory, emotional disorder (reduced anxiety-like behavior)</td>
</tr>
<tr>
<td>SAMP9</td>
<td>Cataract, thymic lymphoblastic lymphoma, senile amyloidosis</td>
</tr>
<tr>
<td>SAMP10</td>
<td>Brain atrophy, deficits in learning and memory</td>
</tr>
<tr>
<td>SAMP10/Ta</td>
<td>Deficits in learning and memory, emotional disorder (depressive behavior)</td>
</tr>
<tr>
<td>SAMP11</td>
<td>Contracted kidney, senile amyloidosis.</td>
</tr>
<tr>
<td>SAMR</td>
<td>Nonthymic lymphoma*, histiocytic sarcoma, ovarian cyst</td>
</tr>
<tr>
<td>SAMR1</td>
<td>Nonthymic lymphoma*</td>
</tr>
<tr>
<td>SAMR1TA</td>
<td>Nonthymic lymphoma*, histiocytic sarcoma</td>
</tr>
<tr>
<td>SAMR4</td>
<td>Colitis</td>
</tr>
<tr>
<td>SAMR5</td>
<td>Nonthymic lymphoblastic lymphoma, immunoblastic lymphoma, and follicular center cell lymphoma.</td>
</tr>
</tbody>
</table>

* Includes nonthymic lymphoblastic lymphoma, immunoblastic lymphoma, and follicular center cell lymphoma.
Changes observed in SAMP8 and SAMP8/Ta were summarized as follows: periodic acid-Schiff-positive granular structures, spongiiform degeneration in the brain stem, β/AA protein-like immunoreactive granular structures, reduction of dendritic spines of hippocampal pyramidal neurons, spheroid in gracile nuclei, lipopigmentation, thalamic neuronal inclusion, and astrocytosis (Akiyama and others 1986). A series of molecular genetic and biochemical studies indicated that 3 variants of apoA-II protein (types A, B, and C) with different amino acid substitutions at 4 positions are present in SAM strains. SAMP1, SAMP2, SAMP7, SAMP9, SAMP10, and SAMP11 strains with a high incidence of senile amyloidosis have type C apoA-II (Apoa2c) with glutamine at position 5. Other strains of SAM with a low incidence of senile amyloidosis have type A (Apoa2a) or type B (Apoa2b) apoA-II, both of which have proline at position 5 (Higuchi and others 1991a). Examination of the genotypes of apoA-II gene and amyloid deposition in the F1 and F2 strains, and mice backcrossed between strains with Apoa2c and Apoa2a or Apoa2b, showed that (1) murine senile amyloidosis is linked to Apoa2c and transmitted in an autosomal dominant manner with incomplete penetrance, and (2) amyloidosis is far more severe in mice homozygous for Apoa2c (Higuchi and others 1991a; Naiki and others 1993; Yonezu and others 1987). A kinetic analysis of amyloid fibrillogenesis in vitro was performed using a novel method based on the unique characteristics of the fluorescent indicator thioflavine-T (Naiki and others 1989). The results indicated that extension of amyloid fibrils proceeds by consecutive association of precursor proteins that attach onto the ends of existing fibrils (Naiki and others 1991). In addition to senile amyloidosis, secondary amyloidosis with AA amyloid deposition was often observed in SAM mice with inflammatory lesions, particularly in SAMP2 and SAMP6 (Higuchi and others 1983b; Takeda and others 1997).

Deficits in Learning and Memory and Brain Atrophy

A series of behavioral studies on SAMP8 and SAMP8/Ta disclosed age-related behavioral disorders, such as deficits in learning and memory (Miyamoto and others 1986; Yagi and others 1988; Ohta and others 1989; Flood and Morley 1992; Flood and Morley 1993), emotional disorder, and abnormality of circadian rhythms (Miyamoto 1997; Miyamoto and others 1992). Characteristic emotional disorder in SAMP8/Ta was assessed by elevated plus-maze test, water-drinking conflict, and neophobia test. Ingram and others (1994), however, did not find behavioral impairment in the SAMP8/Ta in swim maze performance. Ikegami and others (1992) reported no age-accelerated decline in radial-arm maze performance in SAMP8/Ta mice, although they showed a marked age-accelerated deficit in acquisition performance relative to SAMR1TA in a passive avoidance task, suggesting a disso- ciative effect of aging in spatial learning and passive avoidance performance. Morphological, mostly age-related, changes observed in SAMP8 and SAMP8/Ta were summarized as follows: periodic acid-Schiff-positive granular structures, spongiiform degeneration in the brain stem, β/AA protein-like immunoreactive granular structures, reduction of dendritic spines of hippocampal pyramidal neurons, spheroid in gracile nuclei, lipopigmentation, thalamic neuronal inclusion, and astrocytosis (Akiyuchi and others 1994; Akiyama and others 1986; Sugiyama and others 1987; Takemura 1993; Yagi and others 1989). Neurochemical studies on SAMP8 brains performed by Dr. Nomura and his colleagues demonstrated that (1) the contents of glutamate (Glu) and glutamine (Gln) in hippocampus were greater than those of SAMR1; (2) high K+-evoked release of Glu, aspartate, Gln, and alanine was increased; (3) N-methyl-D-aspartic acid (NMDA)-induced release of [3H]-acetylcholine (Ach) and [3H] noradrenaline was markedly reduced; (4) the number of several neurotransmitter receptors such as M1, Ach, 5-HT1A, serotoninn, and NMDA receptors and the amount of protein kinase C were decreased; (5) the binding activity of [3H] PK-11195 (for α3-BZ receptor) was greater than that of SAMR1; and (6) 27-kDa proteins that reacted with antibody against the C terminal of amyloid precursor protein were increased with aging (Kitamura and others 1992; Nomura and others 1994; Zhao and Nomura 1990; Zhao and others 1992). In addition, Flood and others (1993) observed an age-related reduction in sensitivity to memory-enhancing doses of cholinomimetics arecoline and tacrine when injected peripherally after footshock avoidance training in SAMP8/Ta. They also showed that reduced cholinergic activity in the hippocampus may be, in part, responsible for the age-related decline in memory retention in SAMP8/Ta mice (Flood and others 1996). In addition, a series of studies was performed to clarify the pathogenesis of age-related deficits in learning and memory and other behavioral disorders (Amano and others 1995; Flood and others 1995; Fujibayashi and others 1994; Kaisho and others 1994; Liu and Mori 1993; Meguro and others 1992, 1995; Sato and others 1994, 1996; Tobita and others 1994; Ueno and others 1993; Vorbrodt and others 1995).

In SAMP10 and SAMP10/Ta, age-related impairment of learning and memory (Miyamoto 1997; Shimada and others 1992, 1993), emotional disorder, and depressive behavior, as assessed by tail-suspension test and circadian rhythms disturbance, were observed (Miyamoto 1997). In addition to the behavioral disorders described above, age-related spontaneous brain atrophy was observed in SAMP10 (Shimada and others 1992, 1994) throughout their life spans, with brain weights decreasing by 8.6% relative to 4 months of age. Morphometric observation revealed that the most vulnerable region to age-related atrophy in SAMP10 was the frontal region of the cerebral neocortex, which showed 29.2% atrophy relative to 2 months of age. Other neocortical regions underwent diffuse atrophy. Posterior piriform cortex, entorhinal cortex, anterior olfactory nucleus, amygdala, nucleus accumbens, caudate-putamen, septum, and cerebellar cortex all were found to be atrophy-prone regions (Shimada and others 1994). The mean cell size of neurons in layers II, III, V, and VI of the cerebral cortex shrank with advancing age. Among the neocortical cells, large neurons in the frontal cortex decreased in number by 35.6% relative to 2 months of age throughout the life span. There was no age-related change in the number of small neurons or glia in the cortex (Shimada and others 1992). Recently, Ohnishi and others (1995) reported that there was an age-related decline in nerve growth.
factor-like immunoreactivity in the substantia innominata of SAMP10 mice at the age of 10 months.

Recently, it became evident that SAMP1TA mice also showed age-related deficits in learning and memory (Kawaguchi and others 1995; Nitta and others 1996). None of the strains with spontaneously occurring deficits in learning and memory with aging had neurological abnormalities such as tremor, convulsion, or disturbances of gait and posture. Thus, they can serve for studies of aging of the brain, particularly in some neurodegenerative disorders associated with dementia, and they may provide new insights into the neurobiology of aging.

Senile Osteoporosis

In the course of development of SAM, we became aware of spontaneous leg fractures in a few aged SAM mice and therefore began to examine systematically the age-related changes in bone in several strains of SAM. Microdensitometrically, these strains showed consistent patterns of changes, that is, femoral bone mass corrected by the diameter of the shaft reached a peak value when the mice were 4 or 5 months of age and then fell linearly with age up to more than 20 months. SAMP6 had a significantly lower peak bone mass than other strains. Strains with a low peak bone mass, however, had the same rate of decrease in bone mass as other strains. Mineral and collagen contents per dry weight of bone showed little difference among the strains of SAM. All these results, along with the histological findings of tibia, femur, and lumbar spine, revealed that osteopenia was due not to osteomalacia, but rather to osteoporosis (Matsushita and others 1986). Furthermore, judging from the concept of bone loss based on human data, osteoporosis observed in SAMP6 might be equivalent to the senile osteoporosis in humans with type B fracture, as described by Riggs and Melton (1983).

Tsuboyama and others (1989b) demonstrated by tetracycline labeling a significant difference among strains regarding rate of the appositional formation at the endosteal surface (SAMP2>SAMR1>SAMP6) but not at the periosteal surface for mice 28 to 60 days old. Therefore, differences in femoral bone mass between SAMP6, SAMR1, and SAMP2 are brought about, at least in part, by interstrain disparities in the endosteal formation rate during growth. The lower peak value can be attributed to some extent to the decreased endosteal formation in the course of the cortical bone modeling. In vivo and in vitro studies by Suda and others (1994) revealed that osteoporotic bone changes in SAMP6 are due to the paucity of osteoblastic progenitor cells. Recently, Jilka and others (1996) showed that the number of osteoblast progenitors in SAMP6/Ta marrow was indistinguishable from control SAMR1TA at 1 month of age. However, a threefold decrease was found at 3 to 4 months of age, and that impairment of osteoblast formation was temporally associated with decreased bone formation and decreased mineral density, as determined by histomorphometric analysis of tetracycline-labeled cancellous bone and dual-energy X-ray absorptiometry, respectively. In addition, a series of studies to clarify the pathogenesis of the osteoporosis in SAMP6 has been conducted (Kawase and others 1989; Okamoto and others 1995; Takahashi and others 1994a,b; Tsuboyama and others 1989a, 1993).

Degenerative Joint Disease

A systematic study of the condyle of the temporomandibular joint in several strains of SAM revealed that all strains develop degenerative joint disease (DJD). However, the short-lived SAMP strains develop degenerative changes earlier and more severely than do the SAMR strains. SAMP3 mice are the first to show degenerative joint changes (approximately 50% at 7 to 9 months of age and 100% over 12 months of age) and thereafter have the highest incidence of severe changes with overt deformity (Chen and others 1989). Results of studies designed to examine the effects of mandibular shape and diet consistency on the development of DJD suggested that "mechanical loading" on the temporomandibular joint, which acts as a local factor, may play a crucial role in the pathogenesis of DJD in SAM in combination with accelerated senescence, which acts as a systemic factor (Chen and others 1994).

Cataract

The cataracts of SAMP9 mice began to appear at around 10 weeks of age. Approximately 81% of females and 49% of males had cataracts after 32 weeks of age. Stereomicroscopic examination of the lens revealed that many of these cataracts were initially posterior and that mature cataracts showed a characteristic protrusion of the posterior pole, degeneration and liquefaction of the lens cortex, nuclear dislocation, and destruction of the posterior lens capsule. Persistence of the hyaloid vascular system is a necessary, but not the only, factor in the formation of cataracts in SAMP9 mice (Hosokawa and others 1988, 1993). The persistence of the hyaloid vascular system might affect the breakdown of the lens capsule, a trigger of cataract formation, and subsequently lead to increased Ca content and transglutaminase activity in the lens to reduce the solubility of β-crystallins (Ashida and others 1994). Teramoto and others (1992) revealed that ophthalmic changes, including cataracts, showed clear increases with age in SAMP2 and that an age-related decrease in glutathione content and an increase in oxidized glutathione of the eye lens may be involved in the pathogenesis of cataracts in SAMP2.

Hearing Impairment

SAMP1 and SAMR1 showed an age-related auditory loss expressed as elevated thresholds, prolongation of interpeak intervals I-III and I-IV, and decreased amplitude of wave I,
as assessed by auditory brainstem responses (Saitoh and others 1994). SAMP1 showed a more rapid and severe auditory loss with age than did SAMR1. Morphological studies showed an age-related decrease in cell density as well as in the size of spiral ganglion neurons in SAMP1 and SAMR1 (Saitoh and others 1994). An age-related loss of the inner and outer hair cells was also observed in both SAMP1 and SAMR1. The changes in the spiral ganglion neurons and hair cells, however, appeared earlier and progressed more rapidly in SAMP1 than in SAMR1. Furthermore, SAMP1 showed greater age-related atrophy of the stria vascularis than did SAMR1. These results suggest that hearing impairment in SAMP is due to a combination of sensory and strial presbycusis as well as to neural presbycusis (Saitoh and others 1995).

Hyperinflation of Lungs

Morphometric and physiological studies of the respiratory system showed senile hyperinflation of the lungs in SAMP1 and SAMR1. Histological observation, however, revealed no evidence of destruction of the alveolar wall or elastic fibers in the lungs. The hyperinflationary changes occurred similarly in both SAMP1 and SAMR1, but in an accelerated manner in SAMP1; and finally, senile hyperinflation of the lungs occurred in the senescence phase in both strains (Kurozumi and others 1994). Teramoto and others (1994) reported that SAMP2 mice also manifested most of the characteristic changes in senile lung.

Impaired Immune Response

From a series of immunobiological studies, in vivo experiments showed that primary antibody response and delayed-type hypersensitivity reaction to sheep red blood cells (SRBC1) were significantly more impaired by 6 months of age in SAMP1 and SAMP2 than in SAMR1 and ordinary strains, such as C3H/He and B10.BR (Mitsuoka and Hanada 1988). Yoshioka and others (1989) reported that sera from SAMP1 mice showed an earlier increase in serum immunoglobulin G (IgG1) 2 levels and an earlier appearance of IgG-containing circulating immune complexes. Furthermore, many kinds of antibodies, including natural thymocytotoxic autoantibody and IgG anti-double-stranded DNA antibodies, were relatively easily detected in the sera of SAMP1 with aging. The earlier appearance of autoantibodies was not as severe as that observed in the autoimmune disease MRL 1/1 or NZB mice models but was distinct enough to discriminate SAMP1 from control SAMR1. Immunopathological observations revealed age-associated glomerular mesangial and capillary lesions with granular IgG and C3 deposition in SAMP1 mice.

To clarify the nature of the immunobiological defects observed in vivo, in vitro experiments were conducted. It became evident that SAMP1 mice had a profound defect in antibody response to a T-dependent antigen, SRBC, at as early as 2 months of age, and a negligible response at a later age (Hosokawa and others 1987b). This impaired antibody response was thought to be closely related to dysfunction of T-helper cells, while other T-cell activities such as mixed lymphocyte reaction, cytotoxic T-lymphocyte generation, and delayed-type hypersensitivity reaction remained normal. B-cell and antigen-presenting cell activities were also normal (Hosokawa and others 1987a). A series of studies to clarify the genetic control of the low immune activity in SAMP mice was also performed in vitro. The low immune responsiveness was controlled by two independent genes, one of which may be located near the Gpi-1 and Akv-1 loci, a proximal site on chromosome 7, while the other has not yet been clarified (Hanada and others 1989; Hanada and others 1991; Hanada and others 1994). Recently, Abe and others (1994) reported that a helper T-cell defect similar to that in SAMP1 was found in SAMP8 mice, which show characteristic deficits in learning and memory with advancing age. Furthermore, low natural killer cell activity was observed in SAMP8 (Abe and others 1994). However, it has been reported that the antigen-presenting activity of the dendritic cells and B cells against antigen-primed T cells is impaired in SAMP1 mice in the in vitro assay system (Haruna and others 1995). Recently, Hosono and others (1997) published a review of the immunobiological abnormalities in SAMP with a detailed discussion of the relationship between immunobiological aging and the age-related manifestation of pathological phenotypes.

Contracted Kidneys

Contracted kidneys had a granular surface and were reduced in size according to the severity of the lesions. Destroyed nephrons were replaced by a proliferation of fibrous tissue. Five of the SAMP strains had contracted kidneys as the second most frequent necropsy finding (Takeda and others 1997): SAMP1 (46.8%), -P2 (63.2%), -P6 (38.8%), -P10 (68.6%), and -P11 (46.3%). Based on the autoimmune abnormalities described above, it was strongly suggested that autoimmune mechanisms play a pathogenic role in the manifestation of contracted kidneys in SAMP1.

Other Phenotypes

Necropsy findings after the natural death of SAM mice revealed that SAMP7 and SAMP9 had a higher incidence of thymic lymphoblastic lymphoma than other genotypes. SAMR1 and SAMR4 showed a high incidence of nonthymic lymphoma (including nonthymic lymphoblastic lymphoma, immunoblastic lymphoma, and follicular center cell lymphoma) and of histiocytic sarcoma (Takeda and others 1997). Ovarian cyst (46.2%) and colitis (33.3%) were the most common pathologies in SAMR1 and SAMR5, respectively. Dr. Sashima and her colleagues have reported age-related oral pathologies such as teeth loss, incisor abnormalities, senile
SIGNIFICANCE OF SAM DEVELOPMENT

Advances in biomedical research depend to a considerable extent on the availability of relevant and appropriate experimental animal models, particularly animals that have not been experimentally manipulated. This is especially true for a model of aging in which aging progresses insidiously and irreversibly, without apparent cause (Takeda and others 1981, 1991). Fortunately, we have succeeded in developing SAMP strains with accelerated senescence and age-associated pathologies in addition to SAMR strains with normal aging except for nonthymic lymphomas and histiocytic sarcoma in aged SAMR1 and SAMR4 (Takeda and others 1997).

As far as we know, 2 mammalian models that spontaneously manifest accelerated senescence have been reported. Pearce and Brown (1960a,b) described hereditary premature senescence in a family of purebred Belgian hares. The rabbit had a senile appearance with abnormalities of the coat and skin and ocular lesions such as conjunctivitis and granulomatous keratitis. Popp (1978) reported accelerated aging in the B10.F strain of mice, which grays early and has severe weight loss and a shortened life span. The plaque-forming reaction to SRBC in this congenic strain of mice decreased irreversibly, without apparent cause (Takeda and others 1981, 1991). Fortunately, we have succeeded in developing SAMP strains with accelerated senescence and age-associated pathologies in addition to SAMR strains with normal aging except for nonthymic lymphomas and histiocytic sarcoma in aged SAMR1 and SAMR4 (Takeda and others 1997).

The SAM model meets most criteria for the use of mammalian models for aging research, such as life table data, short life span, defined environmental conditions, and genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990). The use of mice to study the genetics of aging and age-associated pathologies has definite advantages: the richness of genetic characteristics, as proposed by Masoro (1990).

Most of the “age-dependent” geriatric disorders seen in humans, which were described as a “direct consequence of physiologic senescence” by Cotran and others (1989 p 550), are included in the pathobiological phenotypes in SAM: osteoporosis, degenerative joint disease, cataract, hyperinflation of lungs, and hearing impairment. The evidence provides support for our proposal that the SAM model is valid and useful for aging research.

The SAM model has definite advantages for research on aging as described above. SAM research is advancing worldwide, with efforts to clarify the fundamental mechanisms that are involved in the following: (1) accelerated senescence (Choi and others 1994; Edamatsu and others 1995; Hosokawa and others 1994; Komura and others 1988; Nakamoto and others 1994; Nisitani and others 1990; Nomura and others 1989; Yagi and others 1988b; Yamagishi and others 1985), (2) normal aging, (3) the pathogenesis of age-associated pathologies, and (4) effective methods to modulate or ameliorate the advance of senescence and disease processes involved in age-associated pathologies (Edamatsu and others 1995; Kishikawa and Sakae 1997; Kitamura and others 1991; Kohno and others 1985; Lee and others 1994; Meguro and others 1995; Miyamoto and others 1994; Moriguchi and others 1994; Oomura and others 1995; Takahashi and others 1994b,c; Umezawa and others 1990, 1995; Zhao and others 1990).

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