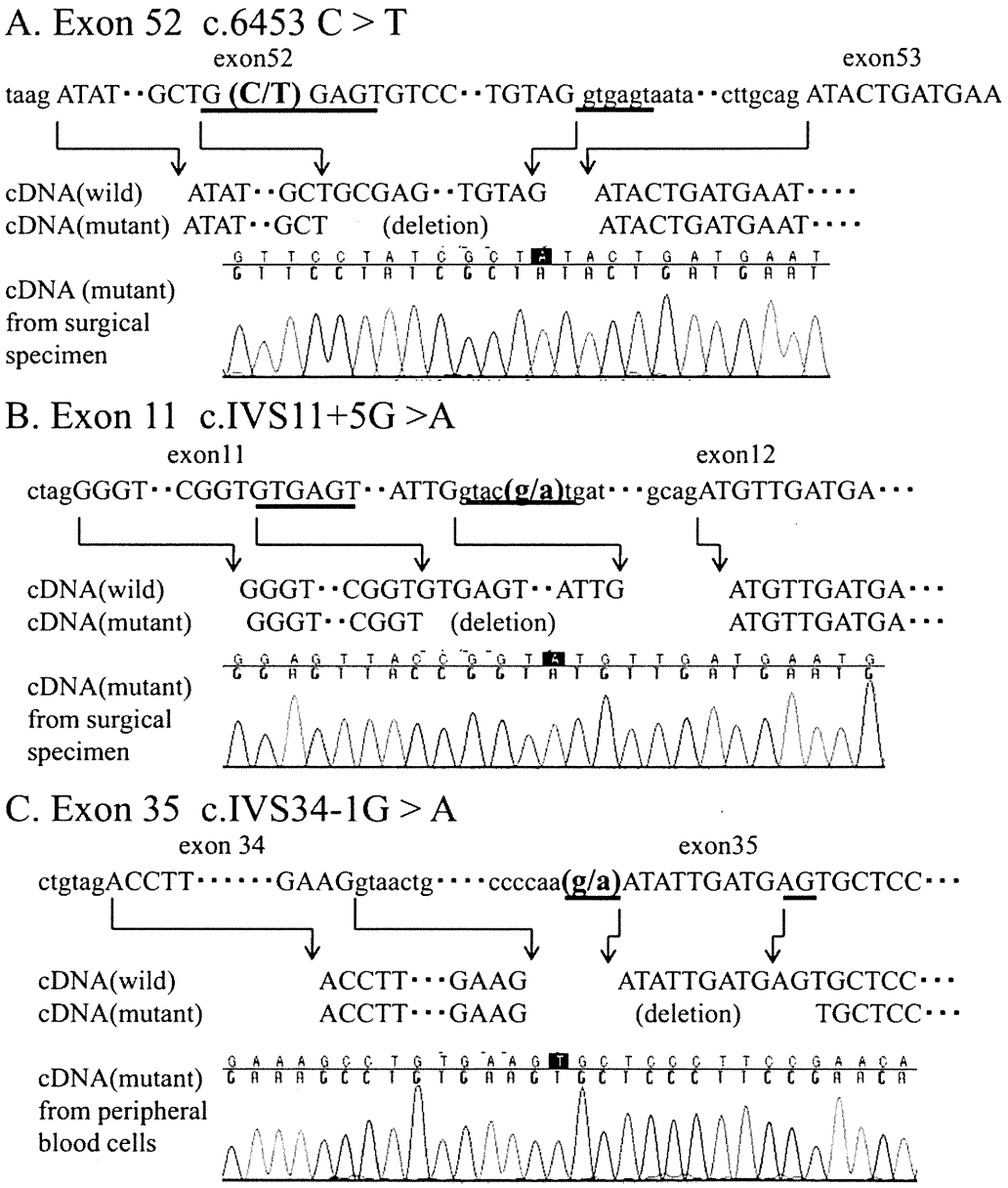

Figure 2. Representative splicing mutations in our study. *(A)* C-to-T substitution at nucleotide position 6453 produced a 6-nucleic acid sequence (c.6452-6457) *(underlined)* identical to that of IVS52+1 to +6 (gtgagt) *(underlined)*, and this was recognized as the splicing donor site. The following nucleotides of exon 52 from this point were deleted in the mutant allele. *(B)* The fifth nucleotide at the beginning of intron 11 was substituted from G to A (c.IVS11+5G>A). Resequencing of complementary DNA revealed that the latent splice donor site within exon 11 *(underlined)* was activated and became a new splice donor site and created the frame-shift mutation. *(C)* The last nucleotide of intron 34 was substituted from G to A (c.IVS34-1G>A). Resequencing FBN1 complementary DNA obtained from the peripheral blood demonstrated the splicing aberration, resulting in the deletion of 11 nucleotides of exon 35.

satisfactory, although their aortas dilated gradually later on. One patient met the revised Ghent criteria after genetic analysis of FBN1. Although further studies are warranted to clarify the properties and usefulness of the novel Ghent criteria, genetic testing is more important, although it is not mandatory. In such a setting, a high-throughput resequencing method such as the present microarray-based resequencing system can be a powerful tool for making an accurate diagnosis of MS.

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Expert Opinion

Novel IκB kinase inhibitors for treatment of nuclear factor-κB-related diseases

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Introduction: NF-κB is a key regulator of inflammation and immunity in cancer development. The IκB kinase (IKK) is a multisubunit complex containing catalytic subunits termed IKK-α, -β and -γ. It is well known that many pro-inflammatory stimuli require the IKK-β subunit for NF-κB activation.
Areas covered: NF-κB affects the progression of inflammation-related diseases, such as myocardial ischemia, bronchial asthma, arthritis, cancer and other diseases. We review the characteristics and effects of these inhibitors on inflammatory and other diseases.
Expert opinion: Various synthesized IKK inhibitors have been developed and they will be used clinically in the near future.

Keywords: chemical compounds, inflammation, IκB kinase, NF-κB

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1. Introduction

NF-κB is known to be a key factor in the regulation of inflammation [1] and immunity in cancer development [2]. The IκB kinase (IKK) is a multisubunit complex containing catalytic subunits termed IKK-α, -β and -γ [3]. To date, two major NF-κB activation pathways have been elicited based on the ligand interaction with surface receptors. Canonical signaling depends on IKK-γ and -β and induces the transcription of genes that regulate inflammation and cell survival. In contrast, non-canonical NF-κB activation is mostly involved in the regulation of B-cell development [4]. Although both pathways can affect development of inflammation, most of our knowledge relates to the canonical pathway. This pathway is triggered by infections and pro-inflammatory cytokines which activate IKK complex. This complex is composed of two catalytic subunits, IKK-α and -β, and a regulatory subunit, IKK-γ (NF-κB essential modulator; NEMO). The IKK complex phosphorylates NF-κB-bound IκBs, thereby targeting them for proteasomal degradation and liberating NF-κB dimers that are composed of REL-A (known as p65), REL and p50 subunits to enter the nucleus and mediate transcription of target genes. This reaction mostly depends on the catalytic subunit IKK-β, which carries out IκB phosphorylation. The non-canonical pathway involves the upstream kinase NF-κB-inducing kinase leading to the phosphorylation and processing of p100 in response to certain members of the TNF family. The two pathways switch on different gene sets and, therefore, mediate different immune functions. The contribution of the canonical pathway to acute inflammation and cell-survival mechanisms is well accepted, and sustained NF-κB activation in various malignancies has been described. Owing to the variety of target genes of the canonical pathway, which include those encoding mediators of inflammation, cytokines, chemokines, proteases and inhibitors of apoptosis (**Figure 1**), it has been proposed that canonical NF-κB activation might link inflammation to tumor promotion and progression [5].

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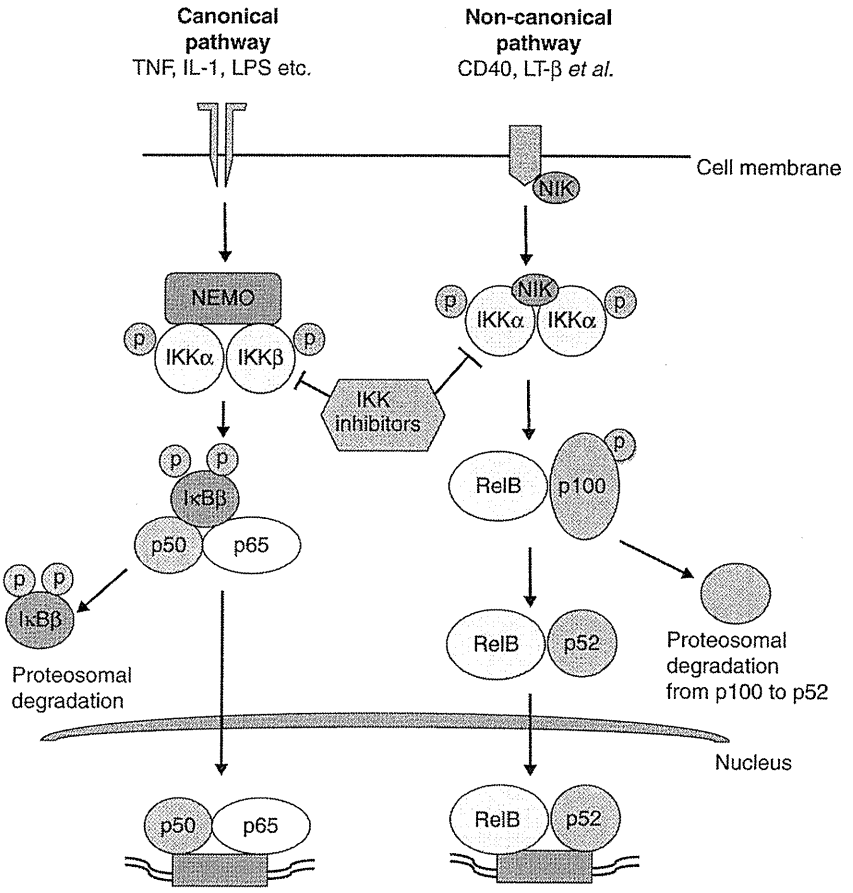

Figure 1. Canonical and non-canonical pathways of NF-κB.

Gene-targeting experiments revealed that many pro-inflammatory stimuli required IKK-β subunit for NF-κB activation [6]. Thus, IKK-deficient mice died in the embryonic or perinatal periods (IKK-$\alpha^{-/-}$, -$\beta^{-/-}$ or -$\gamma^{-/-}$) demonstrating their critical role [7,8]. Dominant-negative IKK-β blocks NF-κB-dependent transcription, while IKK-α plays a role only in response to certain stimuli and in limited cells. Recently, novel synthesized chemical compounds that act as IKK inhibitors have been developed. They are the phosphorylation inhibitors of IκB that act via inhibition of IKK-α and/or -β. To clarify the effects of the inhibitors, we review previous articles on inflammatory diseases.

2. Reagents

IMD-0354 (*N*-(3,5-bis-trifluoromethyl-phenyl)-5-chloro-2-hydroxy-benzamide) [9,10] and IMD-0560 (*N*-(2,5-bis-trifluoromethyl-phenyl)-5-bromo-2-hydroxy-benzamide) [11] were developed as novel IKK inhibitors. They are the phosphorylation inhibitors of IκB that act via inhibition of IKK-β. IMD-0354 (molecular mass, 384.1, **Figure 2A**) was molecular-designed, synthesized and provided by the Institute of Medicinal Molecular Design, Inc. (Tokyo, Japan). The 3D structure of a kinase domain of IKK-β was constructed by homology modeling with protein kinase A as a template. The structure of active IKK-β was estimated by referring to a model of IKK regulation. The molecular structure of IMD-0354 was designed by analyzing a binding mode of aspirin to IKK-β. To investigate the characteristics of IMD-0354, we performed a NF-κB–IKK-β reporter assay with the constitutively active mutant IKK-β. IMD-0354 inhibited the activated expression of NF-κB in a dose-dependent manner in HepG2 cells that were transfected with pFLAG-CMV-IKKh (S177E/S181E) vector. IMD-0354 also decreased the levels of cytosolic phospho-IκBα in TNF-α stimulated cardiomyocytes in a dose-dependent manner. The kinetics of NF-κB translocation was consistent with the degree of phosphorylation of cytosolic IκBα. The translocation was blocked markedly by treatment with IMD-0354. TNF-α-induced production of IL-1α and monocyte chemoattractant protein-1 (MCP-1) from cultured cardiomyocytes were reduced significantly by IMD-0354. Taken together, IMD-0354 inhibits IKK-β, resulting in the blockade of IκBα phosphorylation.

Another IKK inhibitor, IMD-0560 (molecular mass 428.1), was also synthesized and provided by the Institute of Medical

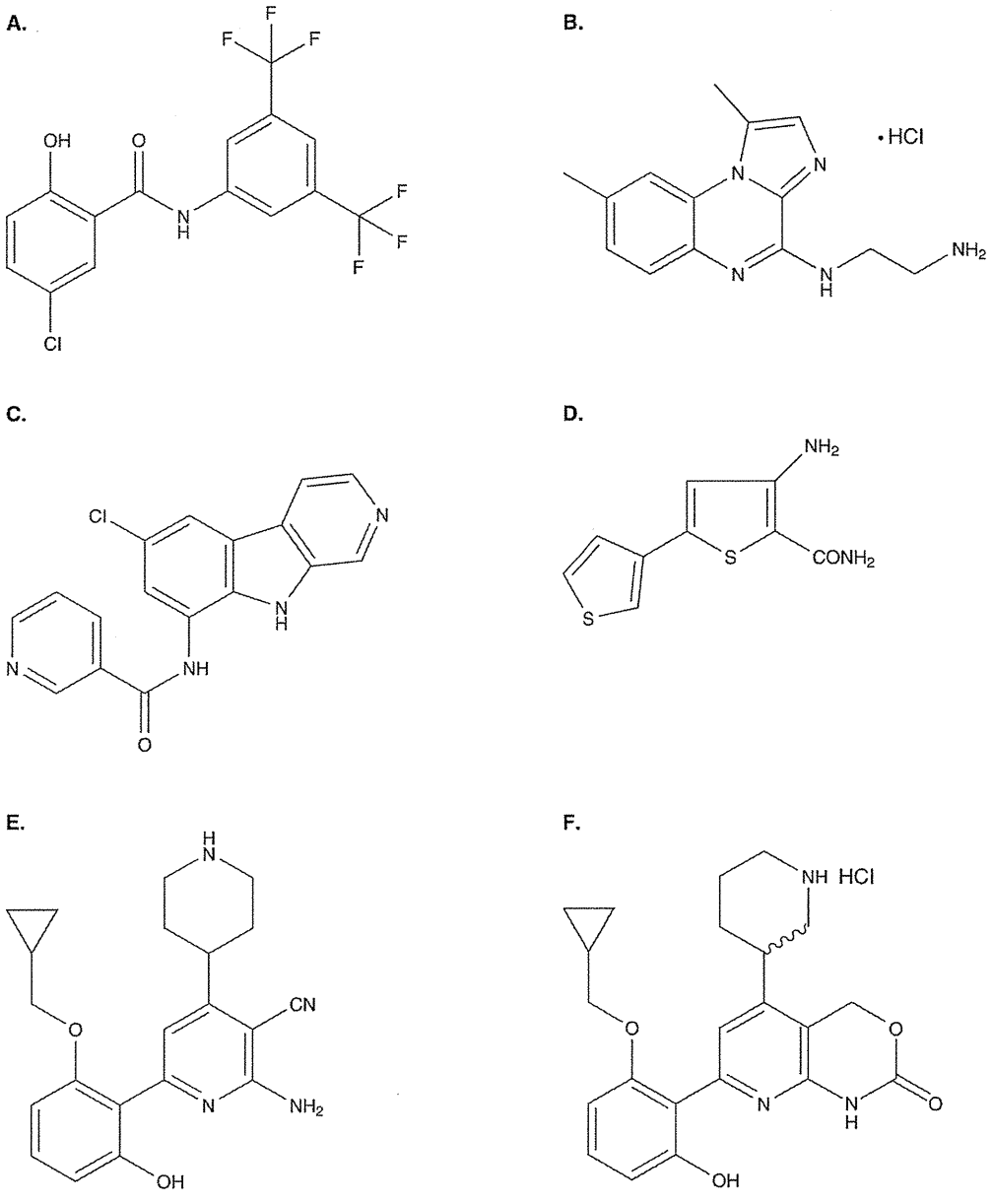

Figure 2. Chemical structures of the chemical compounds A, IMD-0354; B, BMS-345541; C, PS-1145; D, SC-514; E, ACHP and F, Bay 65 - 1942.

Molecular Design using the same methodology of IMD-0354. IMD-0560 inhibited the activated expression of NF-κB in HEK293T cells transfected with the p-FLAG-CMV-IKK-β (S177E/S181E) vector in a dose-dependent manner. Further, pretreatment with IMD-0560 dose-dependently suppressed the DNA binding activity of NF-κB. IMD-0560 also suppressed the nuclear translocation of NF-κB and phosphorylation of IκBα induced by TNF-α in fibroblast-like synoviocytes (FLS). Further, this compound suppressed the production of inflammatory cytokines and chemokines; it also inhibited the proliferation of FLS without showing cellular toxicity [11,12].

BMS-345541, 4(2′-aminoethyl)amino-1,8-dimethylimidazo(1,2-α) quinoxaline, was reported as a highly selective inhibitor of IKK that inhibits NF-κB-dependent transcription of pro-inflammatory cytokines (**Figure 2B**). BMS-345541 was identified as a selective inhibitor of the catalytic subunits of IKK (IKK-β IC_{50} = 0.3 μM, IKK-α IC_{50} = 4 μM). This inhibitor appears to bind to an unidentified allosteric-binding site of the IKK catalytic subunits. The compound failed to inhibit a panel of 15 other kinases and selectively inhibited the stimulated phosphorylation of IκB in cells. It also failed to affect c-Jun and STAT3 phosphorylation, as well as MAPK-2 activation in cells. The compound has good pharmacokinetic

characteristics (oral bioavailability 100%, intravenous half-life 2.2 h), which makes it particularly well suited for use in investigating the utility of IKK inhibitors in disease models [13].

PS-1145, *N*-(6-chloro-9*H*-β-carbolin-8-yl) nicotinamide, was also reported (**Figure 2C**) [14]. The compound PS-1145 was tested for its ability to block the phosphorylation of IκBα in HeLa cells following TNF-α stimulation. Immunoblot analysis showed a dose-dependent inhibition of phosphorylated IκBα. It then evaluated the effects of the compound on NF-κB activation by measuring DNA binding activity after TNF-α treatment in the same HeLa cells. EMSA showed a dose-dependent inhibition of NF-κB activation by the compound. Consistent with the inhibition of NF-κB activation, this compound also blocks the transcription of intracellular adhesion molecule (ICAM)-1 in HUVEC primary cultures [15]. PS-1145 inhibited TNF-α production with an IC_{50} of 4.7 μM/l [16].

SC-514, 5-(thien-3-yl)-3-aminothiophene-2-carboxamide, was identified as another selective IKK inhibitor (**Figure 2D**). This compound does not inhibit other IKK isoforms or other serine–threonine and tyrosine kinases. SC-514 inhibits the native IKK complex or recombinant human IKK-α/-β heterodimer and IKK-β homodimer. IKK-β inhibition by SC-514 is selective, reversible and competitive with ATP. SC-514 has several interesting effects; it does not inhibit the phosphorylation and activation of the IKK complex, and delays but does not completely block IκBα phosphorylation and degradation. Thus, the effect of SC-514 on cytokine gene expression is a combination of inhibiting IκBα phosphorylation/degradation affecting NF-κB nuclear import/export, as well as the phosphorylation and transactivation of p65 [17].

ACHP, 2-amino-6-[2-(cyclopropylmethoxy)-6-hydroxyphenyl] -4-piperidin-4-yl-nicotinonitrile, was developed and evaluated as a potent inhibitor for IKK-α and -β (**Figure 2E**). When massive screening was conducted, ACHP was found to have specific inhibitory action on IKK-α and -β. The IC_{50} values for IKK-α and -β are 8.5 and 250 nmol/l, respectively, measured by *in vitro* kinase assays. ACHP also showed good aqueous solubility and cell permeability, thus, demonstrating high bioavailability in mice and rats [18,19].

Bay 65 – 1942, {7-[2-(cyclopropylmethoxy)-6-hydroxyphenyl]-5-[(3*S*)-3-piperidinyl]-1,4-dihydro-2Hpyrido[2,3-d][1,3]oxazin-2-one hydrochloride}, was composed as an IKK-β inhibitor (**Figure 2F**). Through competitive inhibition of ATP at the IKK-β subunit, Bay 65 – 1942 prevented the phosphorylation of IκBα by the IKK complex [20].

AS602868 is an anilinopyrimidine derivative and ATP competitor, which inhibits IKK-β with an IC_{50} = 62 nmol/l (K_i = 20 nmol/l). The compound showed some inhibitory effect on JNK2. In a series of tests on different cell lines, AS602868 was shown to block phosphorylation of IκB and subsequent NF-κB activation [21].

NEMO binding domain (NBD) peptide was reported as an IKK inhibitor [22]. The specific molecular mechanisms of NEMO–IKK interactions involve a C-terminal hexapeptide core sequence present on both IKK-α and -β. Peptides corresponding to the IKK-β NBD have been found to disrupt the association of recombinant NEMO with recombinant IKK-α or -β *in vitro*. The cell-permeable versions of these peptides blocked NF-κB activation in various cellular and animal models of inflammation [23].

It is well known that some natural products, such as polyphenols, have various effects on IKK inhibition. Pan *et al.* investigated the inhibition of IKK activity in lipopolysaccharide (LPS)-activated murine macrophages by various polyphenols including (-)-epigallocatechin-3-gallate (EGCG) and theaflavin-3,3′-digallate (TF-3). TF-3 inhibited IKK activity in activated macrophages more strongly than the other polyphenols. TF-3 strongly inhibited both IKK-α and -β activity and prevented the degradation of IκBα and IκBβ in activated macrophage cells. The results suggest that the inhibition of IKK activity by TF-3 could occur by a direct effect on IKKs or on upstream events in the signal transduction pathway [24]. Yang *et al.* also revealed that EGCG was a potent IKK inhibitor because EGCG inhibited phosphorylation of IκBα and decreased IKK activity in cytosolic extracts [25].

3. The effects on disease models

3.1 Cardiovascular diseases

Myocardial ischemia reperfusion injury is related closely to inflammatory reactions. Morishita *et al.* revealed that inhibition of NF-κB using decoy oligodeoxynucleotides (ODNs) reduced the extent of myocardial infarction following reperfusion [26]. Thus, we investigated the efficacy of IκB phosphorylation blockade using IMD-0354 in a rat myocardial ischemia/reperfusion injury model [9]. Treatment with IMD-0354 resulted in a significant reduction of the infarction area:area at risk ratio and the preservation of fractional shortening. Histology showed that accumulation of polymorphonuclear neutrophils in the area at risk decreased significantly. *In vitro* study revealed that IMD-0354 inhibited nuclear translocation of NF-κB induced by TNF-α in cultured cardiomyocytes. IMD-0354 caused a significant reduction of chemokine (MCP-1) production in a concentration-dependent manner compared with vehicle-treated cells. Therefore, we concluded that inhibition of nuclear translocation of NF-κB by IMD-0354 could provide an effective approach to attenuate ischemia/reperfusion injury through chemokine suppression. Ventricular remodeling after myocardial infarction is also related to inflammatory reactions. Thus, we studied the effects of IMD-0354 [6] and IMD-0560 [11] in a rat myocardial infarction model. IMD-0354 or IMD-0560 administration reduced plasma brain natriuretic peptide levels after myocardial infarction. Either IMD-0354 or IMD-0560 treatment preserved left ventricular fractional shortening after infarction. Histology

showed that IMD-0354 significantly reduced myocardial macrophage infiltration and fibrosis. Western blot revealed that IMD-0354 suppressed MCP-1 expression in non-infarcted myocardial samples. *In gel* and *in situ* zymography clarified that either IMD-0354 or IMD-0560 treatment significantly suppressed MMP-9 activity in the non-infarcted myocardium. Therefore, we concluded that both IMD-0354 and IMD-0560 significantly affect the prevention of heart failure that is induced by ventricular remodeling after myocardial ischemia via altered MMP activation.

BMS-345541 was tested for its ability to suppress graft rejection in a murine heterotopic cardiac allograft model by Townsend *et al.* The compound did not prolong graft survival when administered at 50 mg/kg as a single agent. However, graft survival was significantly increased when it was administered with a suboptimal dose of cytotoxic T-lymphocyte antigen-4 immunoglobulin or cyclosporine A compared with either agent alone. They concluded that BMS-345541 may serve as a novel adjunctive therapy for the prevention of graft rejection [27].

SC-514 examined the effects using rat aortic smooth muscle cells. SC-514 treated cells significantly reduced iNOS induction, NF-κB DNA binding and IκBα loss. The results suggest that IKK-β plays a predominant, selective role in the regulation of NF-κB-dependent induction of iNOS in smooth muscle cells [28]. SC-514 inhibited all forms of recombinant human IKK-α, including rhIKK-β homodimer, rhIKK-α/-β heterodimer, as well as the constitutively active form of rhIKK-β with comparable IC_{50} values in the 3 – 12 μM range [29].

Moss *et al.* also reported that Bay 65 – 1942 can provide both acute and chronic cardioprotection and offers a clinically accessible target for preventing cardiac injury following ischemia reperfusion [30].

We demonstrated that tea catechins suppressed several cardiovascular diseases. We performed oral administration of catechins into murine and rat models of cardiac transplantation [31], myocarditis [32], myocardial ischemia [33] and atherosclerosis [34] to reveal the effects of catechins on the inflammation-induced ventricular and arterial remodeling. From our results, catechins are potent agents for the treatment and prevention of inflammation-related cardiovascular diseases, as they are critically involved in the suppression of pro-inflammatory signaling pathways.

3.2 Lung injury

NF-κB plays a key role in the progression of lung injury. Matsuda *et al.* revealed that NF-κB decoy ODNs prevented acute lung injury in mice [35]. Thus, we examined the effects of IMD-0354 to attenuate bleomycin-induced pulmonary fibrosis in mice [36]. IMD-0354 reduced the collagen content and fibrotic scores in the mice that received bleomycin. The bronchoalveolar lavage demonstrated that the proportions of neutrophils and lymphocytes decreased in mice treated with IMD-0354. The results suggested that IMD-0354 might be useful to ameliorate inflammation in the lungs induced by chemical injury.

BMS-345541 is also known to affect acute lung injury. Everhart *et al.* administered BMS-345541 to determine whether intervention in the NF-κB pathway could prevent progression of lung injury in the LPS pump model. They revealed that treatment with BMS-345541 reduced lung NF-κB activation, concentration of pro-inflammatory cytokines and chemokines in lung lavage, neutrophil influx and lung edema. Therefore, they concluded that sustained NF-κB activation correlates with severity of lung injury and that BMS-345541 is beneficial to suppress lung inflammation [37]. PS-1145 also tested the effects using human ASM cells and pulmonary epithelial cells *in vitro*. As observed in human ASM cells, PS-1145 reduced expression of several adhesion molecules, cytokines and chemokines [38]. Similarly, PS-1145 reduced NF-κB-dependent transcription induced by IL-1β and TNF-α in primary pulmonary epithelial cells [39]. Chapoval *et al.* revealed the *in vivo* effects of PS-1145 using IL-13 transgenic mice. While IL-13 induced tissue inflammation, fibrosis and alveolar remodeling, PS-1145 inhibited lung inflammatory and structural cell apoptosis with suppression of caspase activation [40].

3.3 Arthritis

Rheumatoid arthritis (RA) is affected by NF-κB activation. Tomita *et al.* showed that NF-κB decoy ODN suppressed the severity of collagen-induced arthritis in rats [41]. Thus, we evaluated the effect of IMD-0560 on collagen type II-induced arthritis in mice [12]. In this investigation, IMD-0560 suppressed the nuclear translocation of NF-κB and phosphorylation of IκB induced by TNF-α. In addition, this compound suppressed the production of inflammatory cytokines, including IL-6 and -8. IMD-0560 was effective against collagen-induced arthritis in mice via suppression of pro-inflammatory cytokines. Thus, we concluded that IMD-0560 could be a new therapeutic agent for RA.

BMS-345541 intensively evaluated the effects on RA. McIntyre *et al.* revealed that BMS-345541 is efficacious against collagen-induced arthritis in mice. BMS-345541 reduced the incidence of disease, inhibiting clinical signs of disease. Histological evaluation of the joints showed that BMS-345541 blocked inflammation and joint destruction. Transcription levels of IL-1 in the joints were also inhibited in the mice that received BMS-345541 [42]. Pattoli *et al.* also examined whether BMS-345541 directly inhibits cytokine-induced metalloproteinase expression and cartilage degradation. BMS-345541 inhibited IL-1-dependent expression of MMP-1, -3 and -13 in chondrosarcoma cells. Thus, BMS-345541 blocks collagen degradation through suppression of metalloproteinase expression [43].

Jimi *et al.* also revealed that the NBD peptide inhibited RANKL-stimulated NF-κB activation and osteoclastogenesis both *in vitro* and *in vivo*. This peptide significantly reduced the severity of collagen-induced arthritis in mice by reducing

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.

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

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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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

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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．

* The High Prevalence of Periodontitis in Patients with Marfan Syndrome(2011年6月6日受付)
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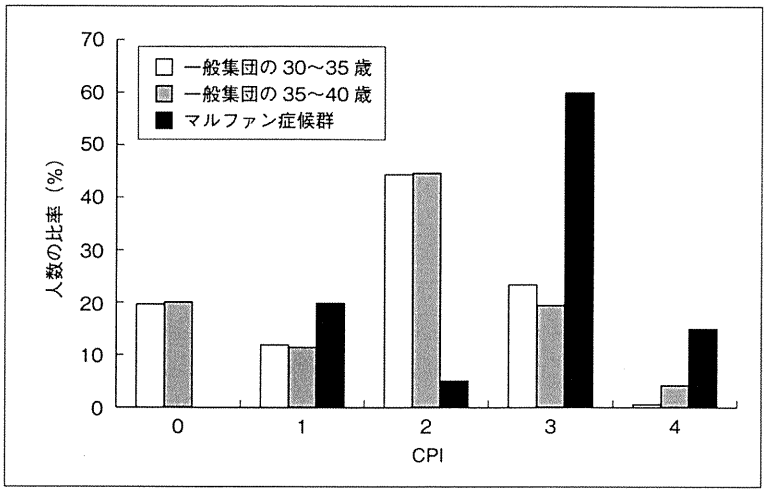

図1 本研究対象者と同年代男性および女性との間でのCPIの比較

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．

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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

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

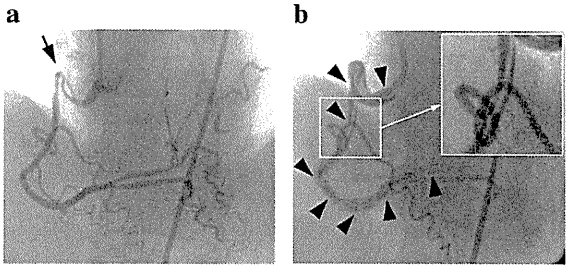

Figure 1. Angiographical findings before (**a**) and after (**b**) complicating coronary dissections in RCA. **a:** severe stenosis in proximal portion of RCA (arrow), **b:** coronary dissections from the ostium to posterior descending artery of RCA (arrow heads).

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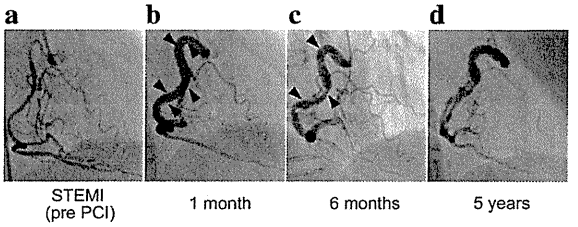

Figure 2. Changes in angiographical findings before (**a**), at 1 month (**b**), 6 months (**c**), and 5 years (**d**) after complicating coronary dissections with intracoronary tears (arrow heads).

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.

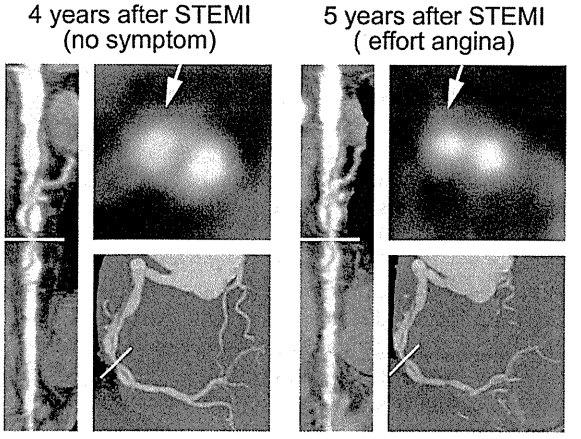

Figure 3. Coronary CT angiography successfully identified the lesion (lines) where the true lumen stenosis of dissected RCA had progressed for a year (arrows).

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