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REVIEW ARTICLE

A Proposal Concept of a Polygene Network in Systemic Vasculitis: Lessons from MRL Mouse Models

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ABSTRACT
In addition to the studies of cellular and molecular events in the pathogenesis of systemic vasculitis, a genome analysis of mouse models may shed some light on the complex clinicopathological manifestations of systemic vasculitis. In the study of susceptibility loci to vasculitis in MRL mouse models, we learned that systemic vasculitis developed in a cumulative effect of multiple gene loci, each of which by itself did not have a significant effect to induce the related phenotype, thus indicating a polygenic system. The mice developed vasculitis in an additive manner of multiple genes with a hierarchical effect. Some of the susceptibility loci seemed to be common to those in other collagen diseases as well. Moreover, the loci controlling tissue specificity of vasculitis were present. One of the positional candidate genes for vasculitis showed an allelic polymorphism in the coding region, thus possibly causing a qualitative difference in its function. As a result, a particular combination of polygenes with such an allelic polymorphism may thus play a critical role in leading the cascade reaction to develop vasculitis, and also a regular variation of systemic vasculitis. This is designated as the polygene network in systemic vasculitis.

KEY WORDS
autoantibody, *Cd72*, collagen disease, *Fas*, genetic polymorphism

INTRODUCTION

Systemic vasculitis is involved in collagen disease, which was first proposed by P. Klemperer in 1945, by showing the characteristic feature of fibrinoid degeneration of connective tissues involving blood vessels.[1] At present, this disease category has been revised as a syndrome overlapping connective tissue diseases, rheumatic diseases and autoimmune or immunological disorders. Systemic vasculitis in collagen disease has been divided into primary and secondary forms based on the clinical and pathological findings.[2-4] The former consists of specific clinical entities in which the pathology involves primarily the blood vessels. This group has been called vasculitis syndromes as represented by polyarteritis nodosa, microscopic polyangiitis, giant cell arteritis, Takayasu arteritis, Wegener's granulomatosis, allergic granulomatous angiitis, Kawasaki disease, etc. On the other hand, the latter has been categorized as vasculitis which developed as a complication of other collagen diseases, such as systemic erythematosus, rheumatoid arthritis and Sjogren's syndrome, systemic sclerosis, inflammatory myopathies, etc. This complication has been understood to be a manifestation of advanced disease, possibly caused by the expansion of autoantibodies, immune complexes and /or abnormal T cell subsets. However, this categorization is complicated when considering the many cases of primary systemic vasculitis overlapping with other collagen diseases or with atypical collagen disease not satisfied with the criteria of each disease.[3] Moreover, several similar pathological manifestations of systemic vasculitis between the primary and secondary forms have been reported as represented by fibrinoid degeneration and cellular inflammatory lesions of arterial media.[5] These manifestations may suggest the existence of common biological rules for systemic vasculitis in collagen disease beyond the primary and secondary forms.

The MRL/MpJ-*lpr/lpr* (MRL/lpr) strain of mice originally established by E. Murphy in 1978,[6] as well

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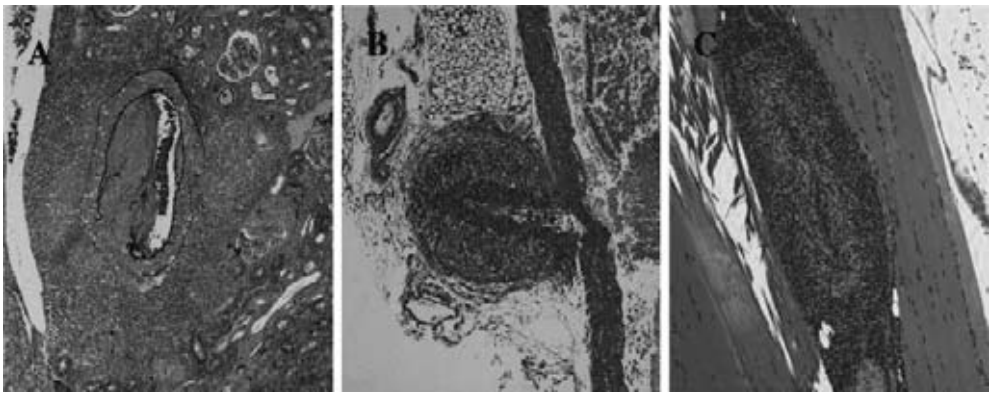


Fig. 1 Representative histopathological manifestations of systemic vasculitis in MRL/lpr mice (**A;** arcuate artery in the kidney, **B;** main branch of the aorta, **C;** artery in the lower extremity), commonly showing granulomatous arteritis characteristic of the accumulation of lymphocytes and macrophages in the perivascular regions, followed by the destruction of the adventitia and tunica media, and then the intimal thickening.

as (NZB x NZW) F1 and BXSB mice, have been used to study systemic lupus erythematosus.[7,8] This strain is designated as a murine lupus model, since MRL/lpr mice develop lethal glomerulonephritis associated with severe immune complex deposition in glomeruli and increased autoantibodies involving anti-ds-DNA and Sm antibodies. However, this strain also develops systemic vasculitis, polyarthritis and sialoadenitis, thus resembling polyarteritis nodosa, rheumatoid arthritis and Sjögren's syndrome, respectively, and shows the high titers of IgG rheumatoid factor and anti-MPO antibodies.[8,9] These findings suggest that this stain should be used as a collagen disease model. Therefore, the systemic vasculitis observed in these mice might be a secondary form associated with other types of collagen disease.

In this paper, we will review the study of vasculitis from a genetic aspect. With our study of MRL mice, we will conclude that systemic vasculitis in these mice can develop independently from other types of collagen disease, and finally that this mechanism of action is under the control of a polygene network.

SYSTEMIC VASCULITIS IN MRL MICE

MRL/lpr mice develop systemic vasculitis associated with the single mutation gene, *lpr (lymphoproliferation)*,[1] which encodes the deletion mutant of Fas, resulting in the immunological disturbance of Fas-mediated apoptosis.[10] At 16 weeks old, more than 80% of the mice spontaneously develop vasculitis in the kidneys, mainly in the arcuate and interlobular arteries (as shown in Fig. 1). Vasculitis in main branches of the aorta, and arteries in the extremities, pancreas and salivary glands also develops to a lesser extent. Similar lesions can be observed in the MRL strain of mice congenic with another single mutation gene, *gld* (*generalized lymphoproliferative disease)*, MRL/MpTn-*gld/gld* (MRL/gld).[11,12] The *gld* mutation was originally derived from C3H/HeJ mice, but in this stain vasculitis was not observed.[13] The relationship of the *lpr* and *gld* genes was suggested to be that of receptor and ligand in a study of bone marrow chimera.[14] Finally the *gld* gene was clarified to be the point mutation of Fas ligand (FasL) that induces a loss of function of the Fas/FasL interaction.[15]

The common histopathological feature of vasculitis in MRL/lpr mice is granulomatous arteritis.[16] In our previous study,[17] the lesion seemed to be initiated by the accumulation of $CD4^+$T cells in the perivascular regions, followed by macrophages positive for Mac-2 (galectin-3) forming a granulomatous lesion involving the adventitia and tunica media. Then, the lesion extended to form fibrinoid necrotic lesions of the media associated with the influx of plasma components from the vascular lumen. In MRL/gld mice, though not in MRL/lpr mice, a large proportion of cells in the vasculitic lesions expressed Fas, mainly including lymphoid cells and macrophages.[17] A single administration of anti-Fas monoclonal antibodies (RA-8 clone) into MRL/gld mice ameliorated vasculitis.[18] These findings indicate that an inefficient interaction between Fas and FasL and a consequent deficit in Fas-mediated apoptosis are critical for the development of vasculitis in the MRL strain of mice.

The reconstruction of the vascular lesions in [MRL/gld- > MRL/+] mice was successful carried out in bone marrow irradiation chimeras.[19] Several trials of cell transfer in [MRL/lpr- > MRL/+] mice had failed to develop both lymphoproliferation and vasculitis because of the development of runt-like disease.[14] This result may be explained by the effect of FasL produced in donor cells of MRL/lpr mice, which induces apoptosis of Fas expressing cells in MRL/+ recipients via Fas/FasL interaction. In the [MRL/gld- > MRL/+] mice, vascular lesions and also glomerular lesions were characteristic of endocapillary prolifera-

tive glomerulonephritis associated with immune complex deposits which were almost the same as those in MRL/lpr mice. Interestingly, vasculitis did not develop when the same H-2^k strain of mice, C3H/HeJ were used as the recipients although they did develop glomerulonephritis as same as that in [MRL/gld- > MRL/+] mice. Between both bone marrow chimeras, there was no difference in the higher serum levels of IgG and immune complexes. This dissociation might indicate a different cellular mechanism for vasculitis from that for glomerulonephritis.

According to these histopathological findings, macrophages seem to be critical effector cells for the destruction of external elastic lamina of the arterial lesions. In previous studies,[20] macrophages in MRL/lpr mice were remarkably activated, characterized by higher ingestion, but lower digestion in comparison with those in MRL/+ mice, and released high concentrations of oxygen radicals when stimulated with zymosan. Yui *et al*.[21] reported that the serum level of M-CSF in MRL/lpr mice was increased before the onset of diseases. The treatment of spleen macrophages of MRL/+ mice with M-CSF induced high expression of Mac-2 positive cells, coincident with Fas.[17] The continuous infusion of M-CSF into the subcutis of an MRL/+ mice *in vivo* causes the development of granulomatous lesions along with the accumulation of Mac-2 positive cells.[17] MCP-1 is also a critical factor for the development of vasculitis. MCP-1 antagonist significantly inhibited the granulomatous lesions in MRL/lpr mice.[22] Recently, it has become clear that MIF deficiency in MRL/lpr mice reduced MCP-1 expression, but it was not associated with a reduction in IFN-γ expression in the kidneys.[23] These findings may indicate that macrophage recruitment to vascular lesions is one of the important steps in the cascade reaction to complete the development of granulomatous vasculitis.

A SINGLE GENE MUTATION BY ITSELF CANNOT CAUSE VASCULITIS

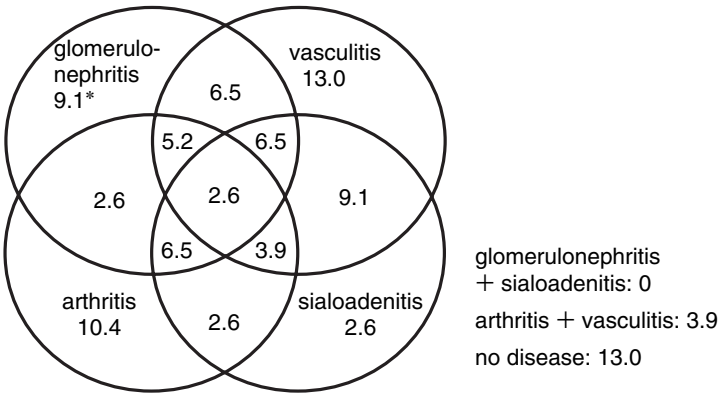
Since the MRL/lpr strain of mice was established, molecular and cellular events associated with vasculitis have been pointed out to elucidate the role of the mutant gene, *lpr* in the developmental mechanisms of autoimmune diseases.[8] However, fundamental evidence shows that MRL/lpr mice require not only the *lpr* gene but also an MRL genetic background for the development of autoimmune diseases involving systemic vasculitis. Namely, other *lpr* congenic strains of mice, such as C3H/HeJ-*lpr/lpr* (C3H/lpr) and C57 BL/6-*lpr/lpr* (B6/lpr), showed no significant disease phenotypes except lymphoproliferation, such as vasculitis, glomerulonephritis, sialoadenitis and arthritis.[11] However, these stains showed autoimmune phenotypes characteristic of the higher serum levels of autoantibodies, rheumatoid factors and immune complexes to a lesser extent to those in MRL/lpr mice.[24] In vascular lesions of C3H/lpr and B6/lpr mice, only the accumulation of lymphocytes into the perivascular regions was observed, but there was no destruction of the vascular wall and no granuloma formation.[13] Hence, MRL/lpr mice also teach us that there is a great discrepancy between autoimmune traits and the disease phenotypes.

In recent studies of several autoimmune disease models using gene targeting, a targeting gene by itself might be seemingly related to disease phenotypes. However, some of the disease phenotypes are significantly controlled by the host's background genes. For example, FcrRIIB gene targeting develops vasculitis and glomerulonephritis in a B6 strain of mice, but these disease phenotypes were remarkably reduced in a BALB/c background.[25] Another example shows that a single gene targeting develops a different disease phenotype in the face of a different genetic background. In targeting of the IL-1 receptor antagonist gene, B6 mice develop aortitis, but BALB/c mice develop arthritis.[26,27] PD-1 gene targeting induces glomerulonephritis and arthritis in a B6 background, but induces dilated cardiomyopathy in a BALB/c strain of mice.[28,29] Looking back at MRL/lpr mice, the mutant gene, *lpr*, may be a landmark giving us a concept that a single gene by itself cannot cause autoimmune diseases and disease phenotypes are primarily dependent on the host's background genes.

GENETIC SEGREGATION OF VASCULITIS FROM OTHER COLLAGEN DISEASES

To develop vasculitis, the background genes of MRL mice are required in addition to the *lpr* or *gld* gene. Do these genes for vasculitis in MRL/lpr mice share those for glomerulonephritis and other collagen diseases? This aspect is important in order to understand the genetic basis of human renovascular diseases and also to validate the categorization of secondary systemic vasculitis associated with collagen diseases. In the pathological studies of MRL/lpr x reciprocal (MRL/lpr x B6/lpr) F1 mice, vasculitis and glomerulonephritis were clearly dissociated.[13] Among the backcross generation, some mice developed only vasculitis or glomerulonephritis, while others developed both or none. Similar findings were observed in MRL/lpr x (MRL/lpr x C3H/lpr) F1 mice, where each of the lesion was clearly dissociated from arthritis and/or sialoadenitis (Fig. 2). The genetic dissociation of vasculitis from glomerulonephritis was more clearly demonstrated by the establishment of the McH5-*lpr/lpr* (McH5/lpr) stain of mice, which is a vasculitis-congenic strain derived from MRL/lpr and C3H/lpr crosses.[30] More than 90% of McH5/lpr mice developed vasculitis, but less than 10% developed glomerulonephritis at 16 to 20 weeks of age in contrast to MRL/lpr mice (vasculitis; 86%, glomerulonephritis; 98%).

Such a genetic segregation of the disease pheno-



*incidence at 4–5 mo old (%) (n=77)

Fig. 2 Genetic dissociation of each lesion of collagen disease in MRL/lpr x (MRL/lpr x C3H/lpr) F1 mice. Among them, mice developing only vasculitis, glomerulonephritis, arthritis or sialoadenitis and also mice with several combinations between them were observed.

types might also give us a novel aspect in the study of the mechanisms of vasculitis. In a previous study of vasculitis in MRL/lpr mice, anti-DNA and anti-myeloperoxidase (MPO) antibodies have been suggested as being involved in the development of vasculitis.[9,31] However, in McH5/lpr mice, the serum levels of anti-DNA and anti-MPO antibodies were almost normal. These findings may teach us that several serological traits seemingly associated with disease phenotypes in autoimmune diseases might in fact be bystanders, thus reflecting neither the results nor the causes of diseases.

VASCULITIS DEVELOPS WITH AN ADDITIVE MANNER OF MULTIPLE GENES

In general, to clarify background genes for disease phenotypes on the whole genome of a mouse model, chromosomal mapping of susceptibility loci to the disease phenotype is useful, which is based on the principle of chromosomal recombination of the germ line during meiosis. That is, an intercross or backcross generation between the disease model strain and non-disease strain is prepared, and then polymorphic gene markers derived from the progenitors closely associated with a disease phenotype can be identified statistically.[32] At present, more than 6,000 of microsatellite markers on mouse chromosomes have been identified. Polymorphic markers are available to use as markers for disease susceptibility loci, and many single nucleotide polymorphism (SNPs) markers in several mouse strains also have became available (http://www.informatics.jax.org/). These markers are dependent on the law of segregation of Mendelian inheritance even if disease phenotypes might not be. By applying this principle, many susceptibility loci to autoimmune and disease phenotypes have been investigated in murine lupus models,[33] but susceptibility loci to vasculitis have so far hardly been investigated.

In the studies of the susceptibility loci to collagen diseases using MRL/lpr x (MRL/lpr x C3H/lpr) F1 and (MRL/lpr x C3H/lpr) F2 mice (Table 1), several genetic roles of vasculitis in this strain were clarified. Three susceptibility loci to vasculitis in the kidneys (*Arvm1*, *Arvm2* and *D3Mit42*) have an additive manner in genetic inheritance (Fig. 3).[34] That is, each of three loci with susceptible genotypes showed a low incidence of vasculitis (40 to 60%), but the combination of all of these loci together induced a higher incidence (90%). This may indicate the existence of an additive or cumulative effect for the development of vasculitis among these three susceptibility loci. Moreover, the combination of *Arvm1* and *Arvm2* with susceptible genotypes showed a 70% incidence of vasculitis; however in another combination of *Arvm1* and *D3 Mit42* or *Arvm2* and *D3Mit42* there was no additive effect in the development of vasculitis. These findings indicate a hierarchical effect among these susceptibility loci. In addition, McH5/lpr mice had the susceptible genotypes in all of these loci.

TISSUE SPECIFIC SUSCEPTIBILITY LOCI TO VASCULITIS

Vasculitis in MRL/lpr mice is systemic involving the renal arteries, main branches of the aorta and arteries in the extremities (Fig. 1). Chromosomal mapping of vasculitis in each artery showed a different position on each of the chromosomes each other (Table 1), namely, vasculitic lesions in different tissues are under the control of different susceptibility loci. Susceptibility loci to vasculitis in the extremities (*Aevm1* and *Aevm2*) were located on chromosome 8 and 5, re-

Table 1 The susceptibility loci to vasculitis and other collagen diseases determined by using MRL/lpr x (MRL/lpr x C3H/lpr) F1 and (MRL/lpr x C3H/lpr) F2 mice.

Lesions	Symbol	Name	MGI: ID	Chr	Position	Refs
Vasculitis	*Arvm1*	autoimmune renal vasculitis in MRL mice 1	MGI: 2149546	4	19.8 cM	34
	Arvm2	autoimmune renal vasculitis in MRL mice 2	MGI: 2149547	4	58.0 cM	34
	Arvm3	autoimmune renal vasculitis in MRL mice 3		3	55–61 cM	34
	Aaom1	autoimmune aortitis in MRL mice 1	MGI: 2680905	4	13.3 cM	35
	Aevm1	autoimmune extremity vasculities in MRL mice 1	MGI: 2680906	8	33.0 cM	35
	Aevm2	autoimmune extremity vasculities in MRL mice 1	MGI: 2680907	5	65.0 cM	35
Glomerulonephritis	*Agnm1*	autoimmune glomerulonephritis in MRL mice 1	MGI: 3582415	4	22.0 cM	36
	Agnm2	autoimmune glomerulonephritis in MRL mice 2	MGI: 3582416	4	53.0 cM	36
	Agnm3	autoimmune glomerulonephritis in MRL mice 3	MGI: 3582417	5	56.0 cM	36
Arthritis	*Paam1*	progression of autoimmune arthritis in MRL mice 1	MGI: 2387302	15	18.0 cM	40
	Paan2	progression of autoimmune arthritis in MRL mice 2	MGI: 2387303	19	49.0 cM	40
	Paam3	progression of autoimmune arthritis in MRL mice 3		7	24.5 cM	40
	Paam4	progression of autoimmune arthritis in MRL mice 4		2	45.0 cM	40
	Paam5	progression of autoimmune arthritis in MRL mice 5		1	100.0 cM	40
	Artmd1 (Amd1)	arthropathy in MRL and DBA/1 mice 1	MGI: 3588383	10	40.0 cM	41
	Artmd2 (Amd2)	arthropathy in MRL and DBA/1 mice 2	MGI: 3588384	3	29.5 cM	41
Sialoadenitis	*Asm1*	autoimmune sialoadenitis in MRL mice 1	MGI: 2150642	10	39.0 cM	42
	Asm2	autoimmune sialoadenitis in MRL mice 2	MGI: 2150643	4	51.0 cM	42
	Asm3	autoimmune sialoadenitis in MRL mice 3		1	65.0 cM	42
	Asm4	autoimmune sialoadenitis in MRL mice 4		18	20.0 cM	42

MGI: ID are available in http://www.informatics.jax.org/.

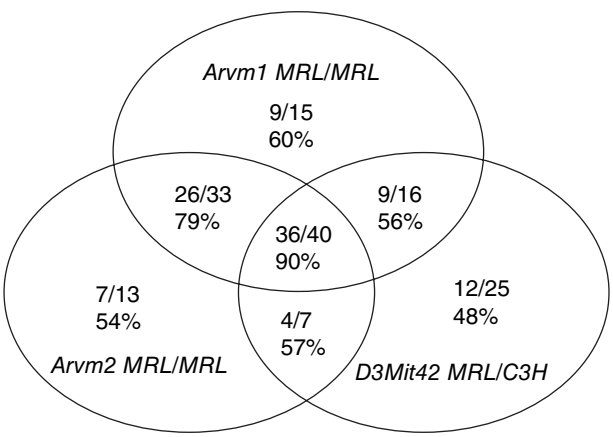


Fig. 3 An additive and hierarchical effect among the susceptibility loci to vasculitis in the kidneys. Combination of the loci with susceptible genotypes (*Arvm1; MRL/MRL, Arvm2; MRL/MRL, D3Mit42; MRL/C3H*) regulates the incidence of vasculitis (%).

spectively, but both of which were not shared with those in the renal arteries *(Arvm1 Arvm2* and *D3Mit 42)* or main branches of the aorta (*Aaom1, D5Mit 23*).[35] *Aaom1* was located on chromosome 4, interestingly close to *Arvm1*, thus indicating a high linkage value between these two loci.

The genome of the MRL strain of mice is a mosaic of the genomes of the LG/J, AKR/J, C3H/Di and C57 BL/6J strains.[6] *Aaom1* in the MRL strain came from the AKR/J or LG/J strain, and *Aevm1* and *Aevm2* loci originated from the AKR/J and LG/J strains, respectively.[35] These findings were similar to those for the two susceptibility alleles to vasculitis in the kidneys, *Arvm1* and *Arvm2* in the MRL strain which originate from the LG/J and AKR/J strains, respectively.[34] Such different allelic origins of the susceptibility loci in the MRL strain may explain why MRL mice seem to develop vasculitis over almost their entire bodies, namely, it may result from the cumulative effect of the susceptible alleles derived from AKR/J and LG/J strains, each of which corresponds to vasculitis in a specific tissue. From these findings we can speculate that the variations in the tissue- or organ- distribution of vasculitis in human in vasculitis syndromes and other collagen diseases might, at least partially, be caused by a combination of susceptible alleles resulting from genome crosses.

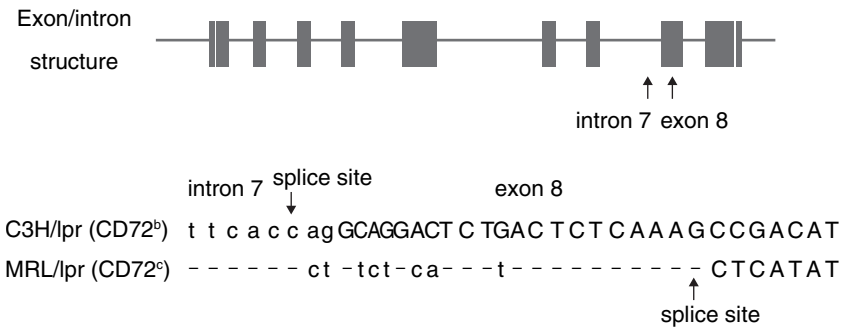


Fig. 4 Genetic polymorphism of *Cd72* between the MRL/lpr and C3H/lpr strains at the intron 7/exon 8 junction. The change of ag- > ct at the splice site in the MRL/lpr strain leads a 21 bp deletion of the exon 8, resulting a deletion of 7 amino acids in the extacellular domain of CD72.

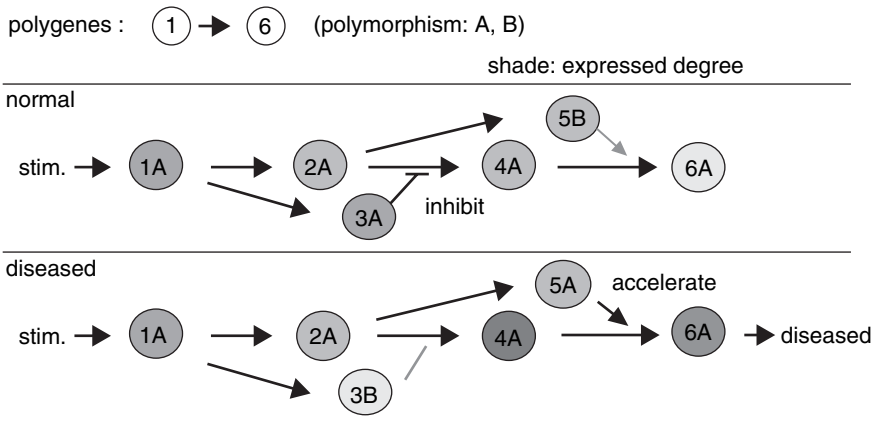


Fig. 5 A proposal concept of a polygene network in vasculitis. Each polygene regulating the susceptibility to vasculitis (gene 1 to 6) may have quantitatively a different function in the cascade reaction to the development of vasculitis, dependent on its genotype (A or B). An environmental signaling stimulates genes 1A and 1B equally to lead the second step of the expression of gene 2A and 2B and genes 3A and 3B. However, gene 3B cannot be expressed higher or lead the stronger effect to inhibit the reaction of gene 2 to gene 4 than gene 3A. On the other hand, gene 5 existing in the down stream of gene 2 and accelerating the step of gene 4 to gene 6, can act stronger with the A genotype. Finally, gene 6 is highly expressed for the development of vasculitis, but which is not required to be polymorphic.

Cd72 AS A POSITIONAL CANDIDATE GENE FOR VASCULITIS AND GLOMERULONEPHRITIS

Vasculitis in MRL/lpr mice was genetically segregated from glomerulonephritis as mentioned above. However, map positions of two of three susceptibility loci to vasculitis on chromosome 4, *Arvm1* and *Arvm 2*,[36] were much closer to two of those to glomerulonephritis, *Agnm1* and *Agnm2*, respectively. This means that these loci may be common to both disease phenotypes or have a high linkage value.

A candidate gene for *Arvm1* and *Agnm1* was determined to be *Cd72* based on the result that there was a severe polymorphism on the coding region between the MRL and C3H strains, namely *Cd72* cDNA in the MRL strain had a 3 bp insertion between positions 950 and 951 in exon 7, and a 21 bp deletion from 966 to 986 at the intron 7/exon 8 junction (Fig. 4), thus resulting from alternative splicing.[34] This indicates that the *MRL* allele of CD72 was consistent with a $CD72^c$ haplotype, while that of C3H was a $CD72^b$ haplotype.[37] Moreover, the MRL strain had 13 amino acid substitutions consisting of acidic, basic and neutral amino acids compared with the C3H strain.

CD72 is a negative regulator of B-cell activation, acting through its immunoreceptor tyrosine-based inhibitory motif (ITIM) in exon 1.[38] Although the ITIM

itself was well conserved in the *MRL* allele, the allelic polymorphism between the MRL and C3H strains including a 21 bp deletion at the intron 7/exon 8 junction and 13 amino acid substitutions may be sufficient to induce the functional difference between the CD72 molecules in the MRL and C3H strains. The $CD72^c$ allele is likely to contribute to the development of vasculitis associated with the other two susceptibility loci via a limited antibody production. This theory is based on the fact that a vasculitis-prone strain of McH5/lpr mice has decreased anti-DNA and anti-myeloperoxidase antibodies, but not rheumatoid factors and circulating immune complexes, compared to the MRL/lpr strain.[30] Actually, this strain had the $CD72^c$ allele. In addition, the other lupus-prone strains of mice such as NZB, NZW and BXSB have the same $CD72^b$ allele as C3H/HeJ, thus suggesting that the *MRL* allele $CD72^c$ might contribute uniquely to the development of vasculitis.[34]

POLYGENE NETWORK OF VASCULITIS

In general, the genetic basis of diseases is divided into two major groups. One is the result of a gene defect or a mutation which induces common disease phenotypes not influenced by the host's genetic background. The other one is that disease develops as the result of a cumulative effect of multiple genes, each of which by itself cannot induce the particular phenotype significantly. The former encodes almost a qualitative phenotype, while the latter encodes a quantitative phenotype, which is not dependent on a Mendelian inheritance. This system was classified as "polygenic inheritance" by K. Mather in 1949.[39] Each polygene may distribute into the population of a species through an evolution process, influenced by a genetic drift, taking advantage of escaping from natural selection. Vasculitis is under the control of polygenes according to the law proposed by Mather, which involves polymorphic genes and also a mutant gene encoding lymphoproliferation in the case of MRL/lpr mice. Some of the polygenes, such as *Cd72*, may also be common in other collagen diseases.

Polygenes may quantitatively regulate the cascade reactions extending to the development of vasculitis and other collagen disease with a regular variation of the pathologic phenotypes based on their combinations. In the cascade reaction, as shown in Figure 5, some polymorphic gene such as $Cd72^{MRL}$ might be less suppressive than $Cd72^{C3H}$, and other ones with MRL alleles might be more accelerative, leading to excessive production of effector molecules or cells having them. In this hypothesis, effectors themselves are not required to be polymorphic for the development of vasculitis. We therefore call this system a polygene network of vasculitis.

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