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MINIREVIEW

Beige Mouse Model for *Mycobacterium avium* Complex Disease

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INTRODUCTION

Mycobacterium avium complex (MAC), comprising *M. avium*, *M. intracellulare*, and *M. scrofulaceum*, has been recognized as an important group of organisms causing severe disease in humans, animals, and birds. Soon after AIDS was discovered, it was observed that MAC is also involved in that syndrome as a serious opportunistic infection and is associated with death within 6 to 12 months after diagnosis (12, 52). The clinical management of MAC disease has been difficult and frustrating, since these organisms are resistant to most of the antituberculosis drugs (98). Serious consideration was given to the discovery of effective agents that could be used to cure and prevent this disease, especially in AIDS patients. In the battery of investigations for the identification of new chemotherapeutic agents, in vivo tests with suitable animal models assume great importance as predictors of chemotherapeutic efficacy and safety (1, 14, 100, 101). Until recently, proper in vivo studies to discover drugs active against MAC could not be done for want of a suitable animal model (11, 28, 29). Earlier claims that the rabbit was susceptible to these infections (65) were not confirmed by others (22); it is also clear that the rabbit is not the optimal animal for use in chemotherapeutic studies. In contrast, a small animal like the mouse possesses several advantages in that small amounts of the drugs can be used, the maintenance costs are low, and larger numbers of animals can be involved for appropriate statistical analysis.

Earlier investigations (13, 19) with $B6D_2$ mice and D673 and TMC 1403 strains of MAC caused a chronic infection, with only a slight increase in the bacterial counts in the lung and spleen even after prolonged periods (>200 days). Since such models of chronic infection would have limited usefulness for chemotherapeutic studies, investigators sought to develop an acute mouse model to facilitate rapid in vivo screening of drugs with potential anti-MAC activity.

Initial studies (44, 45) with several strains of mice essentially confirmed the earlier claims (13, 19) of obtaining a chronic type of infection model, with the disease process taking about 50 weeks. Interestingly, variations in the routes or doses of infection did not result in any differences in the progression of the disease. Subsequent studies dealt with the identification of the most susceptible strains of mice and MAC. Of the seven strains of mice investigated (strains AKR, DBA/2, BDF, CBA/N, S/W, BALB/c, and C57BL/6) only the last one proved to be most susceptible; this mouse strain was also recognized as highly suitable for experimental *M. tuberculosis* infections (84, 97). Of the several strains of MAC investigated (strains 571-8, 8350, and D673), the last one proved to be the most virulent, giving consistently high mortality rates and high numbers of recoverable CFU counts. However, even with a combination of the most susceptible strain of mice and the most virulent strain of MAC, only a chronic disease process was seen. Alteration of the host-parasite balance was attempted by using several immunosuppressive agents (28, 29), but none showed promise for use in the development of an acute infection model, although some could cause slightly higher CFU counts than those caused by the controls.

Recourse was then made to search for an appropriate host among naturally immune compromised mice. Surprisingly, nude mice did not show much higher CFU counts than the other mouse strains studied (28, 29), a finding confirmed by others (59, 94). On the other hand, encouraging leads with beige mice (C57BL/6/bg^j/bg^j), a mutant strain of C57BL/6, made it a possible acute infection model for MAC disease (35).

SALIENT FEATURES OF THE BEIGE (C57BL/6 b/bg^j/bg^j) MOUSE

The first mutation to beige (*bgs*) occurred in irradiated mice at the Oak Ridge National Laboratories. A remutation occurred spontaneously in the C57BL/$bg/6^j$ strain at the Jackson Laboratory and has been perpetuated as a coisogenic strain C57BL/6j/bg^j, which produces experimental pairs, normal and beige (bg^j/bg^j). These mice have lighter coats and eye colors than the parent mice. The mutations also affect the pigment granules of the optic cup, retina, and neural crust, the lysosomal granules, type 2 pneumocytes and mast cells, and natural killer lymphocytes. The syndrome brought about by the mutation in beige mice is the murine representative of the Chediak-Higashi syndrome of humans and of the Aleutian disease of mink and cattle. Because of the genetic abnormalities, such as decreased lysosomal enzymes and degranulation defects, these mice are also susceptible to pyogenic bacterial infections. Thus, prior to its use in experimental MAC disease, several reports showed the increased susceptibility of beige mice to *Candida albicans*, *Staphylococcus aureus*, and pneumococcal challenges and to some neoplastic diseases (23, 25, 73, 77). In spite of its many immunobiological and genetic defects, more than the nude mice, beige mice can easily be bred and maintained under normal vivarium conditions without any cross infections. Besides their extensive use in identifying new drugs for the treatment of MAC disease, these mice have also been used to study many host-parasite interactions of MAC with respect to AIDS. Several routes of MAC challenge besides the intravenous (i.v.) method were also investigated to stimulate the mode of transmission of opportunistic infections in AIDS patients. The facts that beige mice are the direct descendants of C57BL/6 mice, the best mouse model for *M. tuberculosis* (84, 97), and that they have several immunobiological deficiencies similar to those occurring in AIDS patients (26, 37) provided many opportunities for such studies.

INITIAL STUDIES WITH BEIGE MICE AGAINST MAC INFECTION

The first series of studies centered on the comparison of beige mice with their coisogenic control (C57BL/6) mice for their responses to i.v. challenge with MAC isolates. In that (35) and all subsequent studies (30–34, 36–43), a single cell suspension of the predominantly transparent colony type of the organisms was used. The parameters used in that initial study (35) included mortality, body weight, macroscopic and microscopic observations of the visceral organs, and CFU counts of the organisms from spleens, lungs, and blood. The most important observation in that study, which was not seen in any of the earlier investigations, was the death of the animals caused by MAC. The CFU counts from the lungs, spleens, and livers of the animals found dead because of the disease were similar to those from the organs of animals sacrificed at the same times. Several other studies with MAC strains obtained from AIDS patients confirmed this similarity. Thus, in vivo bacterial multiplication, even though it is necessary for establishing the pathogenic potential, may not be the only factor causing the death of the animals as a result of MAC infection, as has been the case with *M. tuberculosis* infections (88). Some factors in addition to bacterial multiplication may be needed to result in full-blown MAC disease.

Another unique finding from that initial study (35) was a positive blood culture for MAC in beige mice from the first week onward. Bacteremia in C57BL/6 and other mouse strains was seen much later, e.g., 19 to 20 weeks after challenge (28, 29, 44, 45). The CFU counts of the organisms recovered from the lungs and spleens of beige mice were much higher than those recovered from the organs of control C57BL/6 mice; the differences between the two strains of mice were greater for the counts in the lungs than those in the spleens (35). More interestingly, the clearance of bacteria from the lungs of control C57BL/6 mice during the first week of infection, a feature noted with several other mouse strains (e.g., S/W, AKR, and BALB/c), was not seen with beige mice, suggesting that the lungs' basic clearance mechanisms are impaired in these mice. Gross examinations of the organs of beige mice following challenge with MAC showed grayish (tubercle-type) lesions, and histopathological examinations revealed several diffused granulomatous changes. The lungs showed massive infiltration of lymphocytes and histiocytes with marked occlusion of the alveoli, and the spleens showed circular clusters of epithelioid cells. In the majority of the liver sections, hepatocytes were overrun with histiocytes and lymphocytes.

Soon after the publication of the results of those initial studies (35), Bertram and associates (10) essentially confirmed the usefulness of this mouse model for disseminated MAC infection. Since then, numerous studies from various parts of the world have used this model to identify active compounds for the treatment of experimental MAC disease.

OPTIMAL CONDITIONS FOR USE OF THE BEIGE MOUSE MODEL

Parallel to its use in experimental chemotherapy studies, optimal conditions with respect to the host and mycobacteria have been described (39).

Host factors. (i) Sources of the animals. Direct comparisons between animals obtained from Jackson Laboratories with those bred locally either by random breeding or by brother-sister mating showed essentially no differences either in mortality or in CFU counts in the spleens, lungs, or livers at various periods postchallenge.

(ii) Influence of the sex of the animals. Comparative data on CFU counts in the spleens and lungs at various times after challenge of male and female animals of the same age revealed insignificant differences.

(iii) Influence of the ages of the animals. In a study with both male and female mice ages 5, 9, and 13 weeks and 1 year, only the older mice of both sexes were less susceptible to MAC infection than younger mice.

Mycobacterial factors (46): strains of MAC. Initial studies with strain 571-8 (serotype 8) isolated from a patient undergoing treatment at the National Jewish Hospital showed highly reproducible results with respect to mortality and CFU counts (35). Subsequent studies by me and my colleagues with 8330 and D673 strains (45) and by Kuze and associates (74–76) with strain 31F0937 also gave equally encouraging results. Most of the other studies dealt with strain 101 (serotype 1), which was isolated from an AIDS patient and which was provided to me and my colleagues by L. S. Young and C. B. Inderlied. Extensive studies were done with this strain to assess the optimal conditions of MAC with respect to its pathogenicity to beige mice (39).

CONSISTENCY OF BEHAVIOR OF MAC 101 IN BEIGE MICE

The consistency of the pathobiological outcome in beige mice infected i.v. with strain 101 was assessed by mortality and CFU counts in spleens and lungs at various periods. Between 40 and 60% of the animals died within 6 weeks after challenge, and all (100%) of the animals died by 14 weeks after challenge. The CFU counts at 1 day and at 2, 4, 6, and 8 weeks postchallenge with this strain were analyzed by using data from 22 experiments. Slight changes in the inoculum were reflected in differences in the CFU counts in 1 day, the baseline counts. The midpoint values of the log CFU counts in the spleens at 1 day followed normal distribution, with the corresponding values at 2 weeks becoming more equivocal and with the pattern becoming bimodal by the fourth week. The overall mean CFU counts at each time point showed an increase with time.

DOSE-RELATED RESPONSES OF BEIGE MICE TO MAC 101

Injections of MAC 101 ranging from 10^3 to 10^9 viable units per mouse were followed by determination of the CFU counts in the spleens, lungs, liver, and lymph nodes at 1 day (baseline) and 2, 4, 6, 8, and 13 weeks postchallenge (39). Detailed examination of the time course curves for each tissue showed interesting results. Irrespective of the initial baseline counts, by 6 weeks the counts in the spleen rose proportionately with respect to the inoculum size. The rate of increase was maximal with the lowest inoculum size (10^3 viable units), in contrast to that with the higher inoculum size (10^9 viable units). All doses of MAC ranging from 10^4 to 10^9 viable units per ml showed parallel increases in the counts in the liver. A similar trend was seen in the lungs with the same dose of infection. In the case of lymph nodes there was a consistent increase up to 8 weeks and then there was a gradual reduction by 13 weeks.

The increase in CFU counts in each tissue at the various time points (2, 4, 6, 8, and 13 weeks) over the baseline (1 day) counts was examined statistically by analysis of variance with respect to inoculum strength and time of observation. Changes in CFU counts in the spleens over a period of 13 weeks did not show a significant association with inoculum strength ($P = 0.36$) or with the time of observation ($P = 0.06$). Changes in CFU counts in the lungs, were significant in association with

both the infecting dose ($P < 0.02$) and time ($P < 0.001$); however, the changes with respect to the inoculum size may be an artifact, since they varied erratically. Changes in CFU counts in the liver did not show a significant trend for either inoculum size or time of observation ($P = 0.86$ and $P = 0.33$ respectively). Finally, changes in CFU counts in lymph nodes showed significant associations with both inoculum size and time ($P < 0.003$ and $P < 0.0002$, respectively).

Similar dose-response studies of beige mice to MAC challenges by the i.v. and intraperitoneal (i.p.) routes were reported recently (95). Those studies have also indicated the usefulness of the i.p. route of challenge, although the mortality and CFU counts in tissues were lower than those after challenge by the i.v. route.

INCREASE IN THE PATHOGENICITY OF MAC STRAINS BY MULTIPLE PASSAGES IN THE HOST

Similar to the findings in earlier studies (14, 91), there was a consistent and marked increase in virulence following passage of the infecting strain in animals, as evidenced by increases in the CFU counts in the spleens and lungs. The culture which was passaged through beige mice twice showed the highest virulence compared with that of a fresh and single-passaged culture.

On the basis of these extensive studies of the MAC 101 strain described here as well as several other studies, it has been suggested (39) that it can be considered a reference strain of MAC along the same lines that strain H37Rv is the reference strain of *M. tuberculosis* (92).

EXPERIMENTAL CHEMOTHERAPY OF MAC DISEASE WITH THE BEIGE MOUSE MODEL

The initial discovery (35, 39) and further confirmation (10) of MAC disease in the beige mouse model have encouraged many investigators to use this model to establish the chemotherapeutic potentials of many promising compounds for the treatment of MAC disease. This is also indicated in the prioritized recommendations of a workshop by the National Institutes of Health (78). Most people have used this model to assess the in vivo activities of compounds which have shown in vitro activities and, in many cases, in macrophage models as well. Many of the compounds which have shown activity in the beige mouse model have also shown clinical usefulness (46).

In most cases, the studies started with the screening of the compounds by the early treatment protocol, in which treatment is commenced immediately or, at most, 1 day after the infection and following mortality and the determination of CFU counts in the spleen, lungs, and blood. Subsequently, more detailed investigations are done by the established infection (delayed treatment) protocol, in which the treatment is commenced not immediately after challenge but 2 or 3 weeks after the infection has progressed; this model is closer to the spontaneous infections in humans and is more predictive of clinical usefulness. Since chemotherapy of mycobacterial diseases should be with multiple drugs, studies are done with drug combinations either with existing drugs or with investigational new drugs. Finally, the beige mouse model has been used extensively to identify the prophylactic use of promising compounds against MAC disease. In addition to conventional chemotherapeutic studies, the beige mouse model has been used for chemotherapeutic assessments of the targeted delivery of drugs encapsulated in several types of liposomes as well as sustained drug release with some biodegradable polymers.

Of nearly 100 compounds found by me and my colleagues to be active in vitro, and of perhaps equal numbers found to be active by others, only a few have shown considerable activity in the beige mouse model. One of the earliest investigations with this mouse model dealt with rifabutin either alone or in combination with clofazimine and other drugs (41). Subsequently, many investigations have assessed the chemotherapeutic potential of several promising drugs (Table 1). It is interesting that rifampin, a powerful antituberculosis drug, has shown limited activity against MAC (47); in contrast, ethambutol has been shown to have a high degree of activity in several studies (3, 41, 47, 48, 51, 60, 62, 63, 70). Some of these drugs, particularly clofazimine and azithromycin, give very low levels in serum, and these levels are much lower than their in vitro MICs; however, they have been demonstrated to have high degrees of activity in the beige mouse model, presumably because of their high concentrations in tissues. Of particular significance is the activity of amikacin in comparison with that of streptomycin. Both drugs demonstrated high degrees of activity in the beige mouse model, but in view of the extensive experience with streptomycin and its relative low cost and possibly less toxicity, it has been suggested that streptomycin should be given serious consideration as an anti-MAC drug (32, 36). Some drugs like gentamicin and capreomycin are not active in the free form but are active only when they are delivered via liposomes, as discussed later.

TABLE 1. Free and liposome-encapsulated drugs and immunomodulators investigated either individually or in combination for their in vivo chemotherapeutic or prophylactic activities against MAC by using the beige (C57BL/6/bg^J/bg^J) mouse model

Drug group and drug	Reference
Established and investigational drugs	
Amikacin	9, 21, 34, 43, 57, 58, 62
Azithromycin	4, 9, 16, 56, 68, 99
B746	33
Capreomycin	80
Cilestin	57
Ciprofloxacin	57, 58
Clarithromycin	2, 3, 24, 49, 59–62, 70, 71, 79, 99
Clofazimine	33, 36, 41, 43, 62, 87, 90
Dapsone	2
Ethambutol	3, 41, 47, 48, 51, 60, 62, 63, 70
Gangamicin	30
Imipenem	57, 58
Kanamycin	75, 90
KRM 1648	3, 76, 93
Minocycline	79
Paromomycin	64
Rifabutin	41, 43, 62, 66, 82
Rifampin	47, 48, 62, 66, 82
Rifapentine	62, 66, 67
Sparfloxacin	62
Streptomycin	20, 31, 32, 36, 87
Liposome-encapsulated drugs	
Amikacin	8, 18, 21, 34
Capreomycin	80
Gentamicin	17, 69
Streptomycin	20, 31, 32
Immunomodulators with or without other drugs	
Interleukin-2	7
Tumor necrosis factor	7, 9
LC 9018	93

Many of the drugs which have been found to be active in the beige mouse model, i.e., clarithromycin, rifabutin, clofazimine, amikacin, azithromycin, and ethambutol, are now used clinically, and others, e.g., KRM 1648, are on the verge of clinical studies. It is also of interest that many other drugs, e.g., CGP 7040, sparfloxacin, and amithiozone (thiacetazone), which have high degrees of activity in vitro (53, 54, 96), failed to show any in vivo activity in the beige mouse model or clinical usefulness against MAC disease.

EMERGENCE OF DRUG RESISTANCE AND COMBINATION CHEMOTHERAPY

The emergence of drug resistance following monotherapy, a common experience in the treatment of tuberculosis, has also been demonstrated with single-drug therapy of MAC disease in the beige mouse model. Specific studies with clarithromycin monotherapy in MAC-infected beige mice showed the rapid emergence of mutants resistant to this drug (49, 61). Likewise, combination chemotherapy could prevent the development of resistance, as has been the extensive experience with *M. tuberculosis* treatment in animals and humans. In a detailed comparison of several drugs (clarithromycin, amikacin, ethambutol, sparfloxacin, minocycline, and clofazimine) alone or in combination in MAC-infected beige mice, Ji et al. (62) have shown that in combination with clarithromycin, amikacin could prevent the emergence of clarithromycin resistant-mutants, while minocycline could not.

Several other studies were done with this mouse model to assess the value of combination chemotherapy of MAC that is contemplated for use in humans, as has been done in tuberculosis chemotherapy (9, 68, 72, 93). The individual drugs were generally given daily, while in some studies (e.g., with azithromycin) the drugs were given intermittently (68). In most cases, all of the component drugs had shown promise individually in the beige mouse model, while in some cases, one of the components was not proven to be active against MAC or one of the components had been used extensively in the treatment of tuberculosis, even though it was not tested specifically for its activity against MAC. The emergence of mutants resistant to the individual drugs was assessed in many, although not all, studies. Thus, Kolonoski et al. (72) assessed the combination of azithromycin with ethambutol and sparfloxacin against MAC in this model. In a few studies, the combination chemotherapy involved an active drug plus an immunomodulator like tumor necrosis factor (9) or a patented immunopotentiator, LC 9018 (93).

TARGETED AND SUSTAINED DRUG DELIVERY SYSTEMS

Because many of the drugs used to treat MAC infections may be toxic when they are given at their full doses for the entire study periods, attempts were made to deliver them via liposomes so that much lesser amounts could be given at a much lower frequency. With aminoglycosides, which by themselves cannot penetrate easily inside macrophages, liposomal encapsulation offers a unique advantage for targeted delivery (8). Initial studies in this series were done with amikacin (21, 34) by using encapsulation into unilamellar and multilamellar liposomes. Liposomal drug delivery with a much lower dose demonstrated a high degree of therapeutic efficacy compared with the efficacy of daily treatment for the entire study period. Studies with amikacin have been extensively confirmed by others (7, 18), and now liposomal amikacin is undergoing clinical trials. My colleagues and I have done similar studies with liposomal streptomycin (20, 32) with the view that it could be a good substitute for amikacin by reducing toxicity and cost yet providing equal chemotherapeutic activity. A recent study from France (80) has shown that liposomal capreomycin at 120 mg/kg of body weight, in contrast to the free drug, was effective in treating MAC in beige mice; this preparation also showed much less toxicity than the free drug. Liposomal gentamicin was also shown to be highly active against MAC disease in beige mouse (17, 69) and has been introduced into clinical studies. In all of those earlier studies with unilamellar or multilamellar liposomes, high degrees of chemotherapeutic activity could be seen in the liver, spleen, and kidneys, but not in the lungs or lymph nodes. Recently, high degrees of activity in these tissues were also achieved by using preparations with long circulation time (stealth) liposomes (31).

SUSTAINED DRUG RELEASE

My colleagues and I made an interesting observation in that when clofazimine is delivered via a biodegradable polylactic glycolic acid polymer into beige mice infected with MAC it shows a high degree of activity, and the pigmentation which is seen when this drug is given orally on a daily basis was virtually eliminated (63). This brings up an important question about the relative toxicities of drugs to the immune-deficient beige mouse compared with their toxicities to healthy animals. In general, different doses of most of the drugs, e.g., rifampin (82), are well tolerated by beige mice for the entire period of chemotherapeutic assessment, although some recent studies with ethambutol (51) have shown that severe MAC infection of beige mice impairs their clearance of this drug, resulting in drug toxicity. Similarly, beige mice could tolerate the recreational drug isobutyl nitrate, which has been used by homosexual male AIDS patients, for much shorter periods of exposure ($<$35 s), whereas the C57BL/6 parent mice could tolerate the drug for longer periods ($>$150 s) (27). Similar evidence has been suggested with respect to alcohol toxicity (5).

PROPHYLACTIC STUDIES

Several investigations were done to suggest the prophylactic roles of promising compounds which have been demonstrated to have some in vivo activity against MAC. Earlier, it was shown that rifabutin was useful as a prophylactic agent against experimental MAC disease in beige mice (41). It is of interest that rifabutin has now been approved for use as prophylaxis against MAC disease in humans. More recent studies were done with azithromycin, dapsone, and clarithromycin for similar purposes (2, 4).

SUSCEPTIBILITIES OF BEIGE MICE BY DIFFERENT ROUTES OF CHALLENGE

Most of the studies dealing with experimental chemotherapy dealt with i.v. challenge. In the earlier stages of the development of the model, comparative studies were done with aerogenic challenge (28, 29). More recently, such aerogenic challenge of beige mice was attempted by Kuze et al. (75) for the chemotherapeutic assessment of KRM 1648 and other drugs. As discussed earlier, Vigen et al. (95) performed an extensive dose-response study of MAC challenge by the i.v. and i.p. routes and found that the i.p. route is equally valuable for routine chemotherapeutic testing. My colleagues and I (42) obtained interesting results when we infected beige mice with MAC by the i.p., intranasal, oral, and intrarectal routes, in addition to the i.v. route, and recovered the organisms in

spleen, liver, lungs, and blood at various stages. Both single and multiple infections were induced by the oral and rectal routes. In those studies, delayed-type hypersensitivity responsiveness to purified protein derivative prepared from MAC and histopathological studies were done with intestinal tissues to confirm the pathobiological involvement in this disease. Those studies were prompted by the fact that beige mice, which have several similarities to AIDS patients (26, 37), should also be highly susceptible to infection with MAC by the gastrointestinal route, the supposed mode of transmission of disease in AIDS patients. A significant finding of that study was the extent to which the beige mice could be infected by the oral or intrarectal route. High CFU counts were seen in the spleens, livers, and lungs after repeated challenges, particularly when infection was induced by the intrarectal route. Infection by the i.v. route gave results similar to those from earlier studies. Likewise, i.p. challenge gave results similar to those of i.v. challenge (an experience similar to those in studies of chronic infection in the non-beige mouse model discussed earlier by me and my colleagues [44, 45] and others [95]).

Histopathological assessment corroborated the findings. Disarray and necrosis of epithelial cells were seen in the rectally infected animals, and the symptoms worsened with multiple infections and time. Lymphohistiocyte aggregates in the adipose tissue outside the bowel wall were seen at 8 weeks in animals infected rectally. Abundant acid-fast bacilli were seen within histocytes in all cases. Animals infected orally, especially after the administration of multiple doses, showed moderate to marked chronic inflammation, similar to that in mice receiving rectal infections. The infiltrates were denser in the lamina propria, including more histiocytes, and extended into the musculus mucosa and adjacent connective tissue. Our observations with the oral infection route have recently been confirmed by Bermudez and associates (6), who have observed large numbers of organisms in the gut and appendix, closely resembling gastrointestinal tract infections commonly seen in AIDS patients.

The rectal and oral routes of challenges thus give opportunities to simulate MAC disease in AIDS patients among whom transmission takes place predominately by the gastrointestinal route, in contrast to the aerogenic route, which is the common mode of transmission of tuberculosis (89).

USEFULNESS OF THE BEIGE MOUSE MODEL TO STUDY HOST-PARASITE INTERACTIONS OF MAC DISEASE

Detailed studies with beige mice in comparison with studies with parent C57BL/6 mice have facilitated the delineation of several important parasite and host factors in the pathobiology of this disease, especially in AIDS patients. An important characteristic of MAC brought out by the beige mouse model, in addition to colony morphology and serotype, is the presence of plasmids (15), which probably carry the virulence factors for this disease (38). Extensive studies with MAC strains from patients with AIDS and without AIDS, as well as those from the environment, have confirmed the association of plasmids with virulence (38, 40, 81, 85, 86). Among the several host factors studied, besides age and sex, which were discussed earlier, other factors involved macrophage, T-lymphocyte, and natural killer cell functions. Macrophage functions, e.g., the release of oxygen metabolites like superoxide anion (O_2^-) and hydrogen peroxide or the lysosomal enzymes, showed little difference between beige and C57BL/6 mice. On the other hand, T-lymphocyte numbers revealed fewer L3T4-reactive T-helper cells and T-helper cell:TS ratio of <1.0; in comparison, control C57BL/6 mice had higher numbers of T-helper cells and a T-helper cell:TS ratio of ≥ 2.0. Another important finding is the absence of or a diminished delayed-type hypersensitivity response in beige mice (26, 37). By far the most important data came from the natural killer cell functions (50); this may be the predisposing factor for the increased susceptibility of beige mice to MAC.

All of these host factors, fewer T lymphocytes, lower T-helper cell:TS ratio, reduced natural killer cell function, diminished delayed-type hypersensitivity response, and decreased blood clotting time, result in increased susceptibility to several pathogens, including MAC, causing bacteremia and disseminated disease, have prompted me and my colleagues to suggest that this mouse model may be a useful animal model for AIDS as well (26, 37).

COMPARISON OF BEIGE MICE WITH OTHER MOUSE STRAINS

Most of the earlier investigations (35, 39) dealt with the comparison of beige mice with parent C57BL/6 mice, the most susceptible to *M. tuberculosis* challenge (84, 97). The response of beige mice in comparison with those of nude and satin mice were also discussed earlier (28, 29, 59). More recently, using aerogenic challenge with virulent MAC, Kuze et al. (75) have seen a greater susceptibility of beige mice than DDY mice; Kuze et al. used DDY mice extensively in several of their earlier studies.

CONCLUSIONS

In summary, the beige mouse model for MAC infection has been confirmed adequately and has been and is still being used extensively for the assessment of the experimental therapeutic potency of promising drugs, immunomodulators, and their combinations. The ease with which these mice can be bred and maintained under normal vivarium conditions, in contrast to the rigid requirements of nude mice, offers great advantages. While this mouse model is the most useful one available so far, it should not be considered the final answer. Further developments in genetic manipulations may facilitate the discovery of a better murine model for this disease. Already, some investigations like those with specific combined immune deficient mutants (55) and the nude-beige crossed strains (83) of these mice are in progress.

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