A Tandem Repeat in Decay Accelerating Factor 1 Is Associated with Severity of Murine Mercury-Induced Autoimmunity

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Decay accelerating factor (DAF), a complement-regulatory protein, protects cells from bystander complement-mediated lysis and negatively regulates T cells. Reduced expression of DAF occurs in several systemic autoimmune diseases including systemic lupus erythematosus, and DAF deficiency exacerbates disease in several autoimmune models, including murine mercury-induced autoimmunity (mHgIA). Daf1, located within Hmr1, a chromosome 1 locus associated in DBA/2 mice with resistance to mHgIA, could be a candidate. Here we show that reduced Daf1 transcription in lupus-prone mice was not associated with a reduction in the Daf1 transcription factor SP1. Studies of NZB mice congenic for the mHgIA-resistant DBA/2 Hmr1 locus suggested that Daf1 expression was controlled by the host genome and not the Hmr1 locus. A unique pentanucleotide repeat variant in the second intron of Daf1 in DBA/2 mice was identified and shown in F2 intercrosses to be associated with less severe disease; however, analysis of Hmr1 congenics indicated that this most likely reflected the presence of autoimmunity-predisposing genetic variants within the Hmr1 locus or that Daf1 expression is mediated by the tandem repeat in epistasis with other genetic variants present in autoimmune-prone mice. These studies argue that the effect of DAF on autoimmunity is complex and may require multiple genetic elements.

1. Introduction

Decay accelerating factor (DAF) is a member of the complement-regulatory protein family that protects cells from attack by autologous complement proteins [1]. DAF inhibits the neoformation and accelerates the dissociation of preformed C3/C5 convertase complexes generated by the classical and alternative pathways, thus blocking both complement split product activity and the formation of the membrane attack complex [2]. DAF is present on inflammatory cells and at sites of tissue inflammation where it most likely inhibits bystander complement-mediated cell lysis [13]. In addition, recent studies suggest DAF regulates T cell activity [3–6]. In humans, DAF is a single gene on chromosome 1q32 encoding a glycosylphosphatidylinositol- (GPI-) anchored cell surface glycoprotein [7]. In contrast, mice have two tandem Daf genes positioned head-to-tail on chromosome 1 [8] with the GPI-linked Daf1 (Daf-GPI) located 5’ to the transmembrane containing Daf2 (Daf-TM). Expression of DAF varies depending on tissue [9] and cell type [10] with DAF widely expressed on the surface of all major circulating blood cells and epithelial and endothelial cells [11, 12]. Studies with Daf1 knockouts showed that absence of the GPI form results in the loss of DAF expression in most tissues, except testis and spleen where Daf2 is expressed (27, 28).
spleen, DAF2 is expressed primarily in CD11c+ dendritic cells. In human cells, DAF expression is modulated by cytokines such as IL-1, IL-6, TNF-α, TGF-β1, and IFN-γ [13–15], prostaglandin PGE2 [16], and tissue specific factors [17]. Although there is evidence that DAF mRNA stability can be affected by tissue specific factors [17] and inflammation [18], most studies suggest that expression is primarily modulated at transcription [15–17, 19, 20]. The human DAF promoter has been identified, the transcription start site mapped, and regions of potential transcriptional regulation proposed [10, 21]. Analysis of the key transcriptional regulatory elements controlling basal expression of mouse Daf1 showed that transcriptional activity requires the functional cooperation of two Sp1-binding sites and is enhanced by the presence of a CREB site [22]. Evidence supports a protective role for DAF in autoimmune disease [6, 23]. Daf1 deficient mice exhibit increased CD4+ T cell proliferation and greater secretion of IFN-γ by T cells [24], and its deletion in lupus prone MRL-Fas(+)/+ mice accelerates disease [25]. During induction of murine mercury-induced autoimmune disease (mHgIA) DAF1 is specifically reduced on dendritic cells [24]. DAF1 expression is controlled by trans elements not within Daf1 promoter. A Sp1-binding site [22] and CREB site [22] have been identified, the transcription start site mapped, and regional differences in DAF expression may impact the deposition of immune complex deposits and contribute significantly to the Hmr1 phenotype. In this study, we show that Daf1 expression is reduced in multiple murine strains susceptible to spontaneous autoimmune disease and identified a pentanucleotide tandem repeat in the second intron of Daf1, which in the mHgIA resistant DBA/2 consisted of eleven repeats while most other strains had 10, except for MRL-Fas(+)/+ and SJL/J, which lacked the repeat. Comparison of the presence or absence of the tandem repeat, in a (DBA/2xSJL/J)F2 intercross, with several disease parameters showed that presence of the DBA/2 repeat was associated with less severe disease. Analysis of NZB mice congenic for the Hmr1 locus of DBA/2, however, showed that Daf1 expression is controlled by trans elements not within Hmr1 and the reduction in Daf1 expression was not associated with changes in levels of its major transcription factor Sp1. These studies document lower levels of Daf1 in lupus-prone mice and show that this is not directly caused by cis elements within the Daf1 gene or by differences in constitutive Sp1 expression.

2. Materials and Methods

2.1. Mice. DBA/2, NZB, MRL/Fas(lpr)/+, BXSB, and C57BL/6 mice were obtained from the Scripps Research Institute Breeding Colony (La Jolla, CA). NZW/LacI, A.SW/SnJ, BALB/cJ, SJL/J, and 129S6 mice were obtained from the Jackson Laboratory (Bar Harbor, ME). (SJL/JxDBA/2)F2 intercross mice have been previously described [31]. NZB, DBA/2-Hmr1(Daf1(sumI)) and DBA/2.NZB-Hmr1(Daf1(sumI)) congenic mice that contained the relevant Daf1 locus were generated by marker-assisted breeding using D1Mit21 (67 Mb) and D1Mit17 (190 Mb) to define the outer limits of the chromosome 1 interval. Breeding and maintenance were performed under specific pathogen-free conditions at the Scripps Research Institute Animal Facility (La Jolla, CA). All procedures were approved by the Scripps Research Institute’s Institutional Animal Care and Use Committee.

2.2. RNA Isolation and Real-Time PCR. Total RNA extraction from splenocytes was performed using TRIzol reagent (Invitrogen, Carlsbad, CA). RNA was denatured at 65°C for 5 minutes, placed on ice, and reverse transcribed in a total volume of 20 ml using random hexamers, dNTPs, RNase inhibitor (RNase-OUT; Invitrogen), and 200 units of SuperScript III reverse transcriptase (Invitrogen). Real time PCR primers, probes, and methods were as previously described [24]. Daf1 expression was relative to cyclophilin A or 18sRNA [24]. Levels of Sp1, Sp3, CREB, and Crem mRNA were determined in spleen cells of naïve female autoimmune prone NZB and healthy DBA/2 mice by real time PCR using iQ SYBR green Supermix (Bio-rad, Hercules, CA). The following primers were used for amplification: Sp1 forward, 5′-CACACACCCAGTGTATCGAGGCAC-3′, and CREB reverse, 5′-CGTGGAGGAGCTCCAGGG-3′; Sp3 forward, 5′-GGCCAGCTCATGGTGACTTAC-3′, and CREB reverse, 5′-GGTGGTTGGGAGTGTTTAACTC-3′; CREB forward, 5′-GGGCGGATCGTACATTCC-3′, and CREB reverse, 5′-GTGTTTCACGCTGCTCA-3′. All PCR reactions were performed using an iCycler iQ (Bio-Rad). The reactions were run in duplicate and relative expression mRNA levels were determined by the ΔΔCT method and normalized against cyclophilin A. Data are expressed as fold change compared to mRNA levels measured in DBA/2 samples.

2.3. Genomic DNA. Genomic DNA was isolated from 5 mm sections of mouse tail incubated in 500 μl lysis buffer (0.1 M Tris, pH 8.0; 5 mM EDTA; 0.2 M NaCl and 0.4% w/v SDS) containing 200 μg/ml proteinase K (Sigma, St Louis, MO).
overnight at 55°C. Samples were spun down and supernatants containing genomic DNA were purified using the ZR Genomic DNA™-Tissue MiniPrep kit (Zymo Research, Irvine, CA) according to the manufacturer's protocol.

2.4. Tandem Repeat PCR. The tandem repeat sequence, which can be represented by either (CTTTT)n or (TTTTC)n, was identified within the second intron of Daf1 using the following primers: 5'-GCTTAAGGCAATTACTGTCTGC-3' (forward) and 5'-GCCATCTAATGTAAAGTAACTCC-3' (reverse). PCR amplifications were performed with the KOD Hot Start Polymerase (EMD Millipore, Billerica, MA) using the following conditions: an initial 2 min denaturation step at 94°C and then 35 cycles of denaturation (94°C), annealing (57°C), and extension (68°C) followed by a final 10 min 68°C incubation step. The PCR products were separated by agarose gel electrophoresis, extracted using the QIAquick Gel Extraction Kit (Qiagen, Valencia, CA), and submitted for sequencing.

2.5. DNA Sequencing. Purified PCR products were submitted to the Scripps Research Institute DNA Core Facility and analyzed with an ABI PRISM 3100 sequencer using appropriate primers. Sequencing data were analyzed with the BioEdit Sequence Alignment Editor software.

2.6. Induction and Assessment of mHgIA in (SJL/JxDBA/2)F2 Intercross Mice. Induction and features of mHgIA including immune deposits in kidney and spleen and serum autoantibodies and MHC class II genotypes in (SJL/JxDBA/2)F2 intercross mice were described previously [31]. Use of mercuric chloride was approved by the Scripps Research Institute Department of Environmental Health and Safety.

2.7. Statistics. Unless otherwise noted, all data is expressed as mean and standard error. Statistical analysis was done using GraphPad Software, San Diego, CA. Mann-Whitney U test was used for comparisons between individual mouse strains. Analysis of variance (ANOVA) with Bonferroni’s Multiple Comparison test was used for comparisons between features of mHgIA in (SJL/JxDBA/2)F2 intercross mice. P < 0.05 was considered significant.

3. Results

3.1. Daf1 mRNA Expression is Reduced in Autoimmune Prone Mice. In a previous study, we found that autoimmune prone NZB mice have reduced endogenous Daf1 expression [24]. To determine if this is common to other lupus-prone strains we analyzed Daf1 mRNA expression in spleen cells from naive female autoimmune prone MRL-Fas<sup>pr</sup> (MRL/lpr), NZB, NZW, and BXSB mice and healthy DBA/2 and BALB/c mice (Figure 1). All the autoimmune prone strains had lower Daf1 mRNA levels than the DBA/2 confirming that reduced DAF1 expression is coupled to a predisposition for autoimmunity. Daf1 expression in BALB/c mice was no different from DBA/2 but was higher than the other strains tested (P < 0.01). Interestingly, SJL/J mice also had reduced Daf1 mRNA expression. This may reflect the propensity of SJL/J mice to develop autoimmunity with age [32] but may also be a manifestation of dysferlin deficiency in these mice [33]. Thus, Daf1 is reduced in strains with a predisposition to autoimmunity.

3.2. Intron 2 of Daf1 Contains a Pentanucleotide Tandem Repeat. Differences in expression of DAF1 might reflect genetic polymorphisms among the different strains. Sequencing of Daf1 transcripts and 2.5 kb of genomic DNA 5' of the Daf1 ATG start site in NZB and DBA/2 mice revealed no differences compared to the C57BL/6 genome. However, further examination identified a tandem repeat in the second intron of Daf1 (Figure 2). Sequencing of this region in a number of mouse strains revealed three different genotypes. DBA/2 mice had the longest repeat sequence with CTTTT (or TTTTC) being repeated 11 times. NZB, NZW, BXSB, B10.S, C57BL/6, A.SW/Sn, BALB/c, and I2956 mice had 10 repeats while MRL-Fas<sup>pr</sup> and SJL/J lacked the tandem repeat. Tandem repeat length did not show a strict correlation with Daf1 mRNA expression, although the longest repeat was found in the strain with the highest expression (DBA/2) while the two strains lacking the tandem repeat, MRL-Fas<sup>pr</sup> and SJL/J, did have significantly lower expression than the DBA/2 (Figure 1). The inability of mercury exposure to decrease DAF1 expression in mHgIA resistant DBA/2 mice [24] suggested the possibility that the DBA/2 tandem repeat may influence the expression of Daf1 and, in turn, the severity of autoimmunity.

3.3. Presence of the DBA/2 Daf1 Tandem Repeat Is Associated with Reduced Immune Deposits. To determine if the DBA/2 tandem repeat variant is associated with facets of mHgIA we examined archived DNA samples from 133 mice from a (SJL/JxDBA/2)F2 intercross which had been used to identify
CTTTT (or TTTTC) repeat length
11-DBA/2
10-NZB, NZW, BXSB, B10.S, C57BL/6, A.SW/Sn, BALB/c, and 129S6
0-MRL-Fas* and SJL/J

Figure 2: Daf1 gene organization showing location of the CTTTT tandem repeat. Diagrammatic representation of exons (E) in Daf1 (top) and the expanded region of sequence in intron 2 (bottom) showing the CTTTT tandem repeat (shaded box) and PCR primers sequences (underlined). DNA sequence is from the C57BL/6 genomic sequence which has ten CTTTT repeats. Note that the repeat can also be represented by TTTTC by simple removal of the C residue at the 5' end and inclusion of the C at the 3' end. DBA/2 mice had the longest repeat sequence with CTTTT (or TTTTC) being repeated 11 times. NZB, NZW, BXSB, B10.S, C57BL/6, A.SW/Sn, BALB/c, and 129S6 mice had 10 repeats while MRL-Fas* and SJL/J lacked the repeat.

Figure 3: PCR determination of presence or absence of CTTTT tandem repeat. Archived DNA from mercury treated (SJL/JxDBA/2)F2 intercross mice was subjected to PCR using appropriate primers (see Figure 2) and products separated by agarose gel electrophoresis. Lane 1, base pair marker; lane 2, homozygous D tandem repeat; lanes 3 and 4, homozygous S tandem repeat; lane 5, heterozygous D/S tandem repeat; lanes 6–25, (SJL/JxDBA/2)F2.

The Hmr1 locus [31]. PCR analysis determined that there were 32 mice with the DBA/2 (D/D) tandem repeat: 28 had the SJL/J (S/S) genotype as they lacked the tandem repeat and 73 were heterozygous (D/S) animals (Figure 3). Tandem repeat status was then compared to previously obtained data [31] of immune deposits in kidney and spleen and serum autoantibodies to determine the relationship between presence or absence of the tandem repeat and severity of mHgIA.

Comparison of autoantibody responses revealed that D/D, S/S, and D/S tandem repeat groups showed no differences in antinucleolar autoantibody (ANoA) response but the antichromatin autoantibody (ACA) response was greater in S/S than D/D animals (P < 0.05) (Figure 4). Comparison of immune deposits found that D/D animals had reduced glomerular IgG deposits (P < 0.05) compared to S/S animals but no differences were found for C3 deposits (Figure 4) or glomerular IgM. Immune deposits in the spleen were also affected by the presence of the D/D tandem repeat with D/D animals having reduced IgG and C3 deposits in splenic vessels compared to S/S animals (P < 0.05) (Figure 4). Splenic vessel deposits of C3 were also reduced in D/S animals compared to S/S animals (P < 0.05). Of the 133 animals, 13 had IgG deposits in both kidney glomeruli and splenic vessels and of these 6 (46%) were S/S, 5 (38%) D/S, and 2 (15%) D/D. When expressed as a percentage of each genotype this revealed that 21% of the S/S mice had deposits in both organs, while only 7% of D/S and 6% of D/D had such deposits. None of 8 DBA/2 mice had deposits in either organ while 5/8 SJL/J had deposits with 4 of these having deposits in kidney and
spleen. These observations suggest that heterozygous and particularly homozygous presence of the D tandem repeat of Daf1 is associated with less severe disease.

3.4. MHC Class II Genotype Is Not Associated with Reduced Immune Deposits. Autoimmunity, including mHglA [31], is associated with class II genes of the MHC [34]. Therefore, differences in severity of mHglA in the (SJL/JxDBA/2)F2 intercross could simply reflect distribution of DBA/2 and SJL/J MHC class II genes. To examine this possibility comparison was made between the MHC class II genotypes and the presence of immune deposits in kidney and spleen and serum.

Figure 4: Presence of the DBA/2 tandem repeat is associated with reduced immune deposits. Tandem repeat genotypes (D/D, S/S D/S) were compared with features of mHglA including glomerular deposits of IgG and C3, splenic vessel deposits of IgG and C3, antichromatin autoantibodies (ACA), and antinucleolar autoantibodies (ANoA) in 133 (SJL/JxDBA/2)F2 intercross mice.
autoantibodies. MHC class II was not associated with deposits of IgG (Figure 5) or C3. Antichromatin autoantibodies were also not associated with MHC class II but, as described previously [31, 35], ANoA was highly associated with mice that were homozygous for H-2^s (P < 0.0001) (Figure 5). Therefore, immune deposits do not reflect the distribution of DBA/2 or SJL/J MHC.

3.5. Expression of Daf1 Is Not Regulated within the Hmr1 Locus. Strain specific differences in the expression of Daf1 [24] and the relationship of Hmr1 to disease severity [31] suggested that transfer of the DBA/2 Hmr1 locus into autoimmune susceptible mice may help determine if Daf1 expression was controlled within the Hmr1 locus. NZB mice made congenic for the DBA/2 Hmr1 locus (NZB, DBA/2-Hmr1(Daf1^{DBA/2})) or ND still had reduced Daf1 expression, while DBA/2 mice congenic for the NZB locus (DBA/2.NZB-Hmr1(Daf1^{NZB})) or DN retained the elevated expression of Daf1 (Figure 6). Thus, Daf1 expression is affected by genetic elements outside of the Hmr1 locus.

3.6. Daf1 Transcription Factor Expression Is Not Reduced in Autoimmune Prone Mice. We previously determined that constitutive expression of Daf1 is under the control of the transcription factor Sp1 [22] which suggested that the reduced expression of Daf1 in autoimmune prone mice may due to reduced expression of Sp1. Real time PCR analysis of Sp1 in splenocytes revealed increased expression in NZB compared to DBA/2 mice although Sp3, another member of the Sp1 family, showed no difference in expression (Figure 7). The Daf1 promoter also contains a CREB binding site [22], however expression of this transcription factor was not different between the two mouse strains although the closely related CREM was increased in NZB mice (Figure 7). Thus reduced Daf1 in NZB mice could not be attributed to the lack of putative transcription factors, including Sp1.

4. Discussion

In this study, we extended our observation that lupus-prone NZB mice have reduced DAF1 [24] to other major lupus strains including MRL-Fas^{lpr}, NZW, and BXSB mice. Thus,
the SJL/J, which lacks the tandem repeat, has significantly reduced Dafl [33], is highly susceptible to mHgIA, and develops significant immune deposits [37]. Our finding that mice congenic for the Hmrl do not display any difference in Dafl expression compared to their original strain suggests that the association of the absence of Dafl tandem repeat with immune deposits might simply reflect the presence of lupus-predisposing genetic variants within the Hmrl locus [31]. However, it is also possible that the Dafl expression mediated by the tandem repeat is in epistasis with other genetic variants present in lupus mice.

Our previous studies showed that constitutive expression of Dafl is regulated by the transcription factor Sp1 [22], but we were unable to demonstrate a correlation of constitutive Sp1 expression with DAF1 levels. Thus, the reduced expression of DAF1 in autoimmune-prone mice likely involves multiple factors. One intriguing possibility is that the TTTTC pentanucleotide sequence may contribute to Dafl expression as it has been identified as an IFN-γ and IRF1 response element of the mouse RANTES promoter [38], both IFN-γ and IRF1 are required for mHgIA [39], and deficiency of Dafl is associated with increased IFN-γ [4]. It can be speculated that the lack the pentanucleotide repeat in lupus-prone MRL-Fas[pr] and the mHgIA-sensitive SJL/If might reduce IRF1s influence on Dafl transcription. This is supported by the observation that mice deficient in IFN-γ or IRF1 have reduced DAF1 on activated CD4+ T cells following mercury exposure even though they do not develop mHgIA [39]. Other mice that are sensitive to mHgIA, such as the B10.S, do have the tandem repeat, and naive mice have approximately equivalent DAF1 on CD4+ T cells as DBA/2 mice [24]. However, induction of mHgIA in the B10.S results in a reduction of DAF1 to levels found in naive NZB while DBA/2 are unaffected [24]. This suggests the possibility that the presence of an additional cis-acting element in the DBA/2 is even more efficient at maintaining Dafl expression.

Although the role of the tandem repeat sequence, (CTTTT)n or (TTTTC)n, in Dafl expression and mHgIA remains to be resolved, similar sequences in other genes have been shown to influence biological responses. CTTTT or TTTTC repeats have been found in human HLA [40], the CD4 locus [41], and the murine RANTES promoter [38]. The repeat at the CD4 locus has been associated with type 1 diabetes [42] and vitiligo [43]. A similar sequence, (CCTTT)n, has been found in the promoter of human inducible nitric oxide synthase (NOS2A) where 14 repeats are associated with absence of diabetic retinopathy [44]. IL-1β induction of NOS2A with 9, 12, or 15 repeats was inhibited by the presence of 25 mM glucose while the 14 repeats maintained transcription. Whether the size of the tandem repeat influences Dafl promoter activity in idiopathic and/or mercury-induced autoimmunity remains to be determined.

5. Conclusions

These studies show that expression of decay accelerating factor 1 is reduced in mice susceptible to systemic autoimmunity. Control of Dafl expression appears to be multifactorial and is not primarily mediated by a pentanucleotide tandem repeat.
Figure 7: 
Dafl transcription factor expression is not reduced in autoimmune prone mice. Real time PCR was used to determine Sp1, Sp3, CREB, and CREM mRNA in spleen cells of naïve female autoimmune prone NZB and healthy DBA/2 mice. mRNA levels were determined by the ΔΔCT method and normalized against cyclophilin A. Data are expressed as fold change compared to mRNA levels measured in DBA/2 samples. N = 5 DBA/2 and 6 NZB.

in intron 2 nor constitutive differences in SPI expression. The absence of the tandem repeat was associated with increased severity of immune deposits in mercury-induced autoimmunity, which may be due to linkage of the repeat with other predisposing variants or epistasis with other genes that promote Dafl expression.

Conflict of Interests
The authors report no conflict of interests.

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