

Systemic Arterial Expression of Matrix Metalloproteinases 2 and 9 in Acute Kawasaki Disease

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Objective—Coronary artery aneurysms are the major complication of Kawasaki disease (KD). Matrix metalloproteinases (MMPs) regulate remodeling and degradation of the extracellular matrix. We hypothesized that MMP-9 expression is increased in acute KD aneurysms when compared with KD nonaneurysmal arteries and arteries from control children.

Methods and Results—MMP-2, MMP-9, tissue inhibitor of metalloproteinase (TIMP)-1, and TIMP-2 were immunolocalized in coronary arteries from children with fatal acute KD and controls. In KD coronary aneurysms, MMP-2 expression was prominent in the thickened neointima and in endothelial cells of new capillaries in areas of angiogenesis. MMP-9 was absent in control coronary arteries but was expressed in coronary artery aneurysms, nonaneurysmal coronary and noncoronary arteries, and cardiac nerves in acute KD, without an increase in TIMP-1 expression.

Conclusions—MMP-2 likely participates in remodeling of the arterial wall in acute KD, particularly in the processes of neointimal proliferation and angiogenesis. MMP-9 may play a role in the development of coronary aneurysms, but its expression is not confined to aneurysmal arteries. Systemic arterial expression of MMP-9 in acute KD, even in the absence of inflammatory changes in the vessel, suggests induction by a circulating factor, or possibly by an infectious agent with tropism for arterial tissue. (*Arterioscler Thromb Vasc Biol.* 2003;23:576-581.)

Key Words: Kawasaki disease ■ matrix metalloproteinases ■ coronary artery ■ aneurysm

Kawasaki disease (KD) is a potentially fatal, acute vasculitis of childhood, which has surpassed acute rheumatic fever as the most common cause of acquired heart disease in children in the United States and other developed nations.^{1,2} Significant cardiovascular sequelae can complicate KD, with up to 20% to 25% of untreated patients developing aneurysmal dilatation of the coronary arteries.³ Sudden death in the acute phase may result from coronary artery aneurysm (CAA) rupture or from myocardial infarction secondary to acute thrombosis.^{3,4} The coronary arteritis of acute KD is characterized by transmural inflammation and alterations of the extracellular matrix (ECM), with thinning of the vascular media and marked destruction of the internal elastic lamina, which leads to aneurysm formation.⁵ The mechanisms underlying destruction of elastin and other components of the ECM in acute KD remain unknown.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteinases that degrade ECM and basement membrane proteins, such as collagen and elastin. The tissue inhibitors of metalloproteinases (TIMPs) are their specific inhibitors; TIMP-2 is the usual inhibitor of MMP-2, and TIMP-1 is the typical inhibitor of MMP-9. Imbalances between MMPs and TIMPs can result in pathologic matrix

degradation in diseases such as cancer, rheumatoid arthritis, and abdominal aortic aneurysms.^{6,7} We hypothesized that MMP-2 and MMP-9 expression is increased in acute KD aneurysms when compared with KD nonaneurysmal arteries and control arteries. To test this hypothesis, MMP-2, MMP-9, and their inhibitors TIMP-1 and TIMP-2 were immunolocalized in coronary artery tissues from children with fatal, acute KD and control children.

Methods

Tissue Samples

Paraffin-embedded, formalin-fixed coronary artery and myocardial tissue from 11 children with acute KD (10 of whom died and 1 of whom underwent cardiac transplantation) (Table I, available at <http://atvb.ahajournals.org>) and from 7 children who died of causes other than KD was studied (Table II, available at <http://atvb.ahajournals.org>). Noncoronary arterial tissues were available from 8 of the 11 KD patients and included mesenteric, pancreatic, and renal arteries.

Immunohistochemical Studies

Paraffin-embedded, formalin-fixed blocks of coronary artery tissue were sectioned (5 μ m), deparaffinized with xylene, and hydrated in graded alcohol. To enhance antigen retrieval, the sections were microwave-heated for 6 minutes in 0.01 mol/L sodium citrate buffer,

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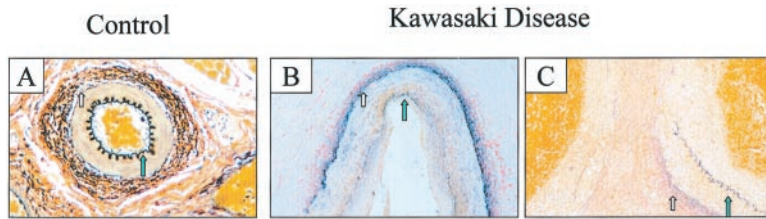


Figure 1. Elastin stain of control and KD coronary arteries. Elastin fibers stain blue-violet and collagen fibers stain red with von Gieson's stain. A, Control coronary artery showing intact internal and external elastic laminae. B, CAA from a patient with fatal, acute KD, showing disruption of internal elastic lamina, reduplication of external elastic lamina, and eccentric proliferation of myointima. C, Thrombosed CAA of a patient with fatal, acute KD, showing disruption of internal and external elastic laminae and loss of distinct trilaminar structure of arterial wall. Green arrows mark internal elastic lamina, and white arrows mark external elastic lamina. A, $\times 20$ objective; B and C, $\times 4$ objective.

pH 6. Endogenous peroxidase activity was quenched with 1% H_2O_2 in phosphate-buffered saline (PBS) for 30 minutes. Nonspecific immunoglobulin binding was blocked with 4% normal horse serum in PBS for 30 minutes. Sections were incubated overnight at $4^\circ C$ with mouse anti-human MMP-2 monoclonal antibody (1:250 in PBS) (MMP-2, AB-4, Neomarkers Inc), mouse anti-human MMP-9 monoclonal antibody (1:100 in PBS) (MMP-9, AB-3, Oncogene Research Products, distributed through Calbiochem), mouse anti-human TIMP-1 (1:50 in PBS) (TIMP-1 Ab-2, clone 102D1, Neomarkers), or mouse anti-human TIMP-2 (1:250 in PBS) (TIMP-2 AB-5, clone 3A4, Neomarkers). Both MMP antibodies react with the pro- and active forms of their respective enzymes. After the tissues were washed in PBS, staining was detected with a biotinylated horse anti-mouse IgG secondary antibody (Vector Laboratories Inc) and an avidin-biotin-horseradish peroxidase system (Vectastain Elite ABC system, Vector Laboratories Inc). With diaminobenzidine tetrahydrochloride as a reaction product, positive cells stained brown. Sections were counterstained with Gill's hematoxylin (Vector Laboratories Inc). In noninflamed KD and normal coronary arteries, the endothelial cell layer (intima), media, and adventitia were each graded for expression of MMP-2 and MMP-9 as described in the following section. In all aneurysmal and nonaneurysmal but inflamed coronary arteries, disruption of the internal elastic laminae generally obscured the normal boundaries of intima and media. To reflect this morphology more accurately, grading of the myointimal and adventitial layers was performed. Immunological staining was graded and scored as follows: 0, no evidence of staining (eg, Figure 1D, all layers); 1, mild focal vascular staining (eg, Figure 1F, adventitial layer); 2, moderate vascular staining (eg, Figure 1F, myointimal layer); and 3, marked vascular staining (eg, Figure 1C, myointimal layer).

Positive control tissues for immunohistochemistry included normal spleen for MMP-9, normal blood vessel for MMP-2 and TIMP-2 (both of these molecules are normally expressed by smooth muscle cells), and breast cancer tissue (Neomarkers) for TIMP-1. Negative controls included sections in which the primary antibody was omitted.

Statistical Analysis

Wilcoxon's sum of ranks test was used to compare the grade of immunohistochemical staining of corresponding layers of control and KD coronary arteries using the antibodies. Wilcoxon's signed rank test was used to compare the grade of staining of the KD CAAs with their matched (in the same patient) nonaneurysmal or noninflamed coronary artery. A value of $P < 0.05$ was considered significant.

Results

Histopathology of CAAs in KD

KD CAAs demonstrated a characteristic pathologic appearance, with disruption of the distinct trilaminar structure of the arterial wall (intima, media, and adventitia) and marked transmural infiltration of inflammatory cells. Von Gieson's elastic stain of a section of control coronary artery demonstrated intact internal and external laminae (Figure 1A), whereas marked fragmentation of the elastic laminae was seen in CAAs of patients with acute, fatal KD (Figures 1B, 1C, and 2G). Marked thinning of the vascular media and thickening of the vascular intima were evident in CAAs, as previously described in KD.⁵

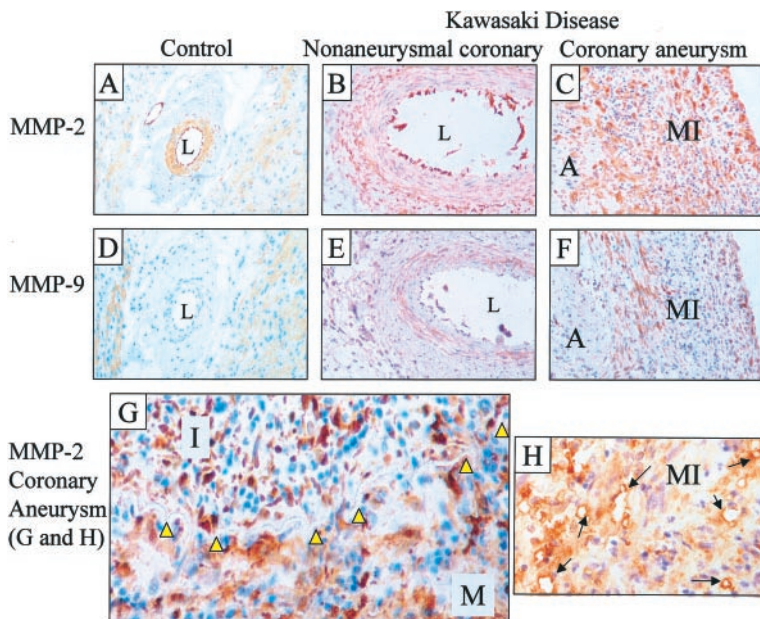


Figure 2. MMP-2 and MMP-9 in coronary arteries of KD patients and controls. A–C, G, and H, Immunohistochemical stains for MMP-2. A, Demonstration of MMP-2 staining of intimal endothelium and medial smooth muscle cells in control coronary artery. In B, MMP-2 expression is observed in nonaneurysmal coronary artery from a KD patient; there is increased expression in adventitia and less expression in media when compared with control vessel. In C, MMP-2 expression is seen in a CAA from a KD patient. There is intense staining of myointima (MI) and of endothelium of new blood vessels arising in this area (H, black arrows). Breaks in internal elastic membrane are evident in G (yellow arrows indicate intact membrane on either side of a break); MMP-2-positive cells appear to be migrating through breaks in the membrane. D–F, Immunohistochemical stains for MMP-9. D, Demonstration of absence of MMP-9 expression in the same control coronary artery in A. E, Demonstration of MMP-9 expression in the same KD nonaneurysmal coronary artery shown in B. MMP-9 expression is observed diffusely throughout the arterial wall but is particularly prominent in myointima. F, MMP-9 expression in the same KD CAA shown in C. MMP-9 expression is seen diffusely throughout the vessel wall but is particularly notable in myointima in this patient. L indicates lumen; I, intima; M, media; MI, myointima. A–F taken with a $\times 20$ objective; panels G, H, with a $\times 40$ objective.

TABLE 1. MMP-2 Expression in KD Cases and Controls

Case	Coronary Vascular Grade							Myocardial Grade
	Aneurysm		Nonaneurysm		Noninflamed vessel			
	MI	A	MI	A	E	M	A	
KD1	2	0	1	1	3	2	0	2
KD2	3	3	3	0	3	1	1	3
KD3	2	1	2	0	1	0	0	1
KD4	2	2	2	0	3	0	0	3
KD5	2	2	2	0	3	0	0	3
KD6	2	2	1	1	3	0	0	1
KD7	2	0	NP		NP			3
KD8	3	2	2	1	3	1	1	2
KD9	2	1	2	0	1	1	0	1
KD10	2	1	1	1	3	2	0	0
KD11	3	2	2	2	3	1	2	3
Control A	NA		NA		2	2	0	3
Control B	NA		NA		2	2	1	2
Control C	NA		NA		2	3	0	3
Control D	NA		NA		2	2	0	1
Control E	NA		NA		3	2	0	1
Control F	NA		NA		1	2	0	0
Control G	NA		NA		2	1	1	0

Immunologic staining was graded as follows: grade 0, no evidence of staining; grade 1, mild staining; grade 2, moderate staining; and grade 3, marked staining.

NA indicates not applicable; NP, not present on available sections; MI, myointimal layer; A, adventitia; E, endothelial cell layer; M, media.

MMP-2 Expression in KD and Control Coronary Arteries and Myocardium

In all control coronary arteries, MMP-2 expression was identified in smooth muscle cells within the media, which was separated from the intima by an intact internal elastic lamina, and in the single layer of endothelial cells within the intima (Figure 2A). Similar semiquantitative MMP-2 expression was identified in KD CAA myointima when compared with nonaneurysmal KD myointima and with noninflamed KD or control intima and media (Table 1). However, increased MMP-2 expression was observed in the adventitia of KD CAAs when compared with the adventitia of controls ($P<0.05$), with the adventitia of the nonaneurysmal KD artery ($P<0.05$), and with the adventitia of the noninflamed KD coronary ($P<0.01$; Table 1). A qualitative difference in the location of MMP-2 expression was also demonstrated in KD coronary arteries when compared with control coronary arteries. MMP-2 expression was most conspicuous in the thickened myointima in KD CAAs (Figure 2C and 2G) and in endothelial cells of new capillary blood vessels in the myointima and adventitia (Figure 2H). MMP-2 expression was also seen in myofibroblasts that had migrated from the media into the thickened neointima through breaks in the internal elastic lamina of KD CAAs (Figure 2G).

MMP-9 Expression in KD and Control Coronary Arteries and Myocardium

MMP-9 expression was not demonstrated in control coronary arteries (Figures 2D and 3C). However, MMP-9 was ex-

pressed in KD CAAs (Figure 2F), nonaneurysmal coronary arteries (Figures 2E and 3D), and in noninflamed coronaries (Table 2). The myointimal layers of CAAs and nonaneurysmal KD arteries both demonstrated a statistically significant increase in MMP-9 staining when compared with either intima or media of controls ($P<0.01$ for CAA vs controls, $P<0.05$ for nonaneurysmal KD arteries vs controls). In addition, noninflamed KD coronary intima and media showed a statistically significant increase in MMP-9 staining when compared with controls ($P<0.05$ for both endothelial cells and media). MMP-9 staining was present in smooth muscle cells and in infiltrating mononuclear cells. KD patients also had a significant increase in MMP-9 staining in myocardium compared with controls ($P=0.01$; Figure 3C and 3D). In KD patient 10, MMP-9 expression was not observed in the coronary artery or myocardium; this patient had received aggressive immunosuppressive therapy with high-dose corticosteroids and methotrexate. To determine whether MMP-9 was expressed in noncoronary arteries in KD, sections of mesenteric, renal, and pancreatic arteries that were available from 8 of the 11 KD patients were examined; MMP-9 staining was also observed in the wall of these noncoronary arteries from 6 of the 8 KD patients. A marked increase in MMP-9 staining of peripheral nerves in the KD coronary artery adventitia when compared with nerves in control coronary artery adventitia was also noted ($P=0.002$; Figure 3A, 3B, and 3C).

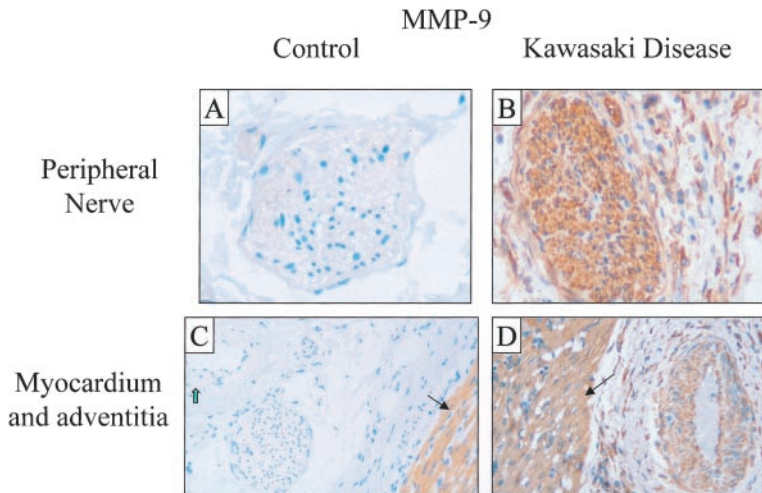


Figure 3. MMP-9 in cardiac peripheral nerves, myocardium, and adventitia from KD patients and controls. A, Control peripheral nerve showing absence of MMP-9 staining. B, KD peripheral nerve showing strong MMP-9 staining. C, Control myocardium and adventitia showing staining of myocardium (black arrow) and no staining of peripheral nerve or nearby coronary artery (green arrow). D, KD myocardium and adventitia showing staining of myocardium (black arrow) and staining of nearby nonaneurysmal coronary artery. A–D taken with a $\times 20$ objective.

TIMP-1 Expression in KD and Control Coronary Arteries and Myocardium

TIMP-1 was either not expressed or minimally expressed in smooth muscle cells of childhood control coronary arteries and in KD arteries (Table III, available at <http://atvb.ahajournals.org>). To confirm this result, we obtained positive-control breast cancer tissue from Neomarkers, which showed strong positive staining, verifying the validity of the antibody and the assay. Myocardium in controls and KD arteries showed mild to moderate staining, without a significant increase in TIMP-1 expression in KD patients.

TIMP-2 Expression in KD and Control Coronary Arteries and Myocardium

TIMP-2 expression in endothelium and media of childhood control coronary arteries was moderate to marked, was absent in the adventitia, and paralleled MMP-2 expression (Table IV, available at <http://atvb.ahajournals.org>). In KD coronary arteries, TIMP-2 expression was similar, except that there was significantly increased expression in the adventitia of aneurysms and nonaneurysmal vessels when compared with controls ($P < 0.01$ and $P < 0.05$, respectively). There was also significantly increased expression in the adventitia of aneu-

TABLE 2. MMP-9 Expression in KD Cases and Controls

Case	Coronary Vascular Grade							Nerve Grade*	Myocardial Grade*
	Aneurysm		Nonaneurysm		Noninflamed Vessel				
	MI	A	MI	A	E*	M*	A		
KD1	0	0	0	0	0	1	0	2	2
KD2	1	2	1	1	0	1	0	1	3
KD3	1	0	1	0	1	0	0	2	2
KD4	1	0	0	0	1	1	0	2	3
KD5	2	1	2	0	2	2	0	3	3
KD6	1	0	1	0	2	1	0	2	3
KD7	2	1	NP		NP			NP	3
KD8	2	1	2	1	2	1	1	2	3
KD9	1	0	1	0	1	2	0	2	3
KD10	0	0	0	0	0	0	0	1	0
KD11	2	2	2	2	3	2	2	3	3
Control A	NA		NA		0	0	0	NP	2
Control B	NA		NA		0	0	0	1	2
Control C	NA		NA		0	0	0	0	1
Control D	NA		NA		0	0	0	NP	2
Control E	NA		NA		0	0	0	0	2
Control F	NA		NA		0	0	0	0	0
Control G	NA		NA		0	0	0	0	0

* $P = 0.01$ comparing values for KD cases and controls, Wilcoxon's sum of ranks test.

Immunologic staining was graded as follows: grade 0, no evidence of staining; grade 1, mild staining; grade 2, moderate staining; and grade 3, marked staining.

NA indicates not applicable; NP, not present on available sections; MI, myointimal layer; A, adventitia; E, endothelial cell layer; M, media.

rysms when compared with the adventitia of noninflamed KD arteries ($P<0.05$); this staining appeared to reside in infiltrating mononuclear cells. Marked staining of myocardium was observed in both KD patients and controls. To view Tables I through IV, please see www.ahajournals.org.

Discussion

MMP-2 and MMP-9 appear to play a role in the formation of abdominal aortic aneurysms in adults^{7,8} and may be involved in aneurysmal dilatation of arteries in other diseases such as KD. MMP-2, which is expressed in the intima and media of normal arteries, was also prominent in the myointima of acute KD CAAs and was identified in medial smooth muscle cells that appeared to be migrating into the intima through breaks in the internal elastic lamina. Notably, MMP-2 expression was observed in endothelial cells of new capillaries in areas of angiogenesis in the myointima and adventitia of KD CAAs. Angiogenesis has been reported in CAAs from KD children who died years after onset,⁹ but has not been reported previously in coronary aneurysms in the acute phase; this interesting finding deserves further study. TIMP-2 expression paralleled MMP-2 expression in acute KD. Increased expression of both molecules was observed in the adventitia of CAAs.

MMP-9, present in abdominal aortic aneurysms in adults but not in normal aortas, appears particularly important in rapid aortic aneurysm dilatation and rupture.⁸ MMP-9 is present in infiltrating macrophages in the aortic aneurysm wall and has been spatially associated with periadventitial vascularization.^{8,10} We hypothesized that MMP-9 would be expressed prominently in KD CAAs but would not be expressed in nonaneurysmal arteries; this hypothesis was not supported. MMP-9 was widely expressed in CAAs, nonaneurysmal coronaries, and noninflamed coronaries in acute KD. This finding highlights the fact that KD is a systemic arteritis.¹¹ Although aneurysms of the coronary arteries are most commonly associated with KD, aneurysms of arteries other than coronaries may occur in up to 2% of untreated KD patients.³ KD arteritis is characterized by variability in the extent of inflammatory changes both in different arteries in the same patient and in different portions of the same artery.¹¹ Interestingly, TIMP-1, an important inhibitor of MMP-9, was not expressed in KD coronary arteries even in the face of increased MMP-9 expression. Therefore, an imbalance between MMP-9 and TIMP-1 could account for overproduction of MMP-9 in acute KD, although other TIMPs may also regulate MMP-9 expression.

A limitation of the present study is that immunolocalization of MMPs in tissue does not necessarily equate to evidence of enzyme activity, because anti-MMP antibodies do not differentiate between active and latent forms of the proteins. Thus, our results include detection of both pro- and active forms of MMP-2 and MMP-9. Zymography, which requires fresh or snap-frozen tissue samples, is the optimal technique to demonstrate the presence of the active form of MMPs. Obtaining fresh or frozen arterial tissue samples from acute KD fatalities has proven problematic; tissue is generally placed in formalin as routine procedure at autopsy. Despite acquiring a large collection of KD autopsy specimens from

throughout the United States and Japan, we have not been able to obtain nonformalin-fixed tissue that could be used in zymography. Additionally, we were not able to confirm the cell types producing the MMPs and TIMPs by double staining, because immunofluorescence studies on archival formalin-fixed, paraffin-embedded tissues are difficult to perform. Staining of sequential sections for cell markers and MMPs or TIMPs was not useful because of a lack of specific landmarks in the inflamed vascular wall. After disruption of the normal architecture of the arterial wall and infiltration by copious inflammatory cells, it was very difficult to be certain, for example, that an MMP-9-positive cell in one section and a CD68-positive cell on an adjacent section were definitely the same cell. We therefore reported cell types positive for the MMPs and TIMPs based on morphological appearance.

Autopsy studies of aneurysms in the acute phase of KD generally reveal marked inflammatory cell infiltration in the aneurysm.⁵ It is possible that invading inflammatory cells in the KD aneurysm result in the production of more active MMP-9 than in noninflamed vessels, leading to more dilatation or aneurysm formation in the segments of coronary artery with the most severe degree of inflammatory cell infiltration.

Widespread expression of MMP-9 in arterial tissue in acute KD, even in the absence of inflammatory or aneurysmal changes in the vessel, suggests induction by factors circulating in the bloodstream. Tumor necrosis factor- α has been shown to induce MMP-9 in monocytes,¹² and circulating levels have been reported to be elevated in acute KD.^{13,14} However, MMP-9 was not detected in coronary arteries of 3 controls who died of bacterial meningitis and Gram-negative sepsis, conditions in which tumor necrosis factor- α is also likely to circulate. Interestingly, MMP-9 was detected prominently in peripheral nerves in KD coronary artery adventitia. Nerve growth factor induces MMP-9 expression in vascular smooth muscle cells,¹⁵ and dramatically increased levels of nerve growth factor have been reported in sera in the acute phase of KD¹⁶; this possible relationship deserves further study. It is also possible that MMP-9 is induced by the infectious etiologic agent of KD. Clinical and epidemiologic features of KD support an infectious cause; however, the etiologic agent remains unknown.¹ Epstein-Barr virus,¹⁷ influenza A virus,¹⁸ human T-cell leukemia virus type 1,¹⁹ respiratory syncytial virus,²⁰ and mycobacteria²¹ induce expression of MMP-9 in a variety of human and animal cell lines. Thus, expression of MMP-9 in acute KD arteries may result from induction by an infectious agent with tropism for arterial tissue.

In summary, systemic arterial expression of MMP-2 and MMP-9 was identified in acute KD. In CAAs, MMP-2 was prominent in thickened neointima and endothelial cells of new capillaries in areas of angiogenesis in the neointima and adventitia. MMP-9 was detected in arteries, nerves, and myocardium in acute KD and was not accompanied by increased expression of TIMP-1. Widespread expression of MMP-9, even in the absence of inflammatory changes in the vessel wall, suggests induction by factor(s) circulating in the bloodstream, or possibly by an infectious agent with tropism for arterial tissue.

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