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Structural development of synthetic retinoids and thalidomide-related molecules

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Abstract The full-scale commercial appearance of antibiotics in the 1950s caused a shift in the nature of lethal diseases from infectious and acute to noninfectious and chronic. In this situation, biological response modifiers (BRMs), which are not based on selective toxicity, could be expected to be useful. Several types of BRM exist, including retinoids, which act directly on cells at the level of gene expression, and thalidomide and related molecules, which modulate the production of various cytokines. We have been engaged in medicinal, chemical, and structural development studies based on these bioactive compounds. Retinoids include all-*trans*-retinoic acid (ATRA), a major active form of vitamin A (retinol), and its bioisosters, which elicit their biological effects by binding to their nuclear receptors, retinoic acid receptors (RARs). ATRA has been used in differentiation therapy, typically for the treatment of acute promyelocytic leukemia, and the treatment of dermatological diseases. Our structural development studies of retinoids, including computer-assisted molecular design, have yielded class/subtype-selective agonists, synergists, and antagonists of RARs and their partner nuclear receptors, retinoid X receptors. Among them, the benzanilide-type compounds, Am80 and TAC101, are under phase II and I/II clinical studies in Japan and the USA, respectively. Thalidomide is a hypnotic/sedative drug that was withdrawn from the market because of teratogenicity. However, thalidomide has been established to be useful in the treatment of various diseases including cancer. Thalidomide elicits a wide range of pharmacological effects, including anticachexia, anti-tumor-promoting, antiangiogenic, immunosuppressing, antiviral, hypoglycemic, and antimetastatic activities. We have found that thalidomide is a multitarget drug. Hypothetical target events/molecules of thalidomide include tumor necrosis factor-α production, nuclear androgen receptor, cyclooxygenases, aminopeptidases, and α-glucosidase. Specific and potent compounds for each of these target phenomena/molecules have been prepared by appropriate modification of the thalidomide structure, and are expected to be superior lead compounds for novel immunomodulators, antiangiogenic agents, and anti-tumor-promoting agents.

Keywords Retinoid · Thalidomide · Structural development

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Introduction

The full-scale commercial appearance of antibiotics in the 1950s resulted in increased longevity in developed countries. The highest mortality rates in Japan before the 1950s were due to tuberculosis. The death rates from infectious diseases dropped dramatically in the 1950s and since then, the death rate from cancer has been rising. Currently, cancer is the number one cause of death in Japan, accounting for one in three deaths. The widespread use of antibiotics, drugs based on species-selective toxicity, has shifted the nature of our lethal diseases from infectious and acute to noninfectious and chronic. Biological response modifiers (BRMs), which are not based on species-selective toxicity, might provide a means to meet this new challenge.

We have been engaged in development studies of two types of BRM: retinoids, which act directly on malignant cells at the level of gene expression to make them behave normally [3, 5, 7] and thalidomide-related molecules, which modulate internal processes in the body to restore a normal state [4, 5, 6]. This paper reviews our

research on the structural development of synthetic retinoids, their antagonists, and thalidomide-related molecules.

Retinoids

Retinoid is a generic name for all-*trans*-retinoic acid (ATRA) and its bioisosters, retinoic acid receptor (RAR) agonists. Partial bioisosters of ATRA or regulators of ATRA function, retinoid X receptor (RXR) agonists are also included with retinoids in this paper. ATRA is an active form of vitamin A (retinol), which is enzymatically oxidized to retinal, an important pigment in vision function, and further to ATRA, to which almost all the biological activity of vitamin A in the maintenance of normal growth/life of mammals can be attributed. Retinoids, typically ATRA, have been used in differentiation-inducing therapy for tumors and the treatment of dermatological diseases. At the cellular level, their mechanism of action is the regulation of cell differentiation, i.e. not cytotoxicity but alteration of cell behavior. The most successful example of retinoid use is in the treatment of acute promyelocytic leukemia (APL). APL had been a lethal disease but now it can be cured by differentiation therapy using retinoids. Retinoids induce differentiation of leukemia cells leading to complete remission in patients.

All retinoids elicit their effects by binding to their specific nuclear receptor, RAR (Fig. 1). RAR is a member of the steroid/thyroid/vitamin D_3 nuclear receptor superfamily, and acts as a dimer with another nuclear receptor, RXR. For both RAR and RXR, three subtypes, α, β, and γ, exist. The clinical usefulness of ATRA, as well as its unfavorable chemical nature, has led many researchers to develop synthetic retinoids targeting RARs. The major disadvantages of ATRA include high lipophilicity and instability. In addition, appearance of ATRA-resistant cells during differentiation therapy is partly explained by overproduction of cellular retinoic acid-binding protein (CRABP), which is one of the fatty acid-binding proteins.

To overcome these problems, we introduced heteroatoms into structural mimics of ATRA to increase polarity. Typical retinoids (named retinobenzoic acids) are shown in Fig. 2 [3, 5, 7, 10, 27]. Am80 is an example of a potent synthetic retinoid [3, 5, 7, 10]. Because Am80 does not bind CRABP [8], it is active toward CRABP-rich ATRA-resistant cells. In addition, Am80 has been established to be RARα/β-selective [3, 5, 8]. It has been designated as an orphan drug in Japan and is under phase II clinical investigation for the treatment of APL. Another retinobenzoic acid under clinical study is TAC101 [27]. TAC101 is a potent RARα-selective retinoid and possesses a unique structure with two trimethylsilyl groups forming a hydrophobic moiety that plays a critical role in the activation of RARα. In addition to its potent cell differentiation-inducing activity, it also possesses antiangiogenic activity and AP-1-inhibitory activity. TAC101 effectively prolongs the survival of solid tumor-bearing mice, more efficiently than 5-fluorouracil or cisplatin, and is under phase I/II trial in the USA.

Further studies on the structural development of retinobenzoic acids led to the development of RAR antagonists (e.g. TD550, BIBn, LE135, and LE540) [1, 2], RXR agonists (e.g. HX600 and DA124), and RXR antagonists (e.g. HX603, PA452, and HX531) [26] (Fig. 3). RAR antagonists were designed on the basis of the ligand superfamily concept, which stresses the importance of the ligand-induced conformational change in the RAR accompanying the folding of helix 12 [1]. Therefore all the RAR antagonists thus designed are based on a retinobenzoic acid structure with steric hindrance, i.e. structures that bind to the ligand-fitting pocket of RAR but sterically hinder the folding of helix 12. Among them, LE135 is a RARβ-selective antagonist [2, 13, 14]. RXR agonists and antagonists were designed

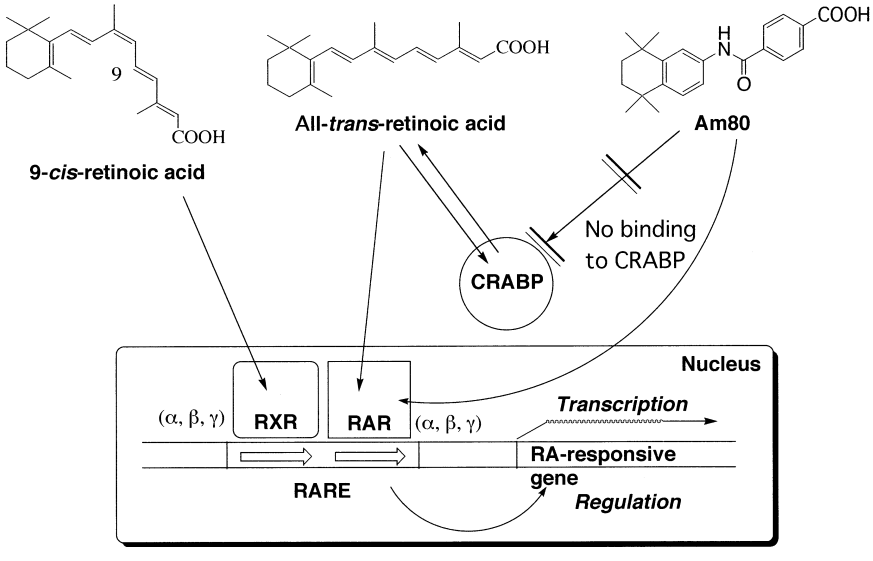

Fig. 1 The molecular mechanisms of retinoids. Cellular retinoic acid-binding protein is sometimes overexpressed in retinoic acid-resistant cells (*CRABP* cellular retinoic acid-binding protein, *RXR* retinoid X receptor, *RAR* retinoic acid receptor, *RARE* retinoic acid-responsive element, *RA* retinoic acid)

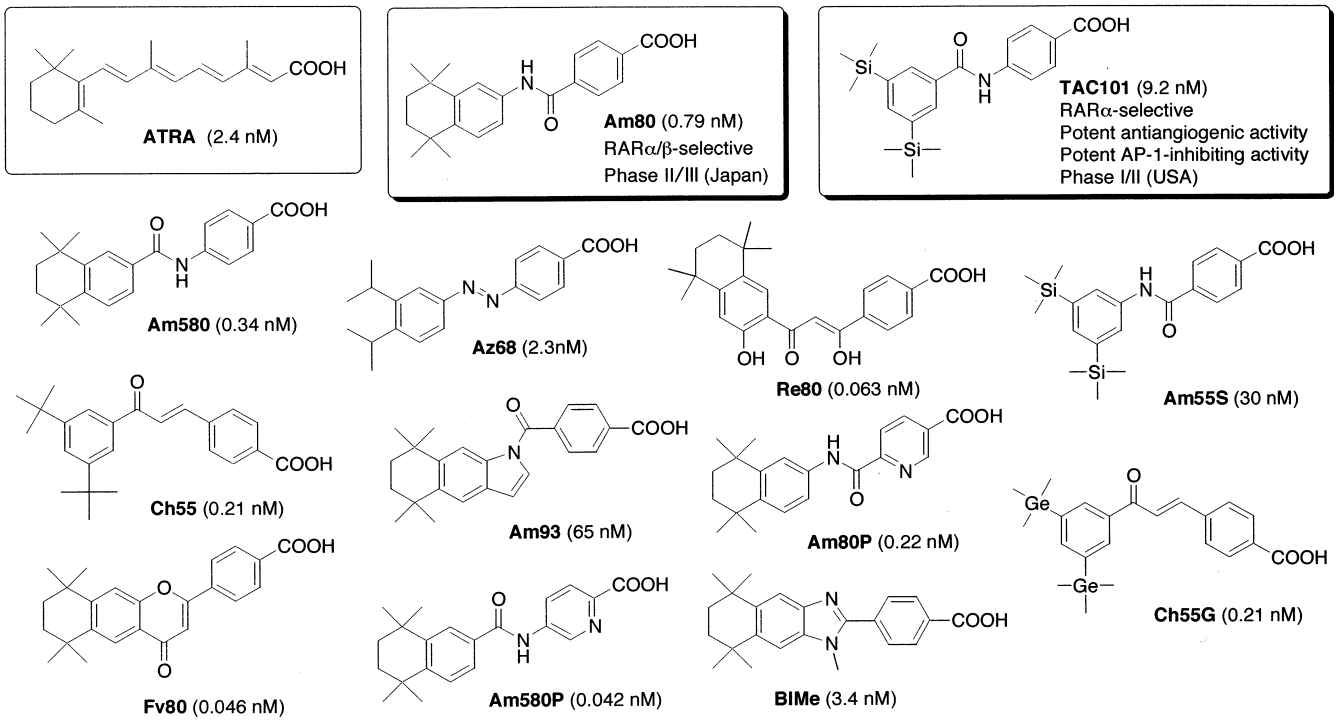

Fig. 2 All-*trans*-retinoic acid and typical retinobenzoic acids. Values in parentheses are the ED_{50} values of cell differentiation-inducing activity on human leukemia HL-60 cells (*ATRA* all-*trans*-retinoic acid, *RAR* retinoic acid receptor)

on the basis of a similar strategy to that used for RAR agonists and antagonists, respectively, and the RXR agonists act as retinoid synergists that enhance retinoidal activity elicited by low-dose RAR agonists [26].

Structurally different types of RAR agonists and antagonists, i.e. RAR agonists of non-benzoic acid structure (e.g. BFX555, TZ181, and Tp140) and RAR antagonists without a bulky hydrophobic group(s) (unpublished data), respectively, have been developed by computer-assisted molecular design (Fig. 3). Computer-assisted retrieval from a chemical database on the basis of a docking study with a three-dimensional RAR structure followed by optimization of the structure resulted in RAR agonists without a carboxylic acid moiety and RAR antagonists without a bulky hydrophobic group(s). The computer-assisted molecular design methodology used can be applied not only to compound databases but also to create a virtual combinatorial library in the computer. These methods led us to produce RXR agonists (e.g. TZ191 and TZ335) (Fig. 3).

Thalidomide

Thalidomide is a hypnotic/sedative drug that was withdrawn from the market because of its severe teratogenicity [4, 5, 6]. However, thalidomide has been found to be useful in the treatment of leprosy, and the drug was formally approved for this purpose by the US Food and Drug Administration in 1998 under critical control. Many reports have appeared on its therapeutic usefulness in various diseases, including colon and other cancers, rheumatoid arthritis, graft-versus-host disease, and acquired immunodeficiency syndrome (AIDS) [4, 5, 6]. Although the pharmacological applications of thalidomide have been widely investigated, the molecular basis of its actions has not yet been clarified. The beneficial pharmacological effects of thalidomide include anticachexia activity (cachexia is a major direct cause of cancer death), antiinflammatory activity, anti-tumor-promoting activity, antiangiogenic activity, anti-cell invasion (antimetastatic) activity, antiviral activity, and a hypoglycemic effect (Table 1). Although thalidomide affects production of various cytokines, the prevailing hypothesis is that all the beneficial effects of thalidomide are elicited through regulation of tumor necrosis factor α (TNF-α) production.

Our studies on the TNF-α production-regulating activity of thalidomide revealed that the effect elicited by the drug is bidirectional, depending both on cell types and cell stimulators [4, 5, 6, 16, 17, 19]. Studies on the structural development of thalidomide resulted in potent bidirectional TNF-α production regulators (e.g. PP-33 and FPP-33) and complete separation of the bidirectionality (pure inhibitors, e.g. R-FPTP and R-FPTN, and pure enhancers, e.g. S-FP13P) (Fig. 4) [4, 5, 6, 15, 19, 20]. Some of our bidirectional TNF-α production regulators and inhibitors prolonged the lifespan of mice with cachexia induced by lipopolysaccharide injection. Ongoing clinical phase II/III studies of thalidomide as an antiangiogenic agent prompted us to assess the antiangiogenic activity of our compounds. Some of our TNF-α production regulators, especially R-FPTP, showed more potent antiangiogenic activity than thalidomide at a

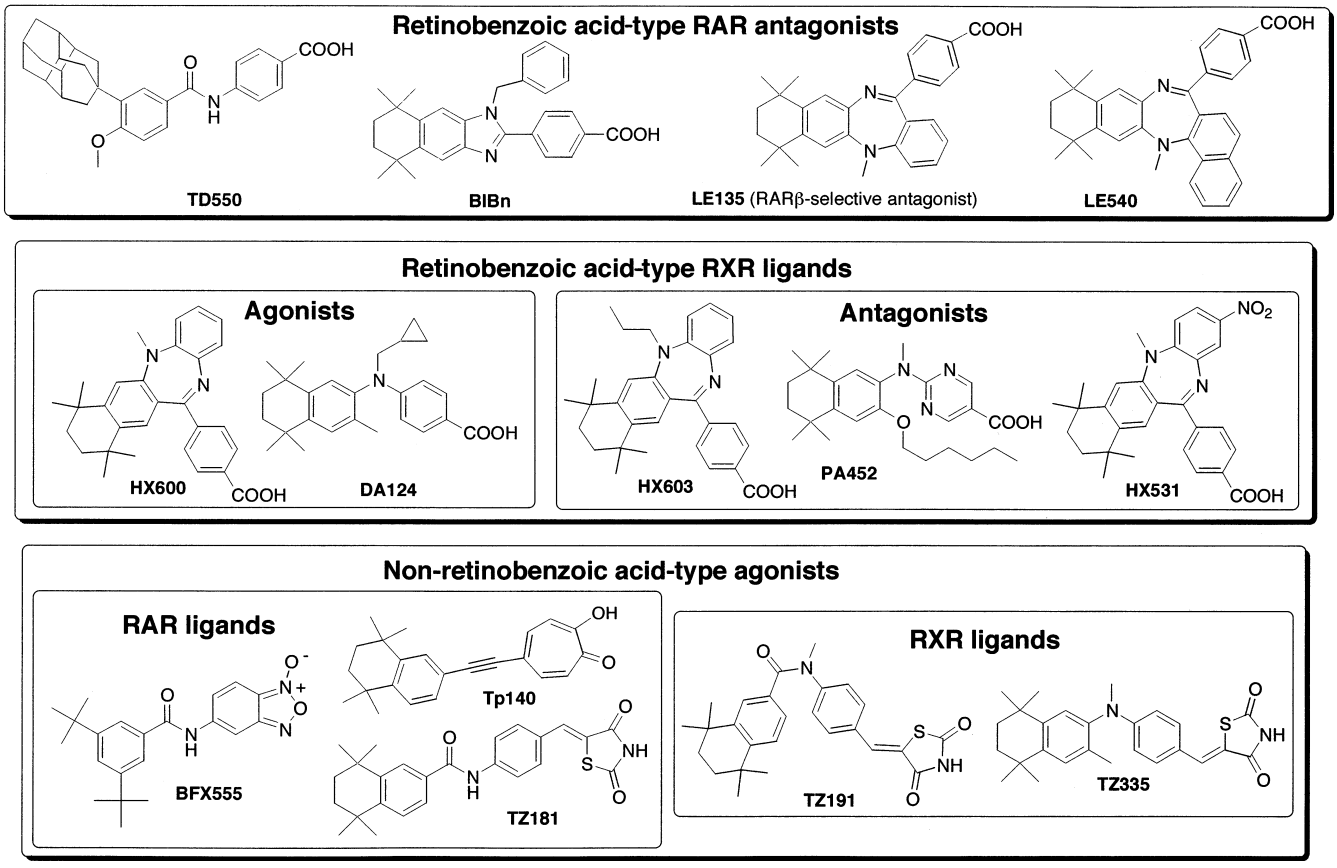

Fig. 3 Typical retinoic acid receptor and retinoid X receptor ligands (*RAR* retinoic acid receptor, *RXR* retinoid X receptor)

Table 1 Typical pharmacological effects elicited by thalidomide and their putative target phenomena/molecules in relation to cancer chemotherapy (*TNF* tumor necrosis factor, *COX* cyclooxygenase)

Pharmacological effect	Possible target phenomena/molecules
Anticachexia effect	TNF-α production inhibition
Anti-tumor-promoting effect	TNF-α production inhibition, nuclear androgen receptor, COX-2
Antiinflammatory effect	TNF-α production inhibition, COXs
Antiangiogenic effect	Thymidine phosphorylase/platelet-derived endothelial cell growth factor inhibition, TNF-α production inhibition
Anti-cell invasion effect	Puromycin-sensitive aminopeptidase inhibition
Antiviral effect	Dipeptidylpeptidase type IV inhibition, α-glucosidase inhibition, TNF-α production inhibition
Hypoglycemic effect	α-Glucosidase inhibition, TNF-α production inhibition

much lower dose [6]. Clinical application studies of these potent antiangiogenic compounds are in progress. However, the structure–activity relationship studies indicated that the pharmacological effects of thalidomide cannot be attributed to its TNF-α production-regulating activity alone [4, 5, 6]. This led us to consider structural modifications of thalidomide based on target molecules/phenomena other than TNF-α, which are considered to be related to the seven pharmacological effects of thalidomide.

For antiangiogenic activity, we considered thymidine phosphorylase (TP)/platelet-derived endothelial cell growth factor (PD-ECGF) as a putative target molecule. Our structural development study targeting TP/PD-ECGF-inhibiting activity yielded several homophthalimide analogs, including NPIQ, which showed more potent inhibitory activity than the classical inhibitor 5-nitrouracil [6, 11]. NPIQ and related inhibitors are considered to be lead compounds for the development of a novel type(s) of TP/PD-ECGF inhibitors.

A preliminary study indicated that our TNF-α production regulators show moderate anti-tumor-promoting activity. This is reasonable because TNF-α is reported to be an endogenous tumor promoter. To develop more potent anti-tumor-promoting agents, we focused on another endogenous tumor promoter, fibroblast growth factor 10 (FGF-10). FGF-10 is reported to act as a tumor promoter especially in prostate cancer, and its production is induced by the steroid hormone androgen. Considering the effectiveness of thalidomide in the treatment of prostate cancer and its structural similarity to the classical androgen antagonist DIMP, we expected that superior nonsteroidal androgen antagonists might be prepared by structural development of thalidomide [6, 9,

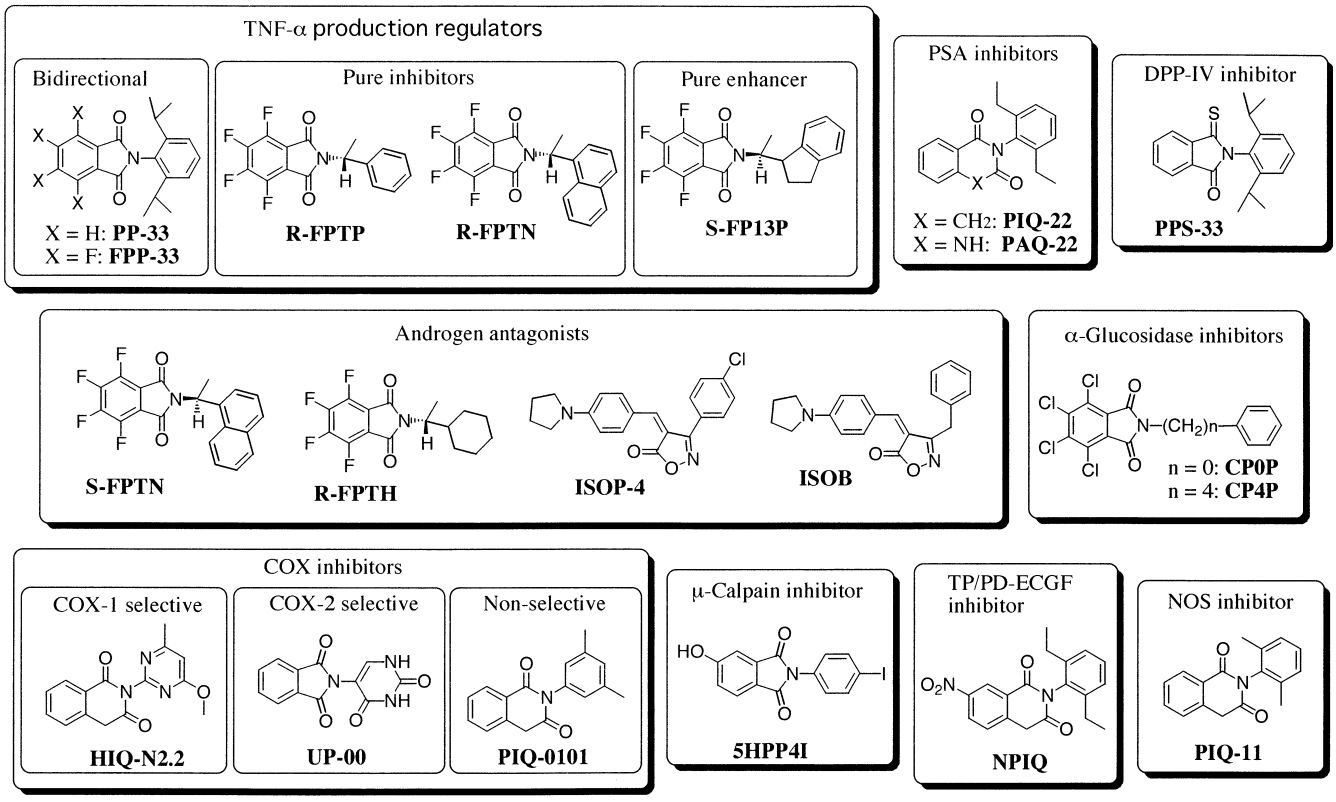

Fig. 4 Typical biological response modifiers and enzyme inhibitors derived from thalidomide (*TNF* tumor necrosis factor, *PSA* puromycin-sensitive aminopeptidase, *DPP-IV* dipeptidylpeptidase type IV, *COX* cyclooxygenase, *TP/PD-ECGF* thymidine phosphorylase/platelet-derived endothelial cell growth factor, *NOS* nitric oxide synthase)

18]. Androgens, typically testosterone and its active metabolite, 5α-dihydrotestosterone (DHT), elicit their biological activity by binding and activating a specific receptor, nuclear androgen receptor (AR), which is a member of the steroid/retinoid/thyroid/vitamin D_3 nuclear receptor superfamily and ligand-dependent specific transcription factor.

Our aim is to create androgen antagonists that antagonize the biological response induced by endogenous or exogenous androgens, by competitively inhibiting their binding to AR. Structural development studies of thalidomide based on antiandrogenic activity resulted in several compounds showing much more potent antiandrogenic activity than flutamide, which is widely used for the treatment of prostate cancer (e.g. S-FPTN and R-FPTH) (Fig. 4) [4, 5, 6, 18]. Further structural development assisted by computer (docking study using the three-dimensional structure of AR) resulted in oxazolone-type compounds, including ISOP-4 and ISOB (Fig. 4) [6, 9]. Evaluation of AR-binding affinity showed that ISOP-4 and ISOB bind AR with an affinity 220- and 214-fold higher than that of flutamide, respectively. Moreover, these nonsteroidal/nonanilide-type androgen antagonists are active toward the human prostate tumor cell line LNCaP, which is generally resistant to known androgen antagonists, possibly because of its mutated aberrant AR [9]. Evaluation of these novel, nonsteroidal, potent androgen antagonists in vivo is in progress.

Another possible target for anti-tumor-promoting activity is cyclooxygenase (COX) [22]. COX is an enzyme that catalyzes synthesis of prostaglandins from arachidonic acid, and is well known as a target molecule of nonsteroidal antiinflammatory drugs, including aspirin. There exist two isoforms of COX. COX-1 is constitutively expressed in most tissues, whereas COX-2 is inducible. Overexpression of COX-2 has been detected in various tumors and its role in carcinogenesis and angiogenesis has been well documented. As such, COX-2 has been suggested to be an important pharmacological target for the prevention and treatment of cancer. In particular, COX-2 inhibitors, including celexocib and sulindac, have been investigated for chemoprevention of various cancers, including colon and prostate cancers. Although thalidomide is known to suppress lipopolysaccharide-induced expression of COX-2, the direct effect of the drug on COX has not been established. Our study showed that thalidomide itself possesses COX-1/2-inhibiting activity with a potency similar to that of aspirin. Structural development studies resulted in COX inhibitors with various COX-1/2 selectivities (e.g. a COX-1-selective inhibitor, HIQ-N2.2, a COX-2-selective inhibitor, UP-00, and a non-selective inhibitor, PIQ-0101; Fig. 4) [22].

With regard to anti-cell invasion/adhesion properties, we focused on aminopeptidase inhibitory activity. Our

structural development studies of thalidomide resulted in specific dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g. PPS-33) (Fig. 4) and specific puromycin-sensitive aminopeptidase (PSA) inhibitors (e.g. PIQ-22 and PAQ-22) (Fig. 4) [6, 11, 12, 21, 23, 24]. DPP-IV appears to be involved in various pathophysiological effects, including tumor cell adhesion and the entry of human immunodeficiency virus (HIV) into $CD4^+$ T cells, and therefore DPP-IV inhibitors are expected to be immunomodulators and to have potential pharmacological/clinical applications. Although the physiological role of PSA has not yet been clarified in detail, specific and potent inhibitors, PIQ-22 and PAQ-22, showed much more potent tumor-cell invasion-inhibiting activity than bestatin or actinonin [6, 11, 12]. This suggests that PSA could be a novel target molecule for the development of antimetastatic agents. PIQ-22 and PAQ-22 are completely inactive toward other aminopeptidases, including aminopeptidase N, which has almost the same substrate selectivity as PSA, and leucine aminopeptidase, against which bestatin and actinonin are potently active. Lineweaver–Burk plot analysis indicated that PIQ-22 and PAQ-22 are noncompetitive inhibitors of PSA, while puromycin and bestatin are competitive inhibitors [6, 11, 12]. This mode of action might explain the high specificity of PIQ-22 and PAQ-22 for PSA. Generally, aminopeptidase family members possess similar substrate selectivity, with similar structures of the substrate-binding pocket. Therefore competitive inhibitors generally cross-inhibit aminopeptidases, as bestatin does. Because PIQ-22 and PAQ-22 are noncompetitive inhibitors, it is thought that PIQ-22 and PAQ-22 bind at a specific site of PSA other than its substrate-binding site. These PSA-specific, potent, nonpeptide, small-molecular inhibitors should be useful as probes to investigate in detail the physiological function of PSA and as lead compounds to develop superior antimetastatic agents.

Of the seven pharmacological effects of thalidomide, only the anticachexia and antiinflammatory effects can definitely be interpreted in terms of TNF-α production-regulating activity. The anti-tumor promotion effect can also be partly interpreted in terms of the same activity but is more likely to be mainly due to antiandrogenic activity, especially in the case of prostate cancer, and COX-2-inhibiting activity. The latter activity should be related to the antiinflammatory effect. The antiangiogenic effect can be interpreted partly in terms of TNF-α production-regulating activity and partly due to TP/PD-ECGF-inhibiting activity. The latter activity might also play a role in the antiviral effect. The antiviral effect, especially against HIV, might be partly explained by TNF-α production-regulating activity. The anti-cell invasion effect can be interpreted in terms of PSA-inhibiting activity. As for the remaining hypoglycemic effect and some antiviral activity, we suspect that α-glucosidase-inhibiting activity might be important. α-Glucosidase is an enzyme that catalyzes the final step in the digestion of carbohydrate. Inhibitors of this enzyme may retard the uptake of dietary carbohydrates and suppress postprandial hyperglycemia, and could be useful in the treatment of diabetes, obesity, and certain forms of hyperlipoproteinemia. They also have potential as antiviral agents controlling viral infectivity through interference with the normal biosynthesis of *N*-linked oligosaccharides by glycosidation of viral coat/envelope glycoproteins, and are being investigated for the treatment of both cancer and AIDS. A well-established classic α-glucosidase inhibitor is 1-deoxynojirimycin (dNM). Some derivatives of dNM have been shown to be effective against HIV and B- and C-types of viral hepatitis. Our structural development studies based on α-glucosidase-inhibiting activity resulted in potent noncompetitive inhibitors (e.g. CP0P) and potent competitive inhibitors (e.g. CP4P) (Fig. 4) [6, 25]. Comparison of the IC_{50} values indicates that CP0P and CP4P are about 13 and 16 times more potent than dNM, respectively.

Discussion

We have been engaged in structural development studies of BRMs based on retinoids and thalidomide. We have created various types of synthetic retinoids, including RAR-agonistic retinobenzoic acids, their antagonists, and RXR ligands. Some of our retinoids are now in clinical phase I–II studies. Computer-assisted molecular design resulted in the development of novel retinoids with completely different skeletons from retinobenzoic acids. This expansion of the structural variation of retinoids should ultimately afford superior differentiation therapy medicaments.

Our studies have also indicated that the effectiveness and potential of thalidomide for the treatment of various diseases cannot be attributed solely to its TNF-α production-regulating activity. Thalidomide should be recognized as a multitarget drug acting on AR, COXs, TP/PD-ECGF, DPP-IV, PSA, and α-glucosidase, at least. Specific and potent compounds for each of these target molecules/phenomena can be prepared by appropriate modification of the thalidomide structure. This means that thalidomide intrinsically possesses pharmacophores with a wide range of activities in its small molecular skeleton. In our studies, we extracted the phthalimide and homophthalimide structures of thalidomide and by using these skeletons were able to obtain specific and potent TNF-α production regulators including bidirectional ones, pure inhibitors, and pure enhancers, TP/PD-ECGF inhibitors, androgen antagonists, DPP-IV inhibitors, PSA inhibitors, and α-glucosidase inhibitors (Fig. 4). We believe that the same strategy will allow the development of hypnotic, antimalarial, and other agents. Creation of antiestrogens and μ-calpain inhibitors (e.g. 5HPP4I) based on the structure of thalidomide was also partially successful. There may also be further biological effects of thalidomide. Inhibition of phosphodiesterases, NO synthase,

and transcription factor NF-κB are candidate actions, as well as induction of cell differentiation [6].

Thalidomide itself has relatively low potency, or is inactive, toward some of the target molecules listed in Table 1. There are at least two possible interpretations of this. One is that the overall effects of thalidomide on the target molecules are additive and thereby appear as clinically useful effects. The other interpretation involves the metabolism of thalidomide. Thalidomide is both chemically and metabolically labile, and various metabolites are known to be produced in vivo. Therefore one or more metabolites might possess potent activity on some or a specific target molecule. The teratogenicity of thalidomide has been reported to be attributed to a metabolite rather than to thalidomide itself. Also, some thalidomide metabolites are known to possess potent cell differentiation-inducing activity, which thalidomide itself does not possess.

Finally, we should emphasize our strategy for the structural development of thalidomide. First, we identified seven pharmacological and biological effects of thalidomide. We then formed a hypothesis as to the molecular target or target phenomenon that might be relevant to each pharmacological/biological effect. It does not matter whether thalidomide itself binds to the hypothetical molecular target. The aim is simply to reproduce the relevant pharmacological/biological effect specifically by using newly prepared compounds. The third step is the creation of potent and specific compounds. Compounds thus prepared might merely mimic thalidomide's pharmacological/biological effects but have no relation to thalidomide at the molecular mechanistic level. Nevertheless, we believe that by preparing compounds that mimic the pharmacological/biological effects elicited by thalidomide (even if the molecular mechanism is different from that of thalidomide) and using combinations of the prepared compounds, we will be able to reproduce or reconstruct the spectrum of pharmacological/biological effects of thalidomide.

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