levels of TNF-α and IL-1β, abrogating joint swelling and reducing destruction of bone and cartilage [44].

3.4 Bronchial asthma

It is well known that NF-κB plays a critical role in induction of allergic airway inflammation. Desmet *et al.* revealed that NF-κB inhibition using decoy ODN was associated with strong attenuation of allergic lung inflammation, airway hyper-responsiveness [45]. Thus, we generated ovalbumin-sensitized mice which had allergic airway inflammation and hyper-responsiveness. Administration of IMD-0354 ameliorated airway hyper-responsiveness and reduced the numbers of bronchial eosinophils in the mice. The total numbers of bronchial eosinophils and IgE production were reduced by treatment with IMD-0354 [46]. Thus, IMD-0354 has therapeutic potential for bronchial asthma.

BMS-345541 inhibited TNF-α-induced expression of IL-6, -8 and eotaxin dose-dependently in the airway smooth muscle (ASM) cells as Keslacy *et al.* revealed [47]. Goto *et al.* also investigated the effect of BMS-345541 using human ASM cells. They demonstrated that treatments with TNF-α and IL-13 induced a translocation of NF-κB to nuclei in ASM cells. However, co-incubation with BMS-345541 markedly inhibited the translocation of NF-κB [48].

PS-1145 reduced the expression of inflammatory factors including adhesion molecules, cytokines and chemokines on ASM cells, suggesting that the IKK inhibitor may be of considerable benefit in inflammatory airways diseases, particularly in severe asthma as Catley *et al.* reported [38].

Bay 65 - 1942 inhibited cockroach allergen-induced airway inflammation and hyper-reactivity in mice. It also efficiently abrogated leukocyte trafficking induced by carrageenan in mice or by ovalbumin in a rat model of airway inflammation [49].

3.5 Skin disorders

NF-κB activation on disease severity in allergic disorders is well known. Nakamura *et al.* showed that ointment containing NF-κB decoy ODN prevented atopic dermatitis in a mouse model [50]. Thus, we examined the relevance of IMD-0354 for atopic dermatitis by its topical application [51]. To investigate the *in vivo* efficacy, IMD-0354 ointment was applied to mice with severe dermatitis. Histological examinations revealed that the hyperplasia of keratinocytes and infiltration of inflammatory cells were significantly reduced in the skin of IMD-0354-treated mice. IMD-0354 suppressed the proliferation of various immunocompetent cells, IgE production from splenic B cells and IgE-mediated activation of mast cells. Therefore, we concluded that IMD-0354 might provide an alternative therapeutic strategy for the treatment of atopic dermatitis. So far, the effects of other IKK inhibitors on atopic dermatitis have not yet been reported; further investigation in this area is needed. di Meglio *et al.* showed that the NBD peptide significantly inhibited edema formation and cellular infiltration in inflamed mouse paws. This anti-inflammatory activity was most likely due to inhibition of expression of pro-inflammatory mediators, such as TNF-α and COX-2, in inflamed tissues [52].

3.6 Malignant diseases

Development and progression of cancers, such as lymphoma and leukemia, and some epithelial cancers are known to be regulated by constitutive NF-κB activity [53,54]. Thus, inhibition of NF-κB may offer promise as a therapeutic approach for the treatment of tumors via manipulation of desired target genes. Kawamura *et al.* reported that NF-κB decoy ODN inhibited hepatic metastasis of reticulosarcoma in mice through a decrease in transactivation of important NF-κB-driven genes [55]. Regarding the contribution of NF-κB in carcinogenesis, IKK inhibition might have a therapeutic potential against cancers. We have reported that IMD-0354 suppressed the growth of human breast cancer cells by arresting cell cycles and inducing apoptosis. In the cells incubated with IMD-0354, cell cycle was arrested at the G0-G1 phase and apoptotic cells were increased. The expression of some cell cycle regulatory molecules and antiapoptotic molecules was suppressed in cells treated with IMD-0354. Daily administration of IMD-0354 inhibited tumor expansion in immunodeficient mice into which cancer cells were transplanted. We concluded that inhibition of NF-κB activity using IMD-0354 might have a therapeutic role in the treatment of human breast cancers.

BMS-345541 investigated the effects on several malignant diseases, such as melanoma, lymphoma, neuroblastoma and others [56-59]. Yang *et al.* revealed that BMS-345541 treatment resulted in the reduction of NF-κB activity, chemokine secretion by cultured melanoma cells and melanoma cell survival. The effect of BMS-345541 on tumor cell growth was through mitochondria-mediated apoptosis based on the reduced ratio of Bcl-2 per Bax. Thus, the mechanisms of antitumor effect of BMS-345541 are downregulation of IKK activity that results in mitochondria-mediated apoptosis of tumor cells because the programmed cell death is highly regulated by NF-κB signaling. Therefore, IKK may serve as a potential target for melanoma therapy [56]. Roué *et al.* reported that BMS-345541 decreased cellular-FLIP expression and allowed mantle cell lymphoma cells to undergo the TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis. They concluded that the combination of TRAIL stimulation and IKK inhibition as a new approach to MCL therapy [57]. Ammann *et al.* also revealed that BMS-345541 significantly enhances TRAIL-induced apoptosis, pointing to an antiapoptotic function of NF-κB in TRAIL-mediated apoptosis in neuroblastoma cells [58].

PS-1145 also tested the effects on malignant diseases, such as myeloma, lymphoma, prostate cancer, pancreatic cancer, breast cancer and others [60-69]. In myeloma, Hideshima *et al.* revealed that PS-1145 blocked TNF-α-induced NF-κB activation in the tumor cells through inhibition of IκB phosphorylation and degradation of IκBα, respectively.

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Moreover, PS-1145 blocks the protective effect of IL-6 against apoptosis. TNF-α-induced ICAM-1 expression on myeloma cells was also inhibited by PS-1145. Moreover, PS-1145 inhibits both IL-6 secretion from bone marrow stromal cells (BMSCs) triggered by multiple myeloma cell adhesion and proliferation of myeloma cells adherent to BMSCs. They also clarified the pathophysiology IKK inhibition in myeloma cells using a JNK-specific inhibitor SP600125. PS-1145 inhibits SP600125-induced NF-κB activation and blocks the protective effect of SP600125 against apoptosis [60,61]. Akiyama *et al.* revealed that PS-1145 blocks telomerase activity [62] and cell migration [63] in the myeloma cells. In solid tumor cells, Yemelyanov *et al.* found that PS1145 induced apoptosis and inhibited cell proliferation in prostate cancer cells. In addition, they found that incubation with PS1145 inhibited the invasion activity of highly invasive prostate cancer cells in an invasion chamber assay [66].

Bay 65 - 1942 induced growth suppression and death in ells of imatinib- or dasatinib-resistant forms of chronic myelogenous leukemia as Duncan *et al.* showed [70]. Lounnas *et al.* revealed that a solid IKK inhibitor AS602868 had a promising new therapeutic potential for the treatment of imatinib-resistant chronic myeloid leukemia patients. Because the mutation escapes all currently used Bcr-Abl inhibitors, it is likely to become a major clinical problem as it is associated with a poor clinical outcome [71]. Other IKK inhibitors, such as SC-514 [72] and ACHP [73,74], also have antitumor effects. Because Bednarski *et al.* revealed that IKK plays a critical role in NF-κB-mediated chemoresistance in response to doxorubicin [75], IKK inhibition may serve as a potential effect in combinational strategies to improve chemotherapeutic response.

3.7 Liver diseases

Because Ogushi *et al.* showed that NF-κB decoy ODN prevented fatal liver failure in a murine model [76], IKK inhibitors may prevent various liver diseases. Beraza *et al.* showed that AS602868 efficiently prevented liver steatosis and inflammation and improved antioxidant response. All the effects contributed to attenuation of the non-alcoholic-steatohepatitis progression, as evidenced by lower hepatocyte apoptosis and early stages of liver fibrosis [77].

3.8 Neurological diseases

Dasgupta *et al.* showed that the NBD peptides are anti-neuroinflammatory and that NBD peptides may have a therapeutic effect in neuroinflammatory disorders such as MS [78]. Acharyya *et al.* demonstrated that a specific pharmacological inhibition of IKK resulted in improved pathology and muscle function in *mdx* mice, which is a model of Duchenne muscular dystrophy [79].

3.9 The potential negative effects of IKK inhibitors

Many papers have reported that IKK inhibition has some potential negative effects. It is well known that NF-κB plays an important role in immunity to infection. Genetic studies using animal models demonstrated the critical role of NF-κB in host defenses against pathogens. Three human primary immunodeficiencies associated with impaired NF-κB signaling were also reported [80]. Therefore, pharmacological IKK inhibition may damage defense systems against bacteria and fungi infection. The relationship between NF-κB and cancer development has also been reported. While the use of NSAIDs, which inhibit activation of NF-κB, reduced the incidence of cancers and lymphomas, some reports showed that NSAIDs might increase the risk of pancreatic cancer or non-Hodgkin's lymphoma. Thus, these relationships are very complicated because NF-κB activation can have either positive or negative, indirect, secondary effects on tumor development. NF-κB usually promotes cell survival that results in decreased cell proliferation, thereby its negative effect on tumor development [2]. Thus, IKK inhibitors may promote cancer development in some cases. Maeda *et al.* revealed that deletion of the gene encoding IKK-β in the cells resulted in a marked increase in tumor number, size, growth rate and aggressiveness [81]. Chen *et al.* also revealed that IKK inhibition prevented systemic inflammation but increased local injury following intestinal ischemia reperfusion [82]. These results showed the dual function of the IKK system, which is responsible for both tissue protection and systemic inflammation, and underscore the caution that should be exerted when using IKK inhibitors.

3.10 Clinical trials

IMD-1041, which is a prodrug of IMD-0354, specifically inhibits IKK-β *in vivo* and *in vitro* [83]. Because this compound is an investigational drug, it is not yet on the market. To prove the effect of IMD-1041 on the treatment of chronic obstructive pulmonary disease (COPD), the Institute of Medicinal Molecular Design started the interventional, randomized, placebo-controlled and double-blind clinical trial entitled 'A Phase IIa, Proof of Concept Study to Evaluate the Reduction in Inflammatory Biomarkers and Assess Airway Function Following Administration of IMD-1041 in Patients With COPD' from 2009 (ClinicalTrials.gov Identifier: NCT00883584). The purpose of this study is to see if IMD-1041 has the ability to reduce inflammatory derived symptoms and airway remodeling by looking at changes in chemical levels in the blood and sputum. Sanofi-Aventis has also started a clinical trial using an IKK inhibitor (SAR113945) in patients with knee osteoarthritis (ClinicalTrials.gov Identifier: NCT01113333). Although these results have not yet been analyzed, potent IKK inhibitors will be available in the near future.

4. Expert opinion

We have reviewed the effects of novel synthesized IKK inhibitors on inflammatory diseases in this article. Because NF-κB plays a critical role in inflammation, IKK inhibition has the

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potential to prevent and treat the cardiovascular, pulmonary, allergic, malignant and other diseases.

To date, various synthesized IKK inhibitors, IMD-0354, IMD-0560, BMS-345541, PS-1145, SC-514, ACHP, Bay 65 – 1942, AS602868 and others, have been reported. However, direct comparison of the effects among the compounds on the same diseases has yet to be elucidated. For example, we have revealed that the IKK inhibitor IMD-0354 had significant effects when used to treat myocardial ischemia, pulmonary fibrosis, bronchial asthma, atopic dermatitis and breast cancer. However, while other IKK inhibitors demonstrated significant effects on liver, colon and neurological disorders, we have not yet elucidated the IMD-0354 effect. On the other hand, other synthesized IKK inhibitors (AS602868 and NDB peptides) have yet to be examined on cardiovascular diseases. Thus, we should perform further comparative analysis to validate the effects using the same experimental disease models.

Further, we have not yet compared the effects between the novel compounds and conservative products such as corticosteroids and NSAIDs. Corticosteroids are known to be potent anti-inflammatory agents and suppressors of cytokine production. The anti-inflammatory effects of corticosteroids are mediated through inhibition of NF-κB activation. Although corticosteroids have not proven to be beneficial in clinical studies on patients with some diseases, specific inhibition of IKK may have superior effects on these diseases compared to corticosteroids. Aspirin is one of the most commonly used NSAIDs because of its ability to inhibit COX activity. It has been reported that NF-κB activation and its associated gene expressions were suppressed by the aspirin supplementation through the inhibition of phosphorylation and degradation of IκBα via the IKK pathway. Although corticosteroids and NSAIDs are known to have adverse effects, they have been broadly used in clinical settings for a long time. Because we need specific IKK inhibitors without detrimental effects in clinical settings, we have to clarify the superior effects of the new compounds in comparison to the other conservative compounds, including corticosteroids and NSAIDs.

Finally, we have to evaluate the adverse effects of the new compounds. Although the deletion of the gene encoding IKK-β in the cells resulted in a marked increase of carcinogenesis, there has been no report to demonstrate the adverse results by IKK inhibitors *in vivo*. Because the carcinogenesis should be evaluated using several factors, such as tumor number, size, growth rate, invasion to other tissues and remote metastasis, the IKK inhibitory effects against malignant diseases should be evaluated using several experimental models. It was also reported that IKK inhibition increased local tissue injury following intestinal ischemia reperfusion. However, there has been no report to demonstrate similar results of ischemia reperfusion injury in other solid organ systems. These adverse effects show the complexity of the IKK system, which is responsible for both local and systemic immunity. Therefore, further investigation is needed to expand the strategy of specific IKK inhibition for clinical applications.

Declaration of interest

The authors declare no conflict of interest and have received no payment in preparation of this manuscript.

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Bibliography

1. Ghosh S, Hayden MS. New regulators of NF-kappaB in inflammation. Nat Rev Immunol 2008;8:837-4
2. Karin M, Greten FR. NF-kappaB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 2005;5:749-59
3. Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-kappaB activity. Annu Rev Immunol 2000;18:621-63
4. Bollrath J, Greten FR. IKK/NF-kappaB and STAT3 pathways: central signalling hubs in inflammation-mediated tumour promotion and metastasis. EMBO Rep 2009;10:1314-19
5. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol 2009;1:a000034
6. Ghosh S, Karin M. Missing pieces in the NF-kappaB puzzle. Cell 2002;109:S81-96
7. Gerondakis S, Grossmann M, Nakamura Y, et al. Genetic approaches in mice to understand Rel/NF-kappaB and IkappaB function: transgenics and knockouts. Oncogene 1999;18:6888-95
8. Caamano J, Hunter CA. NF-kappaB family of transcription factors: central regulators of innate and adaptive immune functions. Clin Microbiol Rev 2002;15:414-29
9. Onai Y, Suzuki J, Kakuta T, et al. Inhibition of IkappaB phosphorylation in cardiomyocytes attenuates myocardial ischemia/reperfusion injury. Cardiovasc Res 2004;63:51-9
10. Onai Y, Suzuki J, Maejima Y, et al. Inhibition of NF-kappaB improves left ventricular remodeling and cardiac dysfunction after myocardial infarction. Am J Physiol Heart Circ Physiol 2007;292:H530-8
11. Wakatsuki S, Suzuki J, Ogawa M, et al. A novel IKK inhibitor suppresses heart failure and chronic remodeling after myocardial ischemia via MMP alteration. Expert Opin Ther Targets 2008;12:1469-76
12. Okazaki Y, Sawada T, Nagatani K, et al. Effect of nuclear factor-kappaB inhibition on rheumatoid fibroblast-like synoviocytes and collagen induced arthritis. J Rheumatol 2005;32:1440-7
13. Burke JR, Pattoli MA, Gregor KR, et al. BMS-345541 is a highly selective inhibitor of IkappaB kinase that binds at an allosteric site of the enzyme and blocks NF-kappaB-dependent transcription in mice. J Biol Chem 2003;278:1450-6
14. Hideshima T, Hayashi T, Chauhan D, et al. Biologic sequelae of c-Jun NH(2)-terminal kinase (JNK) activation in multiple myeloma cell lines. Oncogene 2003;22:8797-801
15. Castro AC, Dang LC, Soucy F, et al. Novel IKK inhibitors: beta-carbolines. Bioorg Med Chem Lett 2003;13:2419-22
16. Lam LT, Davis RE, Pierce J, et al. Small molecule inhibitors of IkappaB kinase are selectively toxic for subgroups of diffuse large B-cell lymphoma defined by gene expression profiling. Clin Cancer Res 2005;12:28-40
17. Kishore N, Sommers C, Mathialagan S, et al. A selective IKK-2 inhibitor blocks NF-kappaB-dependent gene expression in interleukin-1 beta-stimulated synovial fibroblasts. J Biol Chem 2003;278:32861-71
18. Murata T, Shimada M, Sakakibara S, et al. Discovery of novel and selective IKK-beta serine-threonine protein kinase inhibitors. Part 1. Bioorg Med Chem Lett 2003;13:913-18
19. Murata T, Shimada M, Sakakibara S, et al. Synthesis and structure-activity relationships of novel IKK-beta inhibitors. Part 3: orally active anti-inflammatory agents. Bioorg Med Chem Lett 2004;14:4019-22
20. Ziegelbauer K, Gantner F, Lukacs NW, et al. A selective novel low-molecular-weight inhibitor of IkappaB kinase-beta (IKK-beta) prevents pulmonary inflammation and shows broad anti-inflammatory activity. Br J Pharmacol 2005;145:178-92
21. Frelin C, Imbert V, Griessinger E, et al. AS602868, a pharmacological inhibitor of IKK2, reveals the apoptotic potential of TNF-alpha in Jurkat leukemic cells. Oncogene 2003;22:8187-94
22. May MJ, D'Acquisto F, Madge LA, et al. Selective inhibition of NF-kappaB activation by a peptide that blocks the interaction of NEMO with the IkappaB kinase complex. Science 2000;289:1550-4
23. Baima ET, Guzova JA, Mathialagan S, et al. Novel insights into the cellular mechanisms of the anti-inflammatory effects of NF-kappaB essential modulator binding domain peptides. J Biol Chem 2010;285:13498-506
24. Pan MH, Lin-Shiau SY, Ho CT, et al. Suppression of lipopolysaccharide-induced nuclear factor-kappaB activity by theaflavin-3,3′-digallate from black tea and other polyphenols through down-regulation of IkappaB kinase activity in macrophages. Biochem Pharmacol 2000;59:357-67
25. Yang F, Oz HS, Barve S, et al. The green tea polyphenol (-)-epigallocatechin-3-gallate blocks nuclear factor-kappaB activation by inhibiting IkappaB kinase activity in the intestinal epithelial cell line IEC-6. Mol Pharmacol 2001;60:528-33
26. Morishita R, Sugimoto T, Aoki M, et al. In vivo transfection of cis element 'decoy' against nuclear factor-kappaB binding site prevents myocardial infarction. Nat Med 1997;3:894-9
27. Townsend RM, Postelnek J, Susulic V, et al. A highly selective inhibitor of IkappaB kinase, BMS-345541, augments graft survival mediated by suboptimal immunosuppression in a murine model of cardiac graft rejection. Transplantation 2004;77:1090-4
28. Gomez AB, MacKenzie C, Paul A, et al. Selective inhibition of inhibitory kappaB kinase-beta abrogates induction of nitric oxide synthase in lipopolysaccharide-stimulated rat aortic smooth muscle cells. Br J Pharmacol 2005;146:217-25
29. Kishore N, Sommers C, Mathialagan S, et al. A selective IKK-2 inhibitor blocks NF-kappaB-dependent gene expression in interleukin-1 beta-stimulated synovial fibroblasts. J Biol Chem 2003;278:32861-71
30. Moss NC, Stansfield WE, Willis MS, et al. IKKbeta inhibition attenuates myocardial injury and dysfunction following acute ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 2007;293:H2248-53

RIGHTSLINK

31. Suzuki J, Ogawa M, Sagesaka YM, et al. Tea catechins attenuate ventricular remodeling and graft arterial diseases in murine cardiac allografts. Cardiovasc Res 2006;69:272-9

32. Suzuki J, Ogawa M, Futamatsu H, et al. Tea catechins improve left ventricular dysfunction, suppress myocardial inflammation, fibrosis, and alter cytokine expression in rat autoimmune myocarditis. Eur J Heart Fail 2007;9:152-9

33. Suzuki J, Ogawa M, Maejima Y, et al. Tea catechins attenuate chronic ventricular remodeling after myocardial ischemia in rats. J Mol Cell Cardiol 2007;42:432-40

34. Suzuki J, Ogawa M, Izawa A, et al. Dietary consumption of green tea catechins attenuate hyperlipidemia-induced atherosclerosis and systemic organ damage in mice. Acta Cardiologica 2005;60:271-6

35. Matsuda N, Hattori Y, Jesmin S, et al. Nuclear factor-kappaB decoy oligodeoxynucleotides prevent acute lung injury in mice with cecal ligation and puncture-induced sepsis. Mol Pharmacol 2005;67:1018-25

36. Inayama M, Nishioka Y, Azuma M, et al. A novel IkappaB kinase-beta inhibitor ameliorates bleomycin-induced pulmonary fibrosis in mice. Am J Respir Crit Care Med 2006;173:1016-22

37. Everhart MB, Han W, Sherrill TP, et al. Duration and intensity of NF-kappaB activity determine the severity of endotoxin-induced acute lung injury. J Immunol 2006;176:4995-5005

38. Catley MC, Sukkar MB, Chung KF, et al. Validation of the anti-inflammatory properties of small-molecule IkappaB Kinase (IKK)-2 inhibitors by comparison with adenoviral-mediated delivery of dominant-negative IKK1 and IKK2 in human airways smooth muscle. Mol Pharmacol 2006;70:697-705

39. Newton R, Holden NS, Catley MC, et al. Repression of inflammatory gene expression in human pulmonary epithelial cells by small-molecule IkappaB kinase inhibitors. J Pharmacol Exp Ther 2007;321:734-42

40. Chapoval SP, Al-Garawi A, Lora JM, et al. Inhibition of NF-kappaB activation reduces the tissue effects of transgenic IL-13. J Immunol 2007;179:7030-41

41. Tomita T, Takeuchi E, Tomita N, et al. Suppressed severity of collagen-induced arthritis by in vivo transfection of nuclear factor kappaB decoy oligodeoxynucleotides as a gene therapy. Arthritis Rheum 1999;42:2532-42

42. McIntyre KW, Shuster DJ, Gillooly KM, et al. A highly selective inhibitor of IkappaB kinase, BMS-345541, blocks both joint inflammation and destruction in collagen-induced arthritis in mice. Arthritis Rheum 2003;48:2652-9

43. Pattoli MA, MacMaster JF, Gregor KR, et al. Collagen and aggrecan degradation is blocked in interleukin-1-treated cartilage explants by an inhibitor of IkappaB kinase through suppression of metalloproteinase expression. J Pharmacol Exp Ther 2005;315:382-8

44. Jimi E, Aoki K, Saito H, et al. Selective inhibition of NF-kappaB blocks osteoclastogenesis and prevents inflammatory bone destruction in vivo. Nat Med 2004;10:617-24

45. Desmet C, Gosset P, Pajak B, et al. Selective blockade of NF-kappaB activity in airway immune cells inhibits the effector phase of experimental asthma. J Immunol 2004;173:5766-75

46. Sugita A, Ogawa H, Azuma M, et al. Antiallergic and anti-inflammatory effects of a novel IkappaB kinase beta inhibitor, IMD-0354, in a mouse model of allergic inflammation. Int Arch Allergy Immunol 2008;148:186-98

47. Keslacy S, Tliba O, Baidouri H, et al. Inhibition of tumor necrosis factor-alpha-inducible inflammatory genes by interferon-gamma is associated with altered nuclear factor-kappaB transactivation and enhanced histone deacetylase activity. Mol Pharmacol 2007;71:609-18

48. Goto K, Chiba Y, Misawa M. IL-13 induces translocation of NF-kappaB in cultured human bronchial smooth muscle cells. Cytokine 2009;46:96-9

49. Ziegelbauer K, Gantner F, Lukacs NW, et al. A selective novel low-molecular-weight inhibitor of IkappaB kinase-beta (IKK-beta) prevents pulmonary inflammation and shows broad anti-inflammatory activity. Br J Pharmacol 2005;145:178-92

50. Nakamura H, Aoki M, Tamai K, et al. Prevention and regression of atopic dermatitis by ointment containing NF-kB decoy oligodeoxynucleotides in NC/Nga atopic mouse model. Gene Ther 2002;9:1221-9

51. Tanaka A, Muto S, Jung K, et al. Topical application with a new NF-kappaB inhibitor improves atopic dermatitis in NC/NgaTnd mice. J Invest Dermatol 2007;127:855-63

52. di Meglio P, Ianaro A, Ghosh S. Amelioration of acute inflammation by systemic administration of a cell-permeable peptide inhibitor of NF-kappaB activation. Arthritis Rheum 2005;52:951-8

53. Tanaka A, Muto S, Konno M, et al. A new IkappaB kinase beta inhibitor prevents human breast cancer progression through negative regulation of cell cycle transition. Cancer Res 2006;66:419-26

54. Tanaka A, Konno M, Muto S, et al. A novel NF-kappaB inhibitor, IMD-0354, suppresses neoplastic proliferation of human mast cells with constitutively activated c-kit receptors. Blood 2005;105:2324-31

55. Kawamura I, Morishita R, Tsujimoto S, et al. Intravenous injection of oligodeoxynucleotides to the NF-kappaB binding site inhibits hepatic metastasis of M5076 reticulosarcoma in mice. Gene Ther 2001;8:905-12

56. Yang J, Amiri KI, Burke JR, et al. BMS-345541 targets inhibitor of kappaB kinase and induces apoptosis in melanoma: involvement of nuclear factor kappaB and mitochondria pathways. Clin Cancer Res 2006;12:950-60

57. Roue G, Perez-Galan P, Lopez-Guerra M, et al. Selective inhibition of IkappaB kinase sensitizes mantle cell lymphoma B cells to TRAIL by decreasing cellular FLIP level. J Immunol 2007;178:1923-30

58. Ammann JU, Haag C, Kasperczyk H, et al. Sensitization of neuroblastoma cells for TRAIL-induced apoptosis by NF-kappaB inhibition. Int J Cancer 2009;124:1301-11

59. Katdare M, Efimova EV, Labay E, et al. Diverse TNFalpha-induced death pathways are enhanced by inhibition of NF-kappaB. Int J Oncol 2007;31:1519-28

60. Hideshima T, Chauhan D, Richardson P, et al. NF-kappaB as a therapeutic target in multiple myeloma. J Biol Chem 2002;277:16639-47

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61. Hideshima T, Hayashi T, Chauhan D, et al. Biologic sequelae of c-Jun NH(2)-terminal kinase (JNK) activation in multiple myeloma cell lines. Oncogene 2003;22:8797-801

62. Akiyama M, Hideshima T, Hayashi T, et al. Cytokines modulate telomerase activity in a human multiple myeloma cell line. Cancer Res 2002;62:3876-82

63. Tai YT, Podar K, Mitsiades N, et al. CD40 induces human multiple myeloma cell migration via phosphatidylinositol 3-kinase/AKT/NF-kappaB signaling. Blood 2003;101:2762-9

64. Roychowdhury S, Baiocchi RA, Vourganti S, et al. Selective efficacy of depsipeptide in a xenograft model of Epstein-Barr virus-positive lymphoproliferative disorder. J Natl Cancer Inst 2004;96:1447-57

65. Lam LT, Davis RE, Pierce J, et al. Small molecule inhibitors of IkappaB kinase are selectively toxic for subgroups of diffuse large B-cell lymphoma defined by gene expression profiling. Clin Cancer Res 2005;11:28-40

66. Yemelyanov A, Gasparian A, Lindholm P, et al. Effects of IKK inhibitor PS1145 on NF-kappaB function, proliferation, apoptosis and invasion activity in prostate carcinoma cells. Oncogene 2006;25:387-98

67. Domingo-Domenech J, Oliva C, Rovira A, et al. Interleukin 6, a nuclear factor-kappaB target, predicts resistance to docetaxel in hormone-independent prostate cancer and nuclear factor-kappaB inhibition by PS-1145 enhances docetaxel antitumor activity. Clin Cancer Res 2006;12:5578-86

68. Khanbolooki S, Nawrocki ST, Arumugam T, et al. Nuclear factor-kappaB maintains TRAIL resistance in human pancreatic cancer cells. Mol Cancer Ther 2006;5:2251-60

69. Singh S, Shi Q, Bailey ST, et al. Nuclear factor-kappaB activation: a molecular therapeutic target for estrogen receptor-negative and epidermal growth factor receptor family receptor-positive human breast cancer. Mol Cancer Ther 2007;6:1973-82

70. Duncan EA, Goetz CA, Stein SJ, et al. IkappaB kinase beta inhibition induces cell death in Imatinib-resistant and T315I Dasatinib-resistant BCR-ABL+ cells. Mol Cancer Ther 2008;7:391-7

71. Lounnas N, Frelin C, Gonthier N, et al. NF-kappaB inhibition triggers death of imatinib-sensitive and imatinib-resistant chronic myeloid leukemia cells including T315I Bcr-Abl mutants. Int J Cancer 2009;125:308-17

72. Choo MK, Sakurai H, Kim DH, et al. A ginseng saponin metabolite suppresses tumor necrosis factor-alpha-promoted metastasis by suppressing nuclear factor-kappaB signaling in murine colon cancer cells. Oncol Rep 2008;19:595-600

73. Sanda T, Iida S, Ogura H, et al. Growth inhibition of multiple myeloma cells by a novel IkappaB kinase inhibitor. Clin Cancer Res 2005;11:1974-82

74. Sanda T, Asamitsu K, Ogura H, et al. Induction of cell death in adult T-cell leukemia cells by a novel IkappaB kinase inhibitor. Leukemia 2006;20:590-8

75. Bednarski BK, Ding X, Coombe K, et al. Active roles for inhibitory kappaB kinases alpha and beta in nuclear factor-kappaB-mediated chemoresistance to doxorubicin. Mol Cancer Ther 2008;7:1827-35

76. Ogushi I, Iimuro Y, Seki E, et al. Nuclear factor kappaB decoy oligodeoxynucleotides prevent endotoxin-induced fatal liver failure in a murine model. Hepatology 2003;38:335-44

77. Beraza N, Malato Y, Vander Borght S, et al. Pharmacological IKK2 inhibition blocks liver steatosis and initiation of non-alcoholic steatohepatitis. Gut 2008;57:655-63

78. Dasgupta S, Jana M, Zhou Y, et al. Antineuroinflammatory effect of NF-kappaB essential modifier-binding domain peptides in the adoptive transfer model of experimental allergic encephalomyelitis. J Immunol 2004;173:1344-54

79. Acharyya S, Villalta SA, Bakkar N, et al. Interplay of IKK/NF-kappaB signaling in macrophages and myofibers promotes muscle degeneration in Duchenne muscular dystrophy. J Clin Invest 2007;117:889-901

80. Puel A, Picard C, Ku CL, et al. Inherited disorders of NF-kappaB-mediated immunity in man. Curr Opin Immunol 2004;16:34-41

81. Maeda S, Kamata H, Luo JL, et al. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell 2005;121:977-90

82. Chen LW, Egan L, Li ZW, et al. The two faces of IKK and NF-kappaB inhibition: prevention of systemic inflammation but increased local injury following intestinal ischemia-reperfusion. Nat Med 2003;9:575-81

83. Fukuda S, Horimai C, Harada K, et al. Aldosterone-induced kidney injury is mediated by NF-kappaB activation. Clin Exp Nephrol. 2010. [Epub ahead of print]

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研究

マルファン症候群では歯周病は極めて高頻度に認められる

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研究

マルファン症候群では歯周病は極めて高頻度に認められる*

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要旨　マルファン症候群は，骨格異常，眼異常，心血管異常など多くの器官に病変を引き起こす常染色体優性遺伝の全身性結合組織疾患である．以前より口腔内所見として，高口蓋，歯列不正などが知られている．近年，諸外国においてマルファン症候群と歯周病との関係が注目されてきており，日本人におけるマルファン症候群の実態調査としてGhent基準陽性20名のマルファン症候群症例につき歯周病罹患状態を評価した．現在歯数は27歯とほぼ保たれていたが，歯周ポケットの深さ(PD)は2.815±0.624 mm，PD測定部位での出血の有無(BOP)は11.567±8.394%，地域歯周疾患指数(CPI)は中等度・重度に該当するコード3，4の症例が15名(75%)も認められた．以上よりマルファン症候群では，中等度から重度の歯周病が高頻度に認められマルファン症候群における歯周組織の脆弱性が示唆された．

キーワード　マルファン症候群，歯周病，地域歯周疾患指数(CPI)

マルファン症候群は，1896年にパリの小児科医Antoine Marfanにより初めて報告された常染色体優性遺伝性の疾患である[1]．全身において骨格異常，眼異常，心血管異常など多くの器官に病変を引き起こし，また，口腔においては高口蓋，歯列不正，歯の形態異常などがみられることが知られている[2,3]．今日その診断には，Ghentの基準[4]を採用することが一般的であり，骨格異常や眼異常，心血管異常といった多彩な病態の表現型ごとに設定された大基準と小基準および家族歴や遺伝的要素を加味したものとなっている．

近年，諸外国においてマルファン症候群と歯周病との関係が注目されている[5]．以前より国内ではマルファン症候群を有する顎変形症症例に対する外科処置の報告は散見されるものの，マルファン症候群の口腔内所見に関する報告は少なく，また骨格系に関する表現型は同じマルファン症候群であっても欧米人と日本人では相違点が少なくないことが知られている[6]．そこで，今回マルファン症候群の口腔内の状態を把握する目的で歯周病罹患状態を調査し，またマルファン症候群の表現型と歯周病所見との関係にも注目し検討したので，文献的考察を加えて報告する．

対象と方法

東京大学マルファン症候群専門外来を受診し，Ghent基準においてマルファン症候群と診断された症例で，本研究の主旨に同意が得られた患者20名(男性11名，女性9名，平均年齢35.7歳)を対象とした．

患者には事前に研究の目的を十分に説明し，同意を書面で確認後，口腔内診査を行った．本研究は，東京大学医学部研究倫理審査委員会で承認を得た．

1. 歯周組織の評価

各対象者について現在歯数をはじめ以下の項目について歯周組織検査を実施した．

1) Probing Depth (PD)

歯周病の現在の進行度を表すため歯周ポケットの深さを測定した．カラーコードポケット探針(PCP-11，Hu-Friedy社製)を用い，約20 g前後の力で1点法にて測定した．被験者の1歯あたりの平均値をmm単位で算出した．

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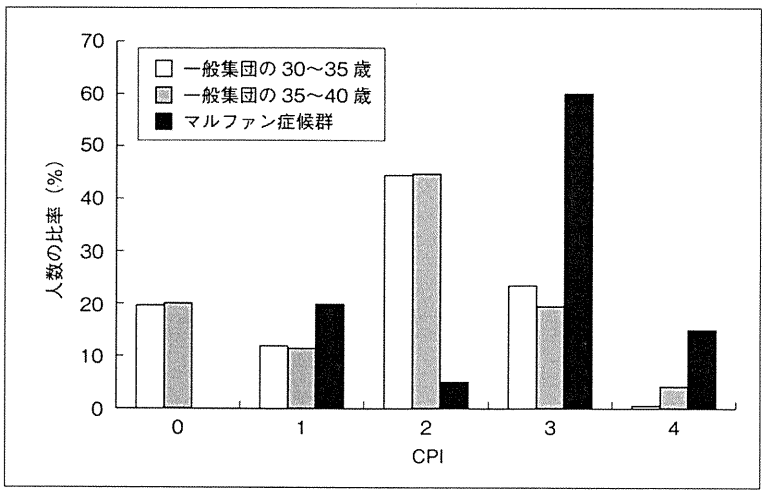

図1 本研究対象者と同年代男性および女性との間でのCPIの比較

2) Bleeding on Probing (BOP)

歯周ポケット内の現在の炎症を調べるためPD測定部位での出血の有無を測定し，被験者の全被験歯に対する検出率(%)を算出した．

3) 歯の動揺度

Millerら[7]の方法により0度～3度の4段階で測定し全被験歯に対する平均値を算出した．

4) Community Periodontal Index (CPI)

1982年にAinamoら[8]がWHOの提案として発表した地域歯周疾患指数CPIにて歯周組織の評価を行った．口腔内を6群に分割し，それぞれの分画の代表歯を被験歯として評価した．

2. マルファン症候群の表現型と歯周病所見との関連性

マルファン症候群の診断基準であるGhent基準の各臓器所見，すなわち骨格系，眼，心血管系，肺，皮膚，硬膜のどの表現型，あるいは表現型の合計数と歯周病罹患状態との間に相関があるか否かを検証した．

3. 統計解析

統計処理は，一元配置分散分析を用いた(SPSS11.0 J for Windows. SPSS Japan. 東京)．特に指示がなければp値が0.05未満のものを有意とし，全体として有意差を認めたものはpost hoc解析を追加した．

結　果

1. 歯周病所見

20名の現在歯数の平均は27歯であった．PDは2.815±0.624 mm，BOPは11.567±8.394%，動揺度はすべての症例において0であった．さらにCPI codeは，CPI code0の者が0名，code1もしくはcode2の者(歯肉炎)5名(25%)，code3の者(軽～中等度歯周炎)が12名(60%)，code4の者(中～重度歯周炎)が3名(15%)であった．すなわち4 mm以上の歯周ポケットを有する者(CPI＝3または4の者)は15名(75%)と非常に高頻度であった(CPI 2.70±0.98)(**図1**)．

このことは平成17年歯科疾患実態調査による報告における30～35歳(CPI：1.73±1.05)，35～40歳(CPI：1.76±1.09)の年齢層(本研究の対象集団の平均年齢は35歳)と比較して統計的に明らかな有意差をもってCPIが高値を示している．一元配置分散分析にて3群を比較するとp値＝0.001，post hoc解析(Scheffe法)にてわれわれの症例と30～35歳，35～40歳の一般集団と比較して$p<0.001$と有意にCPIの値が高値であることが示された．

2. 表現型

20名にみられた表現型は心血管系が20名(100%)と全症例に認められた．次いで皮膚が12名(60%)，眼が11名(55%)となった(**表1**)．

3. 表現型と歯周病所見との関係

表現型の数とPDの比較を行った結果，表現型3つではPDが2.808 mm，表現型4つではPDが2.819 mm，表現型5つではPDが2.822 mmと表現型が多くなるにつれてPDは深くなる傾向であったが，両者の間に有意差は認めなかった．さらに表現型の数とBOPの比較を行った結果，表現型3つではBOPが12.81%，表現型4つではBOPが10.98%，表現型5つではBOPが10.23%と表現型とBOPの間に有意な差はみられなかった．

考　察

マルファン症候群は5,000人～10,000人に1人の確率で発症するといわれている[9]．特徴的な表現型として，クモ状指，側弯症，後弯症，胸郭変形，バルサルバ洞を含め大動脈弁逆流，大動脈解離，水晶体亜脱臼，硬膜拡張などが挙げられる．本症例でもバルサルバ洞を含む上行大動脈の拡大は全症例においてみられた．また約半分に眼症状がみられた．

治療にあたってはβ遮断薬，アンジオテンシンⅡ受容体拮抗薬による血圧のコントロール，運動制限，妊娠出産時の厳格な管理，大動脈径の定期的な評価と人工血管置換術などが挙げられる．このように多臓器に表現型を呈する全身疾患であり，集学的な検査および治療体制が必要とされる．そのため当院では，診療科の枠を越えて循環器内科，心臓外科，小児科，整形外科，眼科，放射線科，臨床ゲノム情報部・診療部がチーム体制を作り，マルファン症候群専門外来を開設して対応している[10]．

歯科的な特徴として，下顎後退症，高口蓋，口蓋垂裂，口蓋正中部の偏位，舌の奇形，歯列不正，歯の先天欠如，形態異常や形成不全などが挙げられる．

近年，マルファン症候群に有意に歯周病罹患率が高いことが指摘されている[5]．しかしマルファン症候群の口腔内所見の報告は少なく，特に国内において歯周病罹患状態に関した報告は皆無に近いのが現状である．今回の結果，本症例ではPDが4 mm以上の部位を有する者(CPI＝3または4の者)は15例(75%)であった．これは平成17年歯科疾患実態調査[11]によると35～39歳で23.7%であり，全国調査に比較して非常に高いことが明らかになった．また，今回の結果ではCPIの最も多い値はCPIが3であったのに対し，平成17年歯科疾患実態調査によるとCPI2が最も多く，マルファン症候群は歯周炎が重度の傾向を示した．このように高頻度に認められる歯周病は，あわせて存在する心臓弁膜疾患(大動脈弁閉鎖不全，僧帽弁逸脱症など)において口腔内細菌を起因菌とする感染性心内膜炎の発症母地となり得るとともに，最近ではこのような口腔内の慢性炎症によって大動脈解離や拡大といった血管病変の進行に寄与する可能性も十分に考えられる．

マルファン症候群の原因として1991年に15q21.1に座位を有する*FBN1*遺伝子が発見された[12,13]．その後2004年には*TGFBR2*遺伝子[14]，さらには*TGFBR1*が新たにマルファン症候群の原因遺伝子として特定され，最近ではフィブリリン異常とTGF-βシグナルとの関連性がマルファン症候群の病態生理に重要であることが明らかになりつつある．*FBN1*遺伝子は全身の結合組織の構成要素となる主要蛋白のフィブリリンをコードする．フィブリリンは歯周組織の歯根膜にも存在する．歯周組織は歯の支持組織で，セメント質，歯根膜，歯槽骨，歯肉の一部によって構成されている．特に歯根膜は特殊化した線維性結合組織であり，フィブリリンを主成分とする微細線維が集まって構成されたオキシタラン線維から成る．オキシタラン線維は歯根膜以外にも血管外膜，神経上皮，神経周膜，腱などほとんどの結合組織に存在する．歯根膜でのオキシタラン線維は，歯根を歯軸方向に三次元的に囲み，しばしば血管やリンパ管の複合体に終わるか近接している．機能は脈管周囲や圧力のかかる部分に分布していることから，脈管の機械的支持と血流調整作用が考えられている．また，歯の萌出方向をガイドしているという報告もある[15]．よってフィブリリンの異常は，オキシタラン線維の正常な働きを阻害する．すなわち，*FBN1*遺伝子の異常は歯根膜の機能異常を来している可能性があり，マルファン症候群における歯周病の重症度と関係があるかもしれない．また，*TGFBR1*および*2*遺伝子は*TGF-βI*またはⅡ型受容体をコードしており，この異常は結合組織の脆弱性を引き起こすといわれているが，歯周組織との関連性は不明である．

表1　本症例における各表現型

	大基準	小基準	合計
骨格系症状	3例	2例	5例（25%）
眼症状	11例	0	11例（55%）
心血管系症状	19例	1例	20例(100%)
肺症状	—	4例	4例（20%）
皮膚症状	—	12例	12例（60%）
硬膜拡張	8例	—	8例（40%）

マルファン症候群の表現型である眼症状や心血管系異常と歯周病との関連に関する報告は検索する限りではみられず，本研究でも明確な示唆は得られなかったが，今後さらに症例を重ねることで他臓器の表現型との関連性について検証が可能と考える．

マルファン症候群は突然死の恐れのある予後不良な病気と認識されていたが，最近の治療成績の向上およびマルファン症候群の早期診断により予後は改善している．これは一方ではマルファン症候群の長期生存を意味し，今後ますますこれらの患者が歯科を受診する機会が増加することが予想される．よってマルファン症候群の口腔症状を理解し，歯周病のマネージメントを行うことは患者のQOLの維持の点からも急務であ

る．

結　語

本研究から，マルファン症候群の患者は中等度から重度の歯周病に罹患している確率が非常に高く，歯周組織の脆弱性が示唆された．

文　献

1) Marfan AB: A case of congenital deformation of the four limbs-especially fingers and toes-characterized by long bones (in French). Bull Mem Soc Med Hop Paris 13: 220-226, 1986
2) Beighton P, De Paepe A, Danks D, et al: International nosology of heritable disorders of connective tissue. Am J Med Genet 29: 581-594, 1988
3) De Coster PJA, Martens LCM, De Paepe A: Oral manifestations of patients with Marfan syndrome: a case-control study. Oral Med Oral Pathol Oral Radiol Endod 93: 564-572, 2002
4) De Paepe A, Devereux RB, Dietz HC, et al: Revised diagnostic criteria for the Marfan syndrome. Am J Med Genetics 62: 417-426, 1996
5) Straub AM, Grahame R, Scully C, Tonetti MS: Severe periodontitis in Marfan's syndrome: a case report. J Periodontol 73: 823-826, 2002
6) Akutsu K, Morisaki H, Takeshita S, et al: Characteristics in phenotypic manifestations of genetically proved Marfan syndrome in a Japanease population. Am J Cardiol 103: 1146-1148, 2009
7) Miller SC: Textbook of Periodontia. 3rd ed. Blakiston Co Inc, Philadelphia, pp 125-212, 1950
8) Ainamo J, Barmes D, Beagrie G, et al: Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). Int Dent J 32: 281-291, 1982
9) Gray JR: Ascertainment and severity of Marfan syndrome in Scottish population. J Med Genet 31: 51-54, 1994
10) 今井　靖，小川直美，西村敬史，他：東京大学医学部附属病院におけるマルファン症候群専門外来：包括的な診療体制の実践　呼と循 57: 1099-1103, 2009
11) 歯科疾患実態調査報告解析検討委員会編：平成17年歯科疾患実態調査．口腔保健協会，東京，2007
12) Lee B, Godfrey M, Vitale E, et al: Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes. Nature 352: 330-334, 1991
13) Dietz HC, Cutting G, Pyeritz R, et al: Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature 352: 337-339, 1991
14) Mizuguchi T, Collod-Beroud G, Akiyama T, et al: Heterozugous TGFBR2 mutations in Marfan syndrome. Nat Genet 004: 36: 855-860
15) 矢嶋俊彦，敦賀英知，入江一元：歯周組織の弾性線維．日歯周誌 46：175-184, 2004

Summary

The High Prevalence of Periodontitis in Patients with Marfan Syndrome

by

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Marfan syndrome is a connective tissue disorder with autosomal dominant inheritance.

The disease affects mainly the skeletal, cardiovascular, and ocular systems. Patients with this syndrome often demonstrate oral and maxillofacial manifestations including highly arched palate with crowding of teeth. In order to evaluate the clinical characteristics in Japanese Marfan syndrome patients, we evaluated the periodontal status of those patients who were diagnosed as Marfan syndrome according to the Ghent nosology (n=20). The results showed that the number of teeth present was 27. Probing pocket depth were 2.815±0.624 mm, bleeding on probing 11.567±8.394%, and percentages of CPI (community periodontal index) codes 3 or 4 75%. Our results demonstrate the significantly high prevalence of severe periodontitis in patients with Marfan syndrome. The connective tissue disorder in Marfan syndrome may also increase susceptibitity to inflammatory breakdown of periodontal tissue.

Key words　Marfan syndrome, periodontitis, CPI

Expert Opinion

informa
healthcare

Periodontitis and cardiovascular diseases

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Periodontitis is characterized by gingival inflammation and periodontopathic bacteria generate immunological inflammatory responses. Recent epidemiological reports suggest that periodontitis is one of the key risk factors for the onset of cardiovascular diseases. Several studies reported that periodontal bacteria in cardiovascular specimens were frequently detected. We revealed that patients with acute coronary syndrome showed significantly higher serum IgG titers to a strain of periodontopathic bacteria compared with patients with chronic coronary disease. Periodontopathic bacteria were also present in a high percentage of specimens of diseased arteries from patients with Buerger disease or abdominal aortic aneurysm. Although periodontopathic bacteria may play a role in the development of cardiovascular diseases, the influence of these bacteria on the disease has not yet been proven. In this article, we review the relationship between periodontopathic pathogens and cardiovascular diseases to conduct further clinical and experimental investigations in near future.

Keywords: aorta, bacteria, cytokine, inflammation, periodontitis

Expert Opin. Ther. Targets [Early Online]

1. Introduction

Periodontitis is a chronic inflammatory disease that degrades the attachment apparatus of the teeth, leading to tooth loosening. Clinical signs of the disease are often seen in middle age and it is a very common disease in adults [1,2]. Epidemiological studies showed that periodontitis significantly increased the risk of cardiovascular disease (CVD) [3-6]. Although data was adjusted for known CVD risk factors such as smoking, diabetes, hypertension and socioeconomic conditions, other points might still explain the apparent association. Levels of risk markers for CVD have been reported to be elevated in patients with periodontitis. Furthermore, animal studies demonstrated an association between the prevalence of periodontal pathogens, bacterial products, periodontitis and the incidence of CVD-related events [7,8]. Although DNA from oral bacteria has been found in atherosclerotic plaque in animal experimental models [9] and humans [10], the contribution of these bacteria to plaque formation remains unknown. Periodontal pathogens and their products were reported to be a trigger of the atherosclerotic process in animal studies [7,8]. However, their effects in the human system remain unclear. The release of host-derived inflammatory mediators, such as cytokines from the chronically inflamed periodontal tissues into the circulation, may provide a link between periodontal disease and CVD [11,12]. Altered serological profiles of risk markers in patients with periodontitis may result from an invasion of bacteria. Additionally, entry of their products from the periodontal lesion into the blood stream and the consequential induction and maintenance of a chronic inflammatory state also contribute to the progression of CVD.

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In this small article, we review pathological and immunological influence of periodontal pathogens to CVD and some promising methodologies for prevention of the disease.

2. Coronary arterial disease and periodontitis

Recent studies suggest that chronic inflammation plays an important role in the development of coronary arterial disease (CAD). Because periodontal disease is an enhancer of several chronic inflammatory factors such as MMPs [13-15], an etiological relationship between periodontal disease and CAD was proposed. For these reasons, there is strong interest in evaluating whether periodontal disease is independently associated with CAD [16-18]. Humphrey *et al.* revealed that periodontal disease is associated with increased risk of CAD using a meta-analysis [19]. They concluded that periodontal disease is a risk factor or marker for CAD, and is independent of traditional CAD risk factors. Nakajima *et al.* also revealed that periodontitis is associated with increased risk of CAD through dysfunction of endothelial cells, induced by either periodontopathic bacteria or their products [20]. CRP concentrations were higher among patients who subsequently developed myocardial infarction compared with those without the disease. However, there was no report to elucidate the relationship between specific gingival bacteria infection and CAD.

We recently revealed that there is an association between periodontitis and CAD, particularly acute coronary syndrome (ACS). A total of 28 CAD patients participated in the study. Coronary angiography, periodontal examination and dental radiography were performed in all patients. Subgingival plaque, saliva and blood samples were analyzed for the periodontopathogens *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Prevotella intermedia* using PCR. Specific serum antibody titers to the five periodontal pathogens were determined by ELISA. We found that 33% of the ACS patients harbored *A. actinomycetemcomitans* in oral samples, whereas no *A. actinomycetemcomitans* was found in the patients with chronic CAD. Furthermore, ACS patients showed significantly higher serum IgG titers to *A. actinomycetemcomitans* compared with chronic CAD patients. Thus, we concluded that a specific periodontal pathogens may play a crucial role in the development of ACS [21].

3. Peripheral arterial disease and periodontitis

There are several papers demonstrating the relationship between peripheral arterial disease (PAD) and periodontitis. Buhlin *et al.* revealed the association by determining the plasma levels of some risk markers for PAD in cases with periodontitis [22,23]. Statistical analyses revealed a significant association between periodontitis and high levels of C-reactive protein (CRP), fibrinogen, IL-18 and antibodies against heat shock protein (Hsp) 65 and 70. They also showed the effect of infection control of periodontitis on the prevalence of the risk factors. One year after the initial treatment, IL-18 and other levels decreased. Thus, standard treatment for periodontal disease induces systemic changes in several biochemical markers that reflect the risk for PAD.

Chen *et al.* also revealed that periodontitis was associated with PAD using tissue specimens [24]. They identified *P. gingivalis, T. denticola, A. actinomycetemcomitans, P. intermedia* in tissue specimens taken from the anastomotic site of distal bypasses PCR. In the study, periodontopathic bacteria were detected in 52% of atherosclerotic specimens. Severe (Fontaine grade III or IV) patients showed higher detection frequency of *P. gingivalis* than mild (Fontaine grade II) patients. After adjusting for age, sex, diabetes and smoking, periodontitis increased fivefold the risk of having PAD. They also showed that periodontitis was associated with increased serum IL-6 and TNF-α concentrations.

Buerger disease also showed the significant relationship to periodontitis. Iwai *et al.* revealed that DNA of oral bacteria was detected in 13 of 14 arterial samples and all oral samples of patients with Buerger disease [25]. While *T. denticola* was found in 86% of the arterial samples, other pathogens were found in 14 to 43% of the samples. A pathological examination revealed that arterial specimens showed the characteristics of an intermediate-chronic-stage or chronic-stage lesion of Buerger disease. They reported that the patients with Buerger disease had high prevalence of severe periodontitis with higher serum IgG titers against *T. denticola, P. gingivalis* and *A. actinomycetemcomitans* [26]. They also found that the patients had increased titers of serum anti-cardiolipin antibody compared with healthy subjects [27]. These results suggest that periodontitis influences the development of PAD.

4. Aortic aneurysm and periodontitis

Abdominal aortic aneurysm (AAA) is a common and lethal disorder in the aging population [28,29]. Inflammation and MMPs appear to play a critical role in AAA development and progression [30]. Human AAA tissue samples demonstrated severe inflammatory infiltrates in both the media and adventitia [31,32]. An increased expression of MMPs has been observed in human aneurysm tissue specimens [33-37]. It is well known that MMPs play key roles in periodontal diseases. Periodontopathic bacteria generate host immunological inflammatory responses, thus resulting in the secretion of cytokines and MMPs [38], and eventually leading to the extracellular matrix destruction of the periodontal tissues [39]. Some studies reported the detection of periodontal bacteria in AAA specimens. Periodontopathic bacteria, especially *P. gingivalis* was present in a high percentage of specimens of AAA and were also found throughout the whole aneurysmal wall [40]. Thus, periodontopathic bacteria may play a role in the development of AAA, but the influence of these bacteria on the aneurysmal wall has not yet been

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proven. To determine the effect of the periodontal microorganism on the AAA, we made a novel murine AAA model, which was produced by the periaortic application of 0.25 M $CaCl_2$. The mice received inoculations of either live *P. gingivalis*, *A. actinomycetemcomitans* or vehicle. Four weeks after the application of $CaCl_2$, the *P. gingivalis*-challenged mice showed a significant increase in the aortic diameter in comparison with the vehicle control mice while the *A. actinomycetemcomitans*-challenged mice showed no significant increase. Immunohistochemically, the CD8- and MOMA2-positive cells and the level of MMP-2 in the aneurysmal samples of *P. gingivalis*-challenged mice were also significantly higher than that inoculated with vehicle. We found that the *P. gingivalis*, but not *A. actinomycetemcomitans*, infection accelerated the progression of AAA due to the increased expression of MMPs (Aoyama N, unpublished).

5. Vitamin D is a key factor for periodontitis and cardiovascular diseases

Although vitamin D is well known to regulate calcium and phosphorus metabolism, it also has a physiological effects beyond its role in skeletal homeostasis. Recently, it was revealed that vitamin D is an immunomodulator which targets various immune cells, and modulates both innate and adaptive immune responses. Thus, vitamin D plays a crucial role in maintenance of immune homeostasis [41]. Several epidemiological studies have linked inadequate vitamin D levels to a higher susceptibility to immune-mediated disorders [42,43], including cardiovascular diseases [44]. It is believed that maintaining adequate vitamin D levels might in part prevent these common diseases [45]. It has been reported that low serum vitamin D levels were independently associated with periodontal and cardiovascular diseases [46,47]. Notably, vitamin D insufficiency is associated with increased circulating CRP levels, and vitamin D supplementation decreases circulating CRP levels [48]. Thus, the elevated CRP levels observed in periodontal and cardiovascular disease might be a surrogate for vitamin D insufficiency.

6. Conclusion

In this brief article, we have demonstrated the relationship between periodontopathic pathogens and cardiovascular diseases. We have also elucidated that each gingival bacterium caused different condition of cardiovascular diseases.

7. Expert opinion

Although several periodontopathic bacteria play a serious role in the development of cardiovascular diseases, the influence of these bacteria has to be elucidated because of the lack of appropriate investigations. Thus, further experimental and clinical studies should be conducted to elucidate the pathophysiology and relationship between periodontitis and cardiovascular diseases. Meanwhile, clinicians should optimize the periodontal conditions in patients with cardiovascular risk factors for primary and/or secondary prevention. Finally, it is plausible that this simple treatment of periodontitis might provide as much or even more benefit than the standard treatments for cardiovascular diseases.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Boehm TK, Scannapieco FA. The epidemiology, consequences and management of periodontal disease in older adults. J Am Dent Assoc 2007;138:26S-33S
2. Jain N, Jain GK, Javed S, et al. Recent approaches for the treatment of periodontitis. Drug Discov Today 2008;13:932-43
3. Friedewald VE, Kornman KS, Beck JD, et al. The American Journal of Cardiology and Journal of Periodontology Editors' Consensus: periodontitis and atherosclerotic cardiovascular disease. Am J Cardiol 2009;104:59-68

• **This article shows a standard consensus for physicians and dentists.**

4. Andriankaja OM, Genco RJ, Dorn J, et al. Periodontal disease and risk of myocardial infarction: the role of gender and smoking. Eur J Epidemiol 2007;22:699-705
5. Bahekar AA, Singh S, Saha S, et al. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a metaanalysis. Am Heart J 2007;154:830-7
6. Cairo F, Castellani S, Gori AM, et al. Severe periodontitis in young adults is associated with sub-clinical atherosclerosis. J Clin Periodontol 2008;35:465-72
7. Herzberg MC, Meyer MW. Dental plaque, platelets, and cardiovascular diseases. Ann Periodontol 1998;3:151-60
8. Dorn BR, Dunn WA, Progulske-Fox A. Invasion of human coronary artery cells by periodontal pathogens. Infect Immun 1999;67:5792-8
9. Zhang MZ, Li CL, Jiang YT, et al. Porphyromonas gingivalis infection accelerates intimal thickening in iliac arteries in a balloon-injured rabbit model. J Periodontol 2008;79:1192-9
10. Gaetti-Jardim E Jr, Marcelino SL, Feitosa AC, et al. Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. J Med Microbiol 2009;58:1568-75
11. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. AtheroGene investigators. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. Circulation 2002;105:15-21
12. Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation 2005;111:576-82
13. Sorsa T, Tjaderhane L, Konttinen YT, et al. Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. Ann Med 2006;38:306-21
14. Sorsa T, Tjaderhane L, Salo T. Matrix metalloproteinases (MMPs) in oral diseases. Oral Dis 2004;10:311-18
15. Olsen I. Update on bacteraemia related to dental procedures. Transfus Apher Sci 2008;39:173-8
16. Nakib SA, Pankow JS, Beck JD, et al. Periodontitis and coronary artery calcification: the Atherosclerosis Risk in Communities (ARIC) study. J Periodontol 2004;75:505-10
17. Higashi Y, Goto C, Hidaka T, et al. Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. Atherosclerosis 2009;206:604-10
18. Zaremba M, Gorska R, Suwalski P, Kowalski J. Evaluation of the incidence of periodontitis-associated bacteria in the atherosclerotic plaque of coronary blood vessels. J Periodontol 2007;78:322-7
19. Humphrey LL, Fu R, Buckley DI, et al. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008;23:2079-86
20. Nakajima T, Yamazaki K. Periodontal disease and risk of atherosclerotic coronary heart disease. Odontology 2009;97:84-91
21. Sakurai K, Wang D, Suzuki J, et al. High incidence of Actinobacillus actinomycetemcomitans infection in acute coronary syndrome. Int Heart J 2007;48:663-75
22. Buhlin K, Hultin M, Norderyd O, et al. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol 2009;36:541-9
23. Buhlin K, Hultin M, Norderyd O, et al. Periodontal treatment influences risk markers for atherosclerosis in patients with severe periodontitis. Atherosclerosis 2009;206:518-22
24. Chen YW, Umeda M, Nagasawa T, et al. Periodontitis may increase the risk of peripheral arterial disease. Eur J Vasc Endovasc Surg 2008;35:153-8
25. Iwai T, Inoue Y, Umeda M, et al. Oral bacteria in the occluded arteries of patients with Buerger disease. J Vasc Surg 2005;42:107-15
26. Chen YW, Iwai T, Umeda M, et al. Elevated IgG titers to periodontal pathogens related to Buerger disease. Int J Cardiol 2007;122:79-81
27. Chen YW, Nagasawa T, Wara-Aswapati N, et al. Association between periodontitis and anti-cardiolipin antibodies in Buerger disease. J Clin Periodontol 2009;36:830-5
28. Ernst CB. Abdominal aortic aneurysm. N Engl J Med 1993;328:1167-72
29. Alcorn HG, Wolfson SK Jr, Sutton-Tyrrell K, et al. Risk factors for abdominal aortic aneurysms in older adults enrolled in The Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 1996;16:963-70
30. Longo GM, Xiong W, Greiner TC, et al. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest 2002;110:625-32
31. Bobryshev YV, Lord RS, Parsson H. Immunophenotypic analysis of the aortic aneurysm wall suggests that vascular dendritic cells are involved in immune responses. Cardiovasc Surg 1998;6:240-9
32. Pearce WH, Koch AE. Cellular components and features of immune response in abdominal aortic aneurysms. Ann NY Acad Sci 1996;800:175-85
33. Freestone T, Turner RJ, Coady A, et al. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol 1995;15:1145-51

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34. Davis V, Persidskaia R, Baca-Regen L, et al. Matrix metalloproteinase-2 production and its binding to the matrix are increased in abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 1998;18:1625-33

35. Rizas KD, Ippagunta N, Tilson MD III. Immune cells and molecular mediators in the pathogenesis of the abdominal aortic aneurysm. Cardiol Rev 2009;17:201-10

36. Takagi H, Manabe H, Kawai N, et al. Circulating matrix metalloproteinase-9 concentrations and abdominal aortic aneurysm presence: a meta-analysis. Interact Cardiovasc Thorac Surg 2009;9:437-40

37. Aziz F, Kuivaniemi H. Role of matrix metalloproteinase inhibitors in preventing abdominal aortic aneurysm. Ann Vasc Surg 2007;21:392-401

38. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. J Clin Periodontol 2005;32(Suppl 6):108-29

39. Ashley RA. Clinical trials of a matrix metalloproteinase inhibitor in human periodontal disease. SDD Clinical Research Team. Ann NY Acad Sci 1999;878:335-46

40. Kurihara N, Inoue Y, Iwai T, et al. Detection and localization of periodontopathic bacteria in abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 2004;28:553-8

41. Baeke F, Takiishi T, Korf H, et al. Vitamin D: modulator of the immune system. Curr Opin Pharmacol 2010: published online 27 April 2010, doi:10.1016/j.coph.2010.04.001

42. Pilz S, Tomaschitz A, Obermayer-Pietsch B, et al. Epidemiology of vitamin D insufficiency and cancer mortality. Anticancer Res 2009;29:3699-704

43. Shoenfeld N, Amital H, Shoenfeld Y. The effect of melanism and vitamin D synthesis on the incidence of autoimmune disease. Nat Clin Pract Rheumatol 2009;5:99-105

44. Judd SE, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci 2009;338:40-4

45. Goldstein MR, Mascitelli L, Pezzetta F. Peridontitis, atherosclerotic cardiovascular disease and vitamin D. Am J Cardiol 2009;104:1164

46. Dietrich T, Joshipura KJ, Dawson-Hughes B, et al. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr 2004;80:108-13

47. Kendrick J, Targher G, Smits G, et al. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009;205:255-60

48. Elliott P, Chambers JC, Zhang W, et al. Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA 2009;302:37-48

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Case Reports

Diagnostic Efficacy of Coronary CT Angiography as a Follow-up Modality for Procedure-Related Coronary Dissection

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SUMMARY

Procedure-related coronary dissection is associated with an increased risk of major adverse cardiovascular events after percutaneous coronary intervention (PCI). In most patients with such an iatrogenic complication, further PCI or bypass surgery aimed at complete revascularization is performed. Moreover, conventional coronary angiography has been used as a standard modality in the follow-up of such patients. The present report describes a 70 year old female patient who was complicated by catheter-related extensive coronary dissection in the right coronary artery (RCA) when treated for an acute myocardial infarction. Although RCA flow was insufficient, we decided against revascularization and followed her medically without additional revascularization procedures. Her clinical course had been uneventful for 4 years. However, symptoms of effort angina developed and re-examinations were performed at approximately 5 years after the myocardial infarction. Although conventional coronary angiography failed to show the culprit lesion responsible for the angina symptoms, the superior spatial resolution of the coronary CT angiography clearly identified significant progression of the stenotic lesion in the true lumen of the dissected RCA. Thus, coronary CT angiography might be considered as a possible first-line follow-up modality in patients with procedure-related coronary dissection. (Int Heart J 2011; 52: 240-242)

Key words: PCI-related coronary dissection, Coronary CT angiography, Evaluation of true lumen, Coronary stenosis

Procedure-related coronary dissection is one of the life-threatening complications of percutaneous coronary intervention (PCI) and it is associated with an increasing risk of adverse outcomes. Most patients complicated by coronary dissection are followed by conventional coronary angiography. However, as coronary CT angiography is less invasive and superior in the visualization of the three-dimensional structure of the complex vasculature in dissected coronary arteries, its use may be appropriate in the follow-up of such patients.

CASE REPORT

A 70 year-old female who had a history of medically treated hypertension and dyslipidemia was admitted to our hospital complaining of worsening chest discomfort on effort. Five years before admission, she was admitted to another hospital due to severe chest pain at rest. She was diagnosed as having acute ST-segment elevation myocardial infarction (STEMI) with ST-segment elevation in leads II, III, and aVF in a 12-lead electrocardiogram and had decreased motion in the inferior wall of the left ventricle in echocardiography. Since severe stenosis (90%) in the proximal portion of the RCA was revealed by emergent coronary angiography, although there was no significant stenosis in the left coronary artery (LCA), she was moved to subsequent rescue PCI at the same hospital. A 7 French guiding catheter (Judkins-right shape) was engaged in the RCA and a 0.014 inch soft-tip guide wire was used to pass through the culprit lesion that was located at a severe angulation in the proximal portion of the RCA (Figure 1a, arrow). However, soon after starting the procedure, spiral and

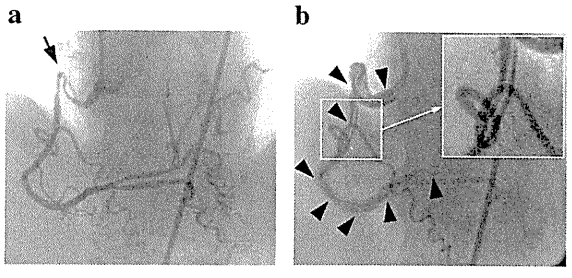

Figure 1. Angiographical findings before (**a**) and after (**b**) complicating coronary dissections in RCA. **a:** severe stenosis in proximal portion of RCA (arrow), **b:** coronary dissections from the ostium to posterior descending artery of RCA (arrow heads).

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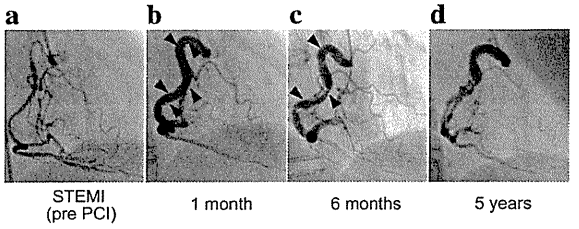

Figure 2. Changes in angiographical findings before (**a**), at 1 month (**b**), 6 months (**c**), and 5 years (**d**) after complicating coronary dissections with intracoronary tears (arrow heads).

extensive coronary dissection in the RCA emerged (Figure 1b, arrow heads). Intracoronary tears were clearly visualized by coronary angiography. Although much effort was expended to identify the true coronary lumen using guide wires, it was unsuccessful due to severe narrowing in the true lumen induced by compression of the false lumen. Since flow in the RCA was not sufficient (TIMI grade 2) at the end of the procedure, an intra-aortic balloon pumping (IABP) device was placed for 3 days. Thallium stress scintigraphy at chronic phase demonstrated the deterioration in the viability of the posterior wall of the left ventricle. However, as the patient was asymptomatic and her hemodynamics were stable, it was decided that no further procedures would be conducted in consideration of procedural risk. Coronary angiograms at 1 month (Figure 2b) and 6 months (Figure 2c) still demonstrated an intracoronary tear (Figure 2b, 2c, arrow heads), as well as insufficient right coronary flow accompanied by an extremely complex coronary vasculature of the true and false lumens.

However, her clinical course had been generally uneventful and asymptomatic for over 4 years, although coronary computer tomography (CT) angiography performed 4 years later demonstrated the narrowing of the true lumen in the RCA (Figure 3a arrow head). Five years after the onset of STEMI, symptoms of effort angina had gradually developed over a 1 month period. Since she was referred to our hospital, we performed detailed and comprehensive follow-up examinations. Conventional coronary angiography failed to clarify the apparent difference from the angiography findings at 6 months after STEMI with complex three-dimensional structure characterized by vascular screws of the true and false lumens in the RCA (Figure 2c and d). On the contrary, the curved planar reconstruction method of coronary CT clearly demonstrated the stenotic lesion responsible for the symptoms. The cross-sectional view revealed significant progression in narrowing of the true lumen, which was separated by an extensive intimal flap in the RCA (Figure 3, arrows), in comparison with the findings of the CT before development of symptoms. After careful consideration regarding the risks and benefits of RCA revascularization, it was decided the patient would be treated with maximal antianginal agents, such as a nitrate, a beta-blocker, and a potassium channel opener. Consequently, the chest symptoms were brought under control and her clinical course has been uneventful for 3 years without a need for rehospitalization.

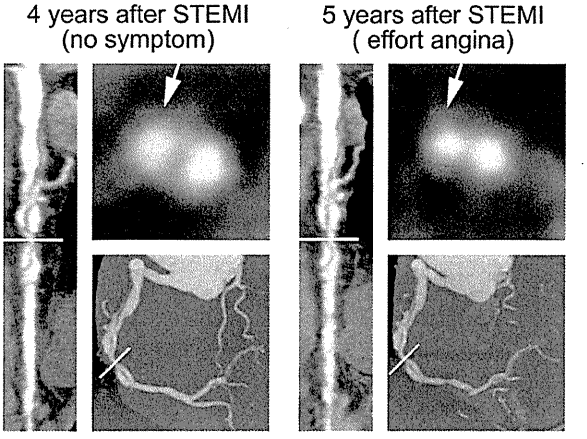

Figure 3. Coronary CT angiography successfully identified the lesion (lines) where the true lumen stenosis of dissected RCA had progressed for a year (arrows).

DISCUSSION

Despite rapid progress in the development of devices and techniques, PCI procedures can still induce life-threatening complications. Coronary dissection induced by PCI is associated with an increased risk of major adverse cardiovascular events. The frequency of PCI-related coronary dissection in the recent drug-eluting stent era has been reported to be 1.2-9.2%.[1] Huber, *et al* described the relationship between morphological complexity in accordance with the classification of the National Heart, Lung, and Blood Institute (NHLBI) and in-hospital adverse outcomes.[2] In addition to extensive manipulation of devices or contrast infusion, established risk factors of procedure-related coronary dissection include the use of Amplatz guiding catheters and coronary artery anatomical anomalies.[3] The gold standard for the treatment of coronary dissection is to pass a guide wire through the true coronary lumen and to secure coronary flow by expanding that with a balloon followed by complete coverage with a stent(s).[4] However, coronary bypass graft surgery should be considered without delay in cases where it is extremely difficult or impossible to pass a guide wire due to severe narrowing or closure of the true lumen and serious consequences caused by residual and ongoing ischemia of the target vessel can be predicted.

In the present case, a procedure-related spiral dissection covering almost the entire length of the RCA was complicated by engaging a guiding catheter for the treatment of STEMI. According to the angiographical classification of procedure-related coronary dissection, the present case was classified into the group in which major adverse events, such as additional revascularization procedures or in-hospital myocardial infarction were found in more than 50% of cases.[2] This case was indeed accompanied by severe stenosis or closure of the true lumen and this resulted in unsuccessful revascularization followed by myocardial infarction. Because the patient was hemodynamically stable with IABP and medications, further revascularization was not performed. At almost 5 years later, symptoms of effort angina gradually developed and reevaluation of the coronary artery was performed. While the extremely

complex coronary vasculature of the true and false lumens made precise evaluation of RCA flow difficult by conventional coronary angiography, coronary CT angiography was able to detect significant progression of the stenosis in the true coronary lumen.

Since affected vessels are usually revascularized in most cases without any insufficient coronary flow remaining, the natural clinical course of procedure-related coronary dissection has been rarely studied and reported. Therefore, a follow-up modality for patients with such a complication has not been established. However, the present case suggests that, for patients with residual dissection caused by procedures, coronary CT angiography might be considered as a first-line follow-up modality because it is less invasive (coronary angiography might cause exacerbation of the coronary dissection) and it is suitable for the accurate evaluation of vascular lumen, even in the presence of a very complex coronary vasculature of true or false lumens.

REFERENCES

1. Boyle AJ, Chan M, Dib J, Resar J. Catheter-induced coronary artery dissection: risk factors, prevention and management. J Invasive Cardiol 2006; 18: 500-3. (Review)
2. Huber MS, Mooney JF, Madison J, Mooney MR. Use of a morphologic classification to predict clinical outcome after dissection from coronary angioplasty. Am J Cardiol 1991; 68: 467-71.
3. Goldstein JA, Casserly IP, Katsiyiannis WT, Lasala JM, Taniuchi M. Aortocoronary dissection complicating a percutaneous coronary intervention. J Invasive Cardiol 2003; 15: 89-92. (Review)
4. Liu X, Tsujita K, Maehara A, *et al.* Intravascular ultrasound assessment of the incidence and predictors of edge dissections after drug-eluting stent implantation. JACC Cardiovasc Interv 2009; 2: 997-1004.

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IRF3 regulates cardiac fibrosis but not hypertrophy in mice during angiotensin II-induced hypertension

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ABSTRACT **Hypertension is a typical modern lifestyle-related disease that is closely associated with the development of cardiovascular disorders. Elevation of angiotensin II (ANG II) is one of several critical factors for hypertension and heart failure; however, the mechanisms underlying the ANG II-mediated pathogenesis are still poorly understood. Here, we show that ANG II-mediated cardiac fibrosis, but not hypertrophy, is regulated by interferon regulatory factor 3 (IRF3), which until now has been exclusively studied in the innate immune system. In a ANG II-infusion mouse model (3.0 mg/kg/d), we compared IRF3-deficient mice ($Irf3^{-/-}/Bcl2l12^{-/-}$) with matched wild-type (WT) controls. The development of cardiac fibrosis [3.95±0.62% (WT) *vs.* 1.41±0.46% ($Irf3^{-/-}/Bcl2l12^{-/-}$); $P<0.01$] and accompanied reduction in left ventricle end-diastolic dimension [2.89±0.10 mm (WT) *vs.* 3.51±0.15 mm ($Irf3^{-/-}/Bcl2l12^{-/-}$); $P=0.012$] are strongly suppressed in $Irf3^{-/-}/Bcl2l12^{-/-}$ mice, whereas hypertrophy still develops. Further, we provide evidence for the activation of IRF3 by ANG II signaling in mouse cardiac fibroblasts. Unlike the activation of IRF3 by innate immune receptors, IRF3 activation by ANG II is unique in that it is activated through the canonical ERK signaling pathway. Thus, our present study reveals a hitherto unrecognized function of IRF3 in cardiac remodeling, providing new insight into the progression of hypertension-induced cardiac pathogenesis.—Tsushima, K., Osawa, T., Yanai, H., Nakajima, A., Takaoka, A., Manabe, I., Ohba, Y., Imai, Y., Taniguchi, T., Nagai, R. IRF3 regulates cardiac fibrosis but not hypertrophy in mice during angiotensin II-induced hypertension. *FASEB J.* 25, 1531–1543 (2011). www.fasebj.org**

Key Words: cardiac remodeling · inflammation · heart failure

CONGESTIVE HEART FAILURE (CHF) is a chronic, costly, and often fatal cardiac-related illness that is most frequently caused by hypertension (1). Hypertension-mediated excessive overload to the left ventricle (LV) causes cardiac remodeling, which includes concurrent myocyte hypertrophy and interstitial fibrosis. In the early stage of hypertension-induced pathogenesis, cardiac remodeling is considered to be an important adaptive response to maintain cardiac output (2, 3). Indeed, an increased LV wall stress is compensated for by an increased contractility of cardiac myocytes, leading to myocyte hypertrophy and LV wall thickening. In addition, an increase in tensile stress from interstitial fibrosis prevents ventricular deformation by transmitting the force generated by hypertrophied myocytes to the entire ventricle. In the later stages of cardiac remodeling, however, excessive mechanical load in myocardium leads to myocyte loss and replacement with fibrosis, which is responsible for increased myocardial stiffness and decreased pumping capacity. Consequently, a prolonged overload of the LV leads to the breakdown of these compensatory mechanisms, leading to CHF (2, 3).

Angiotensin II (ANG II) is a vasopressor, octapeptide hormone intermediate of the renin-angiotensin system (RAS) that has received much attention as a critical factor in the development of hypertension and heart failure. Normally, the RAS is activated to increase blood pressure in response to hypotension, decreased sodium concentration in the distal tubule of the kidney nephron, decreased blood volume, and renal sympathetic nerve stimulation. However, in conditions of cardiac pathogenesis, ANG II levels increase as a result of the aberrant production of ANG II-forming serine

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