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Retinoids: potential in cancer prevention and therapy

Nicole Clarke, Pierre Germain, Lucia Altucci and Hinrich Gronemeyer

Retinoids (derivatives of vitamin A) are signalling molecules that play important roles in cell growth, differentiation and death. Retinoids act through two types of receptors – retinoic acid receptors (RARα, RARβ and RARγ) and retinoid X receptors (RXRα, RXRβ and RXRγ) – which themselves act as ligand-dependent transcription factors. Retinoids are of special interest in cancer research owing to their antiproliferative and cancer-preventative properties. They have been used successfully to cure acute promyelocytic leukaemia (APL) and can suppress carcinogenesis in a variety of tissue types (e.g. skin, lung, breast and oral cancers). Extensive research efforts have been dedicated to elucidating the molecular and cellular networks that are induced by retinoids, and this has recently yielded novel insights into how retinoids can both prevent and combat cancer.

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Retinoids (natural and synthetic derivatives of vitamin A) regulate a variety of important cellular functions, such as signalling for growth arrest, differentiation and apoptosis, and can act in different cellular systems and tissue compartments (Refs 1, 2, 3). There is a strong rationale, based on preclinical, epidemiological and clinical findings, for the use of retinoids in the treatment and prevention of cancer (Ref. 4). Studies in 1925 (Ref. 5) showed that deficiency in vitamin A correlated with the development of squamous metaplasia in rodents. Studies on experimental animal models suggest that retinoids can have chemopreventive effects in animal models of chemical mutagenesis (Refs 6, 7). In addition, preneoplastic diseases such as oral leukoplakia, cervical dysplasia and xeroderma pigmentosum have been successfully treated with retinoids (Ref. 8).

The most successful example of retinoid anticancer activity is the treatment of acute promyelocytic leukaemia (APL), a subtype of acute myelogenous leukaemia (AML) in which myelopoiesis is arrested at the promyelocyte stage (Ref. 9). APL originates from a chromosomal translocation that results in formation of an oncofusion protein, PML–RARα (Ref. 9), thereby altering the signalling of both promyelocyte leukaemia protein (PML) and retinoic acid receptor (RAR)α (Refs 10, 11, 12). Retinoic acid (RA) treatment restores the signalling capacity of the RARα segment that carries the ligand-binding domain and might also restore the signalling capacity of PML, as well as possibly initiating more complex phenomena generated by the PML–RARα fusion.

However, APL is a unique type of cancer in being amenable to 'RA differentiation therapy', and attempts to expand the paradigm exemplified by RA treatment of APL to other types of leukaemias or solid cancers have had only limited success. Nevertheless, this must not be taken as an indication that the antiproliferative action of RA (or retinoids in general) is limited to APL. In fact, in addition to the induction of differentiation, multiple other anticancer activities are exerted by the receptors that retinoids act through. Retinoid receptors are heterodimers composed of one of the three RAR and one of the three retinoid X receptor (RXR) family members. The activities mediated by the retinoid receptors encompass, for example, the induction of cell-cycle regulators (e.g. $p21^{WAF1/CIP1}$), the repression of AP1 (the Fos–Jun proto-oncogene product) in models of chemical carcinogenesis, and the induction of the tumour-cell-selective apoptosis ligand TRAIL (Ref. 13). In some models, the RA-inducible RARβ is required for the antiproliferative effect exerted by retinoids and has features of a tumour suppressor gene. Moreover, in vitro and in vivo analysis of several novel chemical compounds – either RAR-selective 'retinoids' or RXR-selective 'rexinoids' – has shown that a number of antiproliferative signalling pathways can be triggered in different systems. In fact, some reports suggest that combination with a second signalling pathway, such as rexinoid–cAMP crosstalk (Ref. 14), can lead to a novel type of antiproliferative response that overcomes RA resistance or re-sensitises insensitive cells to RA action, as in the case of the combination with an epigenetic drug (Refs 15, 16). These and other findings have anticipated the broad activity of retinoids in cancer therapy or chemoprevention. This review summarises the anticancer and chemopreventive capabilities of retinoids, and discusses potential strategies to overcome the possible resistance to retinoids to improve their clinical impact.

Retinoids from a drug-design perspective

Multiple receptors

The biological effects of RAs are mediated by heterodimers formed between RARs (RARα, RARβ and RARγ) and RXRs (RXRα, RXRβ and RXRγ), which are members of the nuclear receptor (NR) superfamily (Ref. 17). RXRs can also form heterodimers with various other NRs, including peroxisome proliferator-activated receptors (PPARs), thereby modulating multiple signalling pathways (Refs 17, 18). Like other NRs, RARs and RXRs are modular proteins that share a common functional and structural organisation and harbour three major domains (Fig. 1a). The N-terminus (A/B region) contains one autonomous transcriptional activation function (AF-1). The highly conserved C region harbours the DNA-binding domain (DBD) that confers sequence-specific DNA recognition. The ligand-binding domain (LBD) (E region) is a highly structured domain comprising a ligand-dependent activation function (AF-2).

Although RAR agonists can autonomously activate transcription through an RAR–RXR heterodimer, RXR is unable to respond to

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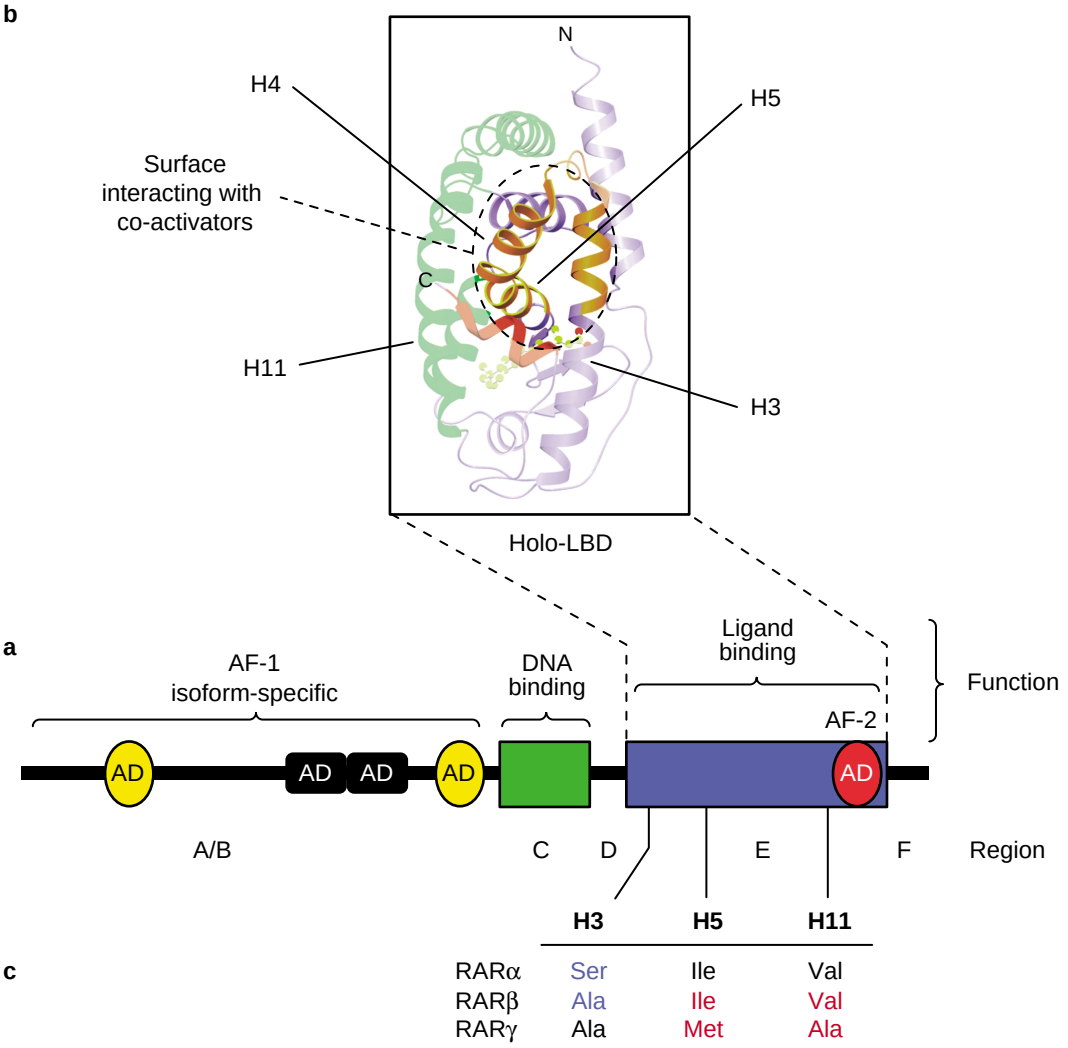

Structural and functional organisation of the nuclear receptor superfamily

Figure 1. Structural and functional organisation of the nuclear receptor superfamily. (a) Nuclear receptors consist of six domains (A–F) based on regions of conserved sequence and function. The evolutionarily conserved regions C and E are indicated as boxes, and a black bar represents the divergent A/B, D and F regions. The N-terminus (A/B region) contains one autonomous transcriptional activation function (AF-1). The highly conserved C region harbours the DNA-binding domain that confers sequence-specific DNA recognition. The ligand-binding domain (E region) is a highly structured domain comprising a ligand-dependent activation function (AF-2). The activation domains (ADs) contain transcriptional activation functions that can activate transcription when fused to a heterologous DNA-binding domain. (b) Schematic drawing of the agonist-bound (holo) nuclear receptor ligand-binding domain (LBD). The α-helices (H1–12) are depicted as ribbons, and the β-turn as broad arrows. The various regions of the LBD are coloured depending on their function: the dimerisation surface is shown in green, the co-activator binding site is shown in orange and the activation helix H12, which harbours the residues of AF-2, is shown in red; other structural elements are shown in mauve. The surface that interacts with the LxxLL motif of co-activators is highlighted by the dotted oval line. (c) The three divergent residues in the ligand-binding pockets (LBPs) of retinoic acid receptor (RAR)α, RARβ and RARγ are located in helices H3, H5 and H11. The residues that differ between RARα and RARβ LBPs are shown in blue; those differing between RARβ and RARγ are shown in red.

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RXR-selective agonists in the absence of an RAR ligand (Refs 19, 20). This phenomenon, referred to as RXR 'subordination' or 'silencing', is biologically important because it avoids confusion between several different NR signalling pathways (e.g. RA, vitamin D3, thyroid hormone). The molecular basis of this subordination is that agonist binding to RXR is unable to induce the dissociation of co-repressor from the RAR–RXR heterodimer, preventing co-activator recruitment (Fig. 2) (Ref. 20). Consequently, the only way for RXR to modulate transactivation in response to its ligand in RAR–RXR heterodimers is through cooperativity with RAR ligands. By contrast to homodimers, which are composed of two identical subunits that bind to the same palindromic DNA sequence (see the corresponding illustrations in Ref. 17) and respond to a single cognate ligand, heterodimerisation allows, in principle, fine-tuning of NR DNA binding and ligand responsiveness by using two different or combinatorial sets of ligands. This fine tuning has been demonstrated by the multiple possibilities for modulating transcriptional co-regulator interactions of RAR–RXR heterodimers (Ref. 20). Whereas RAR cannot form homodimers, RXR is able to activate transcription from cognate reporter genes as homodimers. However, in vitro studies have shown that the RXR LBD forms homodimers with relatively low affinity compared with its heterodimeric association with RAR. Note that ligands can bind to both monomeric and dimeric receptors and that in heterodimers each subunit can autonomously bind its agonist.

Molecular mechanisms of transcriptional regulation in normal and APL cells

RAR–RXR heterodimers act as ligand-dependent transcriptional regulators capable of binding to specific DNA sequences (termed RA response elements or RAREs) found in the promoter regions of target genes, including nuclear hormone receptors, such as RARβ (for a list of RAREs, see Ref. 17). These cognate binding sites correspond to a 5 bp-spaced direct repeat (generally referred to as DR5) of polymorphic arrangements of the canonical motif 5'-PuG(G/T)TCA. When RAR–RXR heterodimers are in the unbound, 'unliganded' state they are known as 'apo-heterodimers' and repress target gene expression by recruiting co-repressors to the RAREs; when bound to agonist, RARs and RXRs are termed 'holo-heterodimers' and recruit co-activators to the RAREs, which ultimately results in gene activation (Fig. 3).

The proposed early steps of the molecular mechanisms by which RAR–RXR heterodimers regulate the transcription of target genes (Refs 17, 21, 22) are described in Fig. 3. In the absence of RAR agonists, and in the presence of certain RAR antagonists, apo-heterodimers are believed to exist associated with promoters of target genes in a complex with co-repressors such as N-CoR and SMRT, and associated factors such as histone deacetylases (HDACs) (Ref. 23); this results in local chromatin condensation and gene silencing (Ref. 24). By contrast, binding of RAR agonists [such as all-trans RA (at-RA) or 9-cis RA (9c-RA)] induces a major change in the structure of the RAR LBD (forming the holo-heterodimer) that leads to co-repressor dissociation and allows the establishment of a complex of co-activators that can acetylate histones [histone acetyl transferases (HATs), such as CBP], relieving the chromatin-mediated silencing induced by HDACs. Recruitment of ATP-dependent chromatin-remodelling machineries, such as SWI–SNF, prepares the template for the action of the basal transcriptional machinery, consisting of RNA polymerase holoenzyme together with the transcription factor TFIID [consisting of TATA-binding protein (TBP) and TBP-associated factors (TAFs)] and mediator complexes (Ref. 21).

As mentioned above, APL originates from a chromosomal translocation that forms the oncofusion protein PML–RARα (Ref. 9). The PML–RARα fusion displays increased binding efficiency to the transcriptional co-repressors N-CoR or SMRT compared with the RARα protein (Refs 25, 26, 27), resulting in recruitment of HDACs and silencing of RAR target genes, which arrests myelopoiesis at the promyelocyte stage. In order to dissociate the co-repressor–HDAC complex and recruit the co-activator–HAT complex, high, nonphysiological levels of at-RA are required (Refs 28, 29). Once HDAC complexes are dissociated, the normal sequence of events leading to gene activation can be initiated, leading to the transcription of RAR target genes (Fig. 3) with concomitant differentiation and post-maturation apoptosis of the myeloid cells.

Structural basis of retinoid action

The resolution of the crystal structures of monomeric, homodimeric and heterodimeric NR

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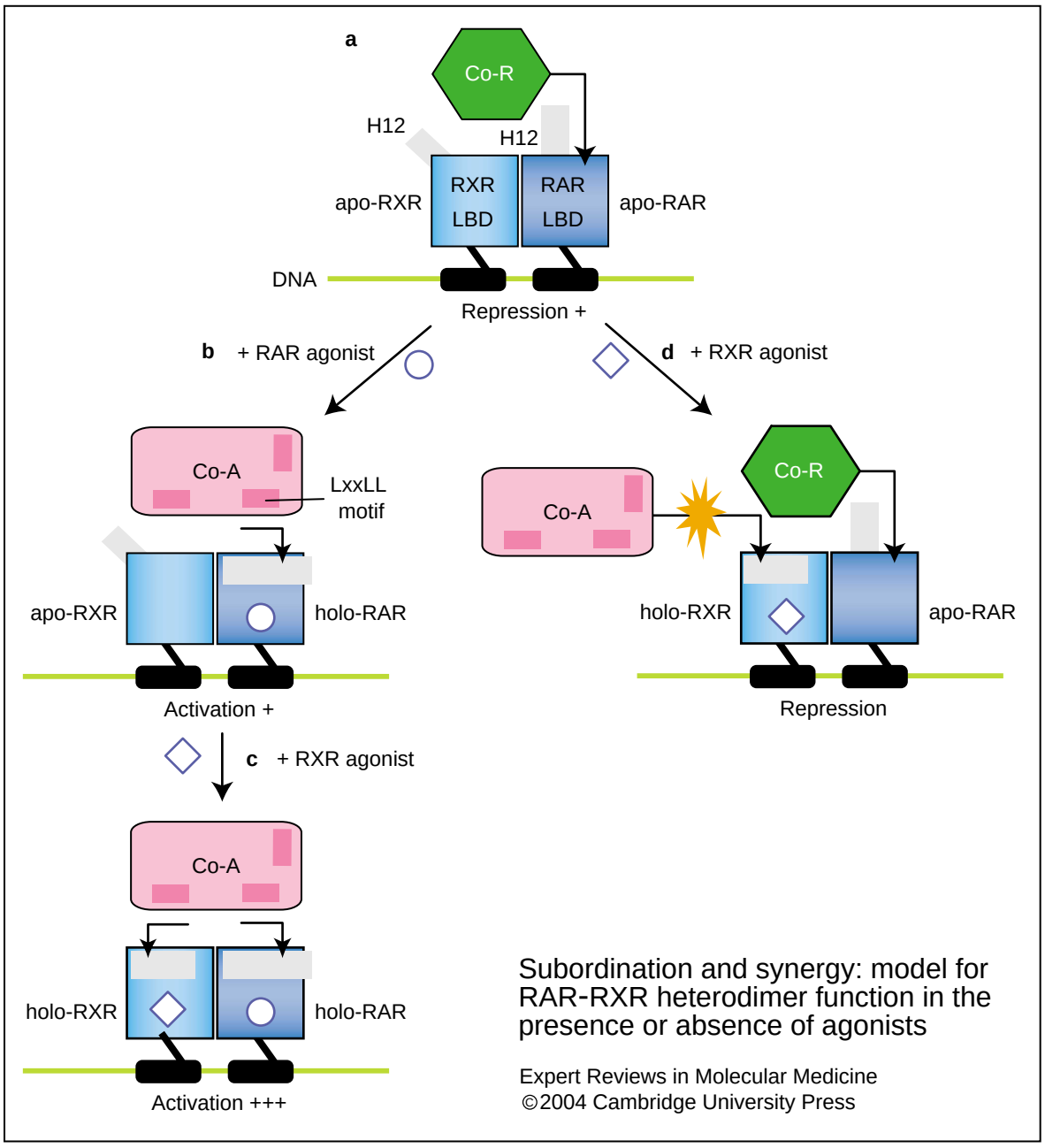

Figure 2. Subordination and synergy: model for RAR–RXR heterodimer function in the presence or absence of agonists. The figure depicts heterodimers of retinoic acid receptors (RARs) and retinoid X receptors (RXRs) bound to retinoic acid response elements on DNA; the C-terminal helix H12 of RXR/RAR, a co-activator (Co-A) harbouring three NR (nuclear receptor) boxes with the LxxLL motif, and a co-repressor (Co-R) are also shown. (a) In the absence of RAR agonists, apo-heterodimers are associated with co-repressors. (b) RAR-agonist-induced transconformation (change in conformation) of the RAR ligand-binding domain (holo-LBD) leads to the association of the co-activator through an NR box (LxxLL) in the co-activator, and destabilises the co-repressor bound to the ligand-free LBD (apo-LBD). (c) In the presence of both RAR and RXR agonists, synergy originates from the cooperative binding of two NR boxes in one co-activator molecule (one to each receptor of the heterodimer). (d) RXR agonists alone can induce co-activator recruitment to RXR, but cannot dissociate co-repressors from heterodimers of RAR–RXR. As the binding of co-activators and co-repressors are mutually exclusive, an agonist-bound RXR within an apo-RAR–RXR heterodimer cannot bind a co-activator in the usual environment, thus accounting for RXR subordination.

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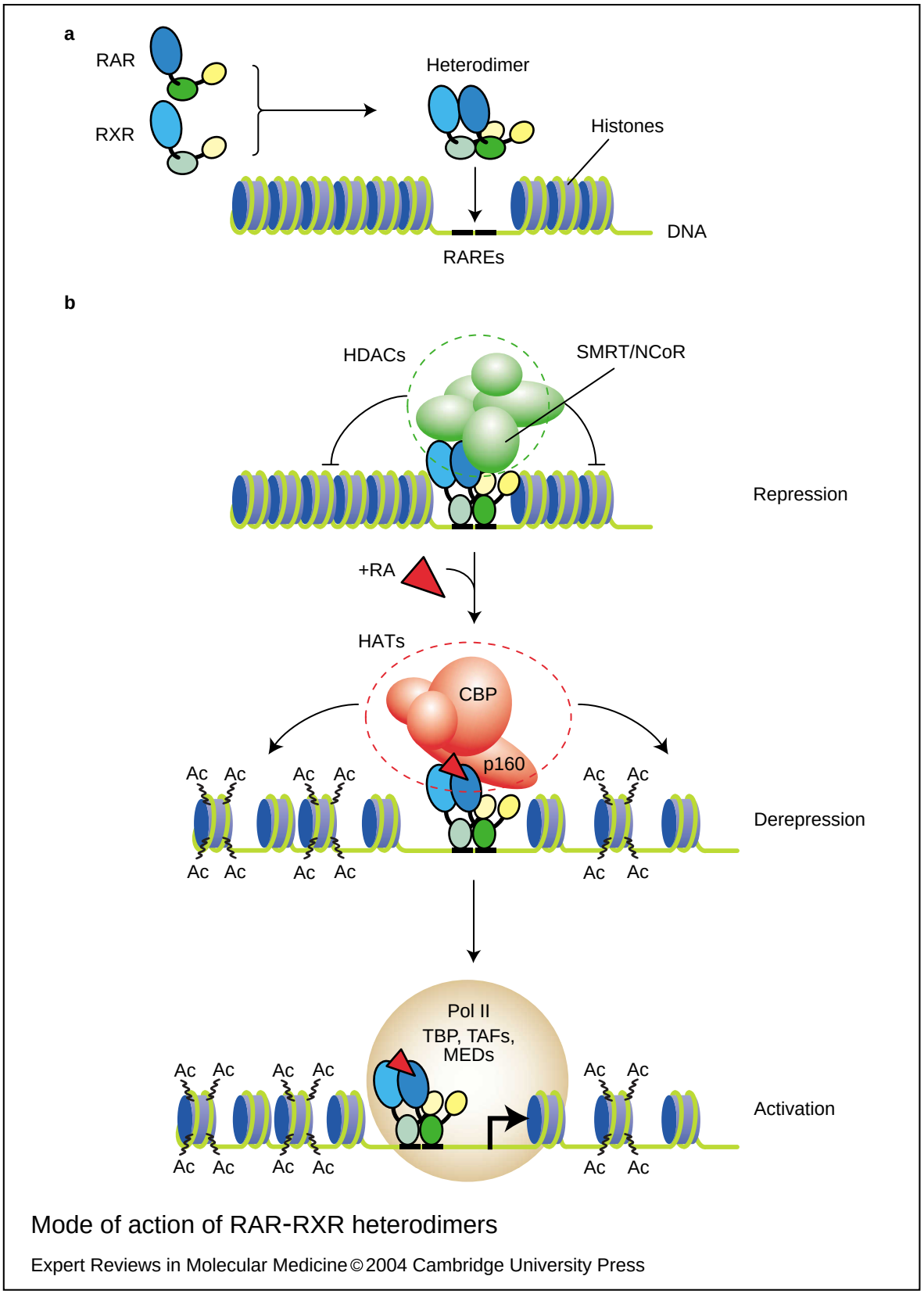

Mode of action of RAR-RXR heterodimers

Figure 3. Mode of action of RAR–RXR heterodimers. *(See next page for legend.)*

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Figure 3. Mode of action of RAR–RXR heterodimers. *(Legend; see previous page for figure.)* (a) Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) form heterodimers that bind within the regulatory region of target genes through the retinoic acid response elements (RAREs). These cognate binding sites on DNA correspond to a 5 bp-spaced direct repeat (generally referred to as DR5) of polymorphic arrangements of the canonical motif 5'-PuG(G/T)TCA (shown as heavy black lines). (b) In the absence of ligand (e.g. RA), RAR–RXR heterodimers (apo-heterodimers) are believed to be bound to RAREs of target genes together with transcriptional co-repressors (N-CoR or SMRT), which then recruit histone deacetylases (HDACs). This is thought to account for a gene-silencing effect of apo-heterodimers through chromatin condensation (repression). Binding of ligand induces the release of the HDAC complex and results in the recruitment of histone acetyltransferase (HAT) co-activators, such as CBP and p160. The subsequent chromatin decondensation (derepression) due to histone acetylation ('Ac') is thought to be necessary, but not sufficient, for target gene activation. As the last step, the RNA polymerase II holoenzyme, together with the TATA-binding protein (TBP) and TBP-associated factors (TAFs), and mediator complexes (MEDs), are recruited, which increases the frequency of transcription initiation. Although the temporal order of factor recruitment is being determined with increasing precision, the composition of the complex and the dynamics and specificities of the events are largely elusive. Abbreviations: CBP, CREB-binding protein; NCoR, nuclear receptor corepressor; p160, co-activator (e.g. TIF2/RAC3/SRC-1); SMRT, silencing mediator for retinoid and thyroid hormone receptor.

LBDs in the presence of agonists (the 'holo' form), or in the presence of antagonists or fragments of coactivators, or in the absence of bound hormone (the 'apo' form) has provided molecular details of the various ligand-induced changes. These structures have also shown how structural alterations translate into protein–protein interactions (Ref. 30).

The first solved structure for an NR LBD, the unliganded RXRα LBD, revealed a canonical 'antiparallel α-helical sandwich' fold of NRs comprising 12 α-helices and one antiparallel β-sheet (Ref. 31). A comparison of the apo- and holo-LBD (Ref. 32) structures suggested a common mechanism by which the activation function AF-2 became transcriptionally competent. Agonist binding induces a major transition of the C-terminal part of the LBD comprising helix H11, loop L11–12 and helix H12 (Fig. 1b). These agonist-induced conformational changes generate the surface to which a short α-helix present in the NR-interacting domain (NID) of co-activators bind. The α-helix contains an LxxLL motif (with L being a leucine residue and x any amino acid) termed the 'NR box' that is present in several copies in the NID of co-activators. The NR interaction surface is composed of a static part of helix H3, helix H4 and the loop L3–4 connecting them, and helix H12. Concomitantly with co-activator recruitment, the repositioning of the helix H12 in its active (holo) conformation prevents interaction with co-repressors.

Recent analyses have provided evidence that co-repressor proteins such as N-CoR and SMRT bind by virtue of a region similar to the NR box, called the CoRNR box, to an NR surface topologically related to that involved in co-activator interactions (Ref. 33). However, these surfaces are entirely distinct as a result of the agonist-induced conformational changes.

RAR isotype-selective ligands and rexinoids

Many synthetic retinoids (see Table 1) have been generated that exhibit a distinct pattern of agonist/antagonist activities with RARs and RXRs. These retinoids are selective tools with which to dissect the pleiotropic functions of the natural agonists, at-RA and 9c-RA, and might constitute new therapeutic drugs. Since 9c-RA can bind to both RXR and RAR, it was crucial to find synthetic molecules that recognise only RXR in order to decipher the role played by this receptor and its ligand activation (Refs 34, 35). Several ligands that specifically bind to RXR and activate RXR-homodimer-dependent transcription have been identified. All these RXR-specific compounds are called 'rexinoids'.

Despite the chemotherapeutic and chemopreventive potential of RAR ligands (Ref. 13), the pharmacological use of at-RA is severely restricted because of a broad spectrum of toxic side effects. Since the individual RAR subtypes have distinct tissue distribution patterns and appear to regulate different subsets of genes, compounds that are selective for each RAR should have more-restricted pharmacological activities, limited side effects and better therapeutic indices in specific disease applications. A structure-based sequence alignment revealed that only three residues have diverged in the LBDs of RARα, β and γ (Fig. 1c). This led to the prediction that these

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Table 1. Retinoid receptors and their ligands[a]

Receptor	Natural ligands	Synthetic agonists	Synthetic antagonists
RARα		BMS753 Am580	BMS614 Ro.41-5253
RARβ		BMS641	None
RARγ		BMS961 CD666	None
	Pan-agonist: all-trans retinoic acid (at-RA)	Pan-agonists: TTNPB, 13-cis retinoic acid	Pan-antagonists: BMS009, BMS493, AGN193109
RXR	No physiological ligand has been definitely defined, but candidates are: 9-cis retinoic acid, docosahexanoic acid and phytanic acid	SR11237 CD3254 LG100268 LGD1069	LG100754 UVI3003

[a]For further information on the synthetic ligands, see Refs 20, 36, 144, 145, 146, 147, 148, 149, 150, 151, 152.

divergent residues would be critically involved in the ability of the receptor to differentiate between selective retinoids. Indeed, swapping of these residues confirmed this hypothesis (Ref. 36). Several RARγ-selective agonists have been characterised. All crystal structures of complexes with such molecules solved so far have shown that RARγ selectivity is supported through formation of a hydrogen bond between a proximal hydroxyl group of the ligand and the RARγ-specific Met272 sulphur atom (Fig. 1c) (Refs 37, 38). For RARα, the possibility of establishing a hydrogen bond between an amino group present in the linker of the identified RARα-selective agonists and the RARα-specific Ser232 (Fig. 1c) is predicted to favour RARα selectivity. This is due to the fact that no such bonds can be formed in the RARβ or RARγ LBPs, which harbour an alanine residue instead of a serine. In both cases, the presence of an alcohol or amino group causes a loss of agonist binding to the three RARs, but this is counteracted by the formation of the hydrogen bond by RARγ or RARα, respectively.

Molecular basis of the anticancer action of retinoids

Retinoid anticancer activity linked to TRAIL

The molecular mechanism behind the action of RAR ligands is increasingly well understood. Using the prototypic APL cell model NB4 and also leukaemic blasts of freshly diagnosed APL patients, certain RAR-selective retinoids (e.g. at-RA) were shown to induce the death ligand TRAIL [for 'tumour necrosis factor (TNF)-related apoptosis-inducing ligand'; also known as Apo-2L or TNFSF10], which resulted in the retinoid-induced death of cells in a paracrine fashion upon cell–cell contact (Ref. 39). TRAIL is a type II membrane protein and maps to human chromosome 3 at position 3q26 (Ref. 40). There are four known receptors capable of binding TRAIL: death receptors 4 and 5 (DR4 and DR5) (Refs 41, 42) and two decoy receptors, DcR1 and DcR2 (Ref. 43). DR4 and DR5 contain cytoplasmic death domains and, when bound by TRAIL, transmit an apoptosis signal to the cell. By contrast, the decoy receptors either lack a functional cytoplasmic death domain or completely lack a cytosolic region and therefore cannot transmit an apoptosis signal.

There are two types of apoptosis that can be induced in a cell, termed the 'cell-extrinsic pathway' and the 'cell-intrinsic pathway' (Fig. 4). In the cell-extrinsic pathway, TRAIL docks at a receptor (e.g. DR4/DR5), which trimerises and recruits specific proteins to its intracellular domains (Fig. 4a). These proteins form what is called the death-inducing complex (DISC), which includes the adaptor protein Fas-associated death domain (FADD) and the apoptosis initiator caspases 8 and 10. The initiator caspases are

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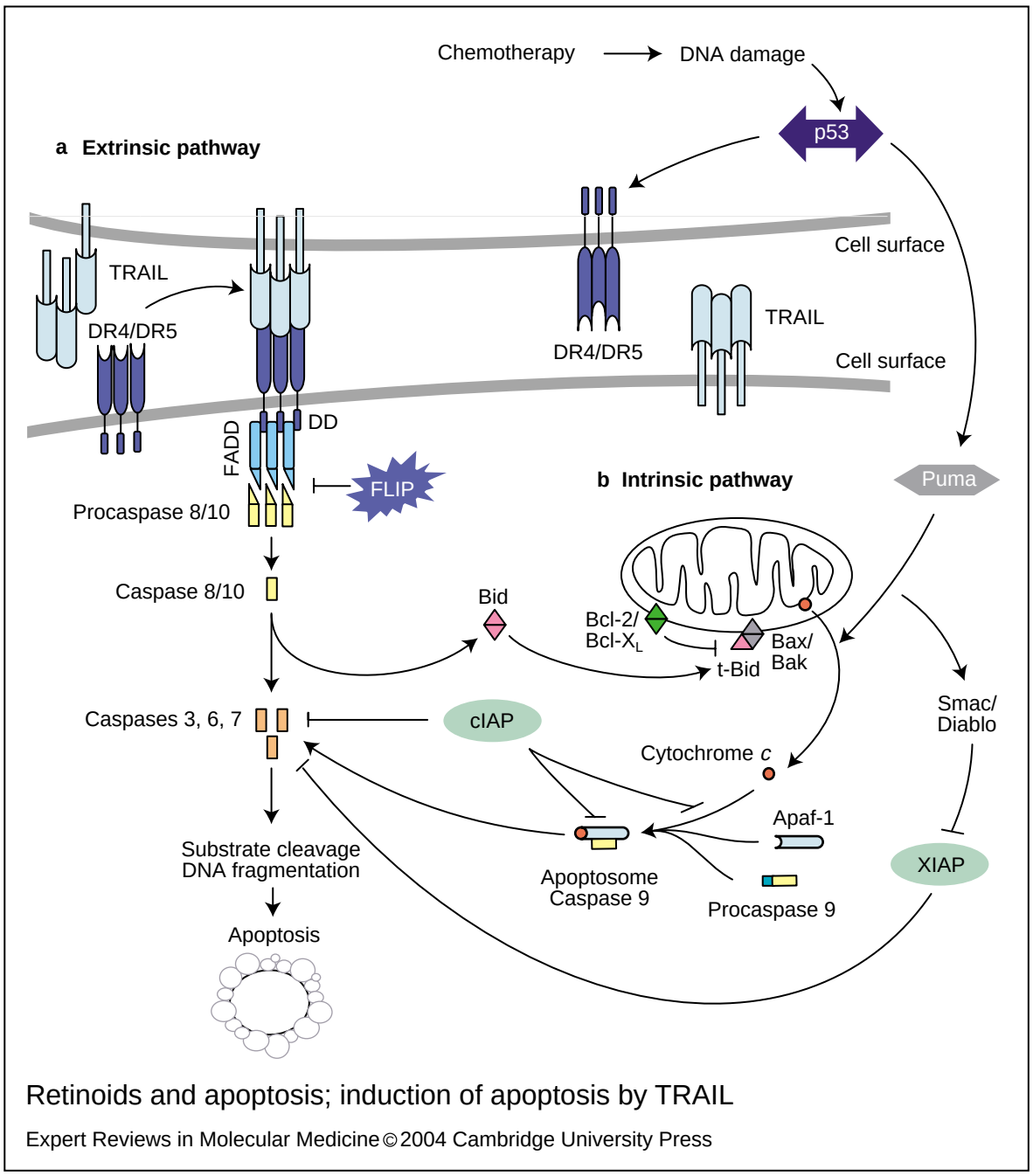

Figure 4. Retinoids and apoptosis; induction of apoptosis by TRAIL. *(See next page for legend.)*

autocatalytically cleaved at the DISC and then transmit a signal to downstream caspases 3, 6 and 7, which execute the death program. Signals that primarily engage the mitochondria (e.g. Bcl-2) are involved in the cell-intrinsic apoptosis pathway (Fig. 4b). Although TRAIL and other death ligands such as Fas utilise the extrinsic apoptosis pathway, evidence exists that some of these death ligands also couple to the intrinsic death pathway (Refs 44, 45, 46).

TRAIL is a novel molecule because many reports support the idea that this death ligand is 'tumour specific': most tumour cells are sensitive to apoptosis induction by TRAIL but most normal cells are not sensitive. This had led to intensive research on this ligand as a potential potent

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Figure 4. Retinoids and apoptosis; induction of apoptosis by TRAIL. *(Legend; see previous page for figure.)* Retinoids induce a circuitry of survival (not described here) and death programmes that results in expression of the membrane-bound tumour-selective death ligand known as tumour necrosis factor-related apoptosis-inducing ligand (TRAIL). Induction of TRAIL appears to act in a paracrine fashion to induce cell death. (a) In certain cell types, the cell-extrinsic pathway is sufficient to activate cell death, and is initiated by the binding and trimerisation of TRAIL death receptors (DR4/DR5), containing an intracellular death domain motif (DD), to form the death-inducing signalling complex (DISC). Trimerisation of the DDs leads to the recruitment of Fas-associated death receptor (FADD). This is an adaptor molecule that recruits and activates caspase 8 (or caspase 10), and consequently activates effector caspases such as caspases 3, 6 and 7. The cellular FLICE-inhibitory proteins (c-FLIPs) have homology to caspase 8 (or 10) but lack protease activity and can act as inhibitors if recruited to the DISC. (b) In other cell types, the extrinsic pathway couples to the cell-intrinsic pathway (the pathway most frequently utilised by the tumour suppressor protein p53 via induction/activation of proteins such as PUMA and Bax/Bak) through a mitochondrial amplification loop to promote apoptosis. This loop involves the cleavage of the Bcl-2 family member Bid by caspase 8 and translocation of the truncated form t-Bid to the mitochondria, where it activates the pro-apoptotic Bcl-2 family members Bax/Bak. Bax action at the mitochondria results in dissipation of the mitochondrial transmembrane potential and release of cytochrome *c* into the cytosol. Cytochrome *c* in the cytosol binds the adaptor Apaf-1 to form an apoptosome that activates the apoptosis-initiating caspase (caspase 9), which in turn activates the effector caspases. The protein Smac/Diablo is able to promote apoptosis by binding to inhibitor of apoptosis proteins (e.g. cIAP, XIAP); this prevents them from inhibiting caspase activation, and thus allows efficient activation of the apoptosis programme.

cancer therapeutic. Although initial experiments revealed selective tumour cytotoxicity of TRAIL, there have been reports that TRAIL is cytotoxic to some normal cells such as hepatocytes (Ref. 47). This cytotoxicity in normal cells might be explained by the fact that different forms of recombinant TRAIL exist. A nontagged, Zn-optimised version of TRAIL has been shown to induce apoptosis in cancer cells, whereas hepatocytes and keratinocytes are resistant to this version. Therefore, TRAIL is an exciting cancer therapeutic for the future, and further work on its action in vivo is ongoing to test its safety and efficacy in cancer patients (Ref. 48).

TRAIL mRNA and protein levels are modulated by several different pathways in cells. We have recently identified a member of the interferon (IFN) response pathway – IFN response factor 1 (IRF-1) – as a key factor involved in the induction of TRAIL by RA and IFN-γ (Ref. 49). IRF-1 was recruited to the promoter of TRAIL at two sequences: the ISRE and a consensus IRF-E. We also found that treatment of cells with both antitumour agents (RA and IFN-γ) resulted in cooperative binding of IRF-1 at the TRAIL promoter, resulting in synergistic levels of TRAIL mRNA and protein. This level of TRAIL was significant as it could potently kill heterologous cancer cells in a paracrine fashion and might underlie the well-documented synergistic antiproliferative and apoptotic effect of retinoid–IFN combinations. IRF-1 is an interesting transcription factor as it has been termed both a 'tumour susceptibility factor' and a 'tumour suppressor gene'. It plays multiple roles in the IFN system as part of the innate antibacterial and antiviral immune responses. There is an enormous amount of data showing that IRF-1 is indeed able to suppress tumour growth both in vivo in mice and in vitro in cell culture using various cancer cell systems (Refs 50, 51, 52, 53), and its link to the TRAIL death pathway is important as it further defines IRF-1 as a tumour suppressor.

Other agents, such as phorbol 12-myristate 13-acetate (PMA)/ionomycin or TNF, have been shown to induce TRAIL transcripts via the NF-κB pathway (Ref. 54). More specifically, NF-κB essential modulator (NEMO/IKKγ) was implicated in its upregulation at the molecular level (Ref. 55). IFNs are also potent inducers of TRAIL in many cell systems (Refs 56, 57, 58, 59, 60). In the case of IFN-α/β, the transcription factor IFN-stimulated gene factor 3 (ISGF3) complex was shown to be important for the induction in mouse embryonic fibroblast cells via the binding of ISGF3 to an ISRE in the promoter region of the TRAIL promoter (Ref. 61). Recently, FOXO/Forkhead proteins have been implicated in the regulation of TRAIL transcription, suggesting a link between the tumour suppressor PTEN (which regulates the activity of FOXO/Forkhead proteins) and TRAIL (Refs 62, 63).

Many of the above proteins and pathways are involved in tumour suppression and indicate that TRAIL is a central figure in the antitumour activities they induce. Therefore, modulation of

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other antitumour pathways by selective drugs (e.g. therapeutic agents to block phosphatidylinositol 3-kinase activity) in combination with RA might cooperate to induce TRAIL-mediated death in cancer cells.

RARβ as a tumour suppressor

Recently, the RARβ member of the retinoid receptor family has emerged as a potential tumour suppressor, following the finding that its expression is selectively lost in many neoplastic epithelial tissues, including non-small-cell lung cancer, squamous cell carcinomas of the head and neck, and breast cancer (Refs 64, 65, 66, 67, 68, 69, 70). RARβ is an RA-inducible RAR as a result of a RARE in its promoter, and might be a key factor in the antiproliferative effect of retinoids (Ref. 71). Experiments where RARβ was stably overexpressed or the RARβ locus was re-activated in retinoid-resistant cell lines sensitised these cells to retinoids (Refs 72, 73, 74). In clinical trials, the restoration of RARβ expression correlated with clinical response and suggested that RARβ was a mediator of the response to RA (Ref. 67). A frequent mechanism of RARβ repression was shown to be hypermethylation-induced silencing of the RARβ promoter (Refs 75, 76, 77, 78), as well as hypoacetylation of the gene (Ref. 79). A mechanism to overcome this type of retinoid resistance and restore RA signalling has been demonstrated by the combination of retinoids with demethylating agents or HDAC inhibitors, which resulted in re-expression of the gene in affected cells (Ref. 73). In the future, experiments geared at elucidating gene networks controlled by RARβ will be useful to understand fully how loss of this retinoid family member might contribute to tumourigenesis.

Atypical retinoids

Atypical retinoids such as fenretinide (4-HPR) and CD437 (see Fig. 5) are synthetic analogues of RA and have shown great promise as cancer therapeutics owing to their antiproliferative and apoptotic effects in vitro. Indeed, fenretinide has shown a high anticancer potential in several preclinical studies (reviewed in Ref. 13) and is being used in clinical trials for ovarian cancer (treatment and prevention), prostate cancer, neuroblastoma, glioblastoma and advanced solid tumours. The atypical retinoids have recently been studied intensively to elucidate the molecular mechanism by which they can induce apoptosis in vivo and in cultured cells. Although these synthetic compounds are retinoids because they can bind and transactivate RARs, this activity does not explain all their growth-inhibitory and apoptogenic effects, because they are active in retinoid-resistant cells and retinoid antagonists do not completely block their activity (Ref. 80). Indeed, 4-HPR induces apoptosis in HL-60 cells independently of the retinoid receptors, probably via the generation of reactive oxygen species (ROS) (Ref. 81). Moreover, several novel analogues of CD437, such as the 3-chloro AHPN analogue MM11453, and MM002 (see Fig. 5), that lack RAR transcriptional activity have also been reported to have anticancer potential (Refs 82, 83).

4-HPR and CD437 or their analogues, as well as several other retinoid-related molecules, have been reported to show antitumour activity with little or low toxicity compared with classical retinoids. Among these retinoid-related molecules, the 'heteroarotinoids' – a group of compounds modified on the basis of arotinoid chemistry (containing aromatic ring(s) and at least one heteroatom within the skeletal framework) – have shown marked anticancer activities in vitro (Ref. 84) and much lower toxicities when compared with some clinically utilised retinoids. One example of a heteroarotinoid was selected by the National Institutes of Health (NIH) for preclinical screening (now in progress) for potential use in treating ovarian and cervical cancer. Another type of retinoid-related molecule, MX781 (unrelated to CD437), is an RAR antagonist that induces apoptosis and showed exceptional anticancer activity against oestrogen-independent breast cancer cells, although high concentrations of the compound are required in vitro to induce apoptosis (Refs 85, 86). Finally, the novel atypical retinoid ST1926 (see Fig. 5) exhibited a potent antiproliferative activity on a large panel of human tumour cells despite no measurable RAR-activating ability in one report (Ref. 87), although some RARγ activity in another report (Ref. 88). Further investigations will clarify whether the anticancer action of certain types of retinoid and retinoid-related molecules is dependent or independent of RAR/RXRs.

Many of these atypical retinoids have been found to induce mitochondrial membrane depolarisation and caspase activation (Refs 89, 90). In the case of the retinoid CD437, treatment of ovarian carcinoma cells caused the translocation of TR3 to the mitochondria (Refs 91, 92). TR3 (also

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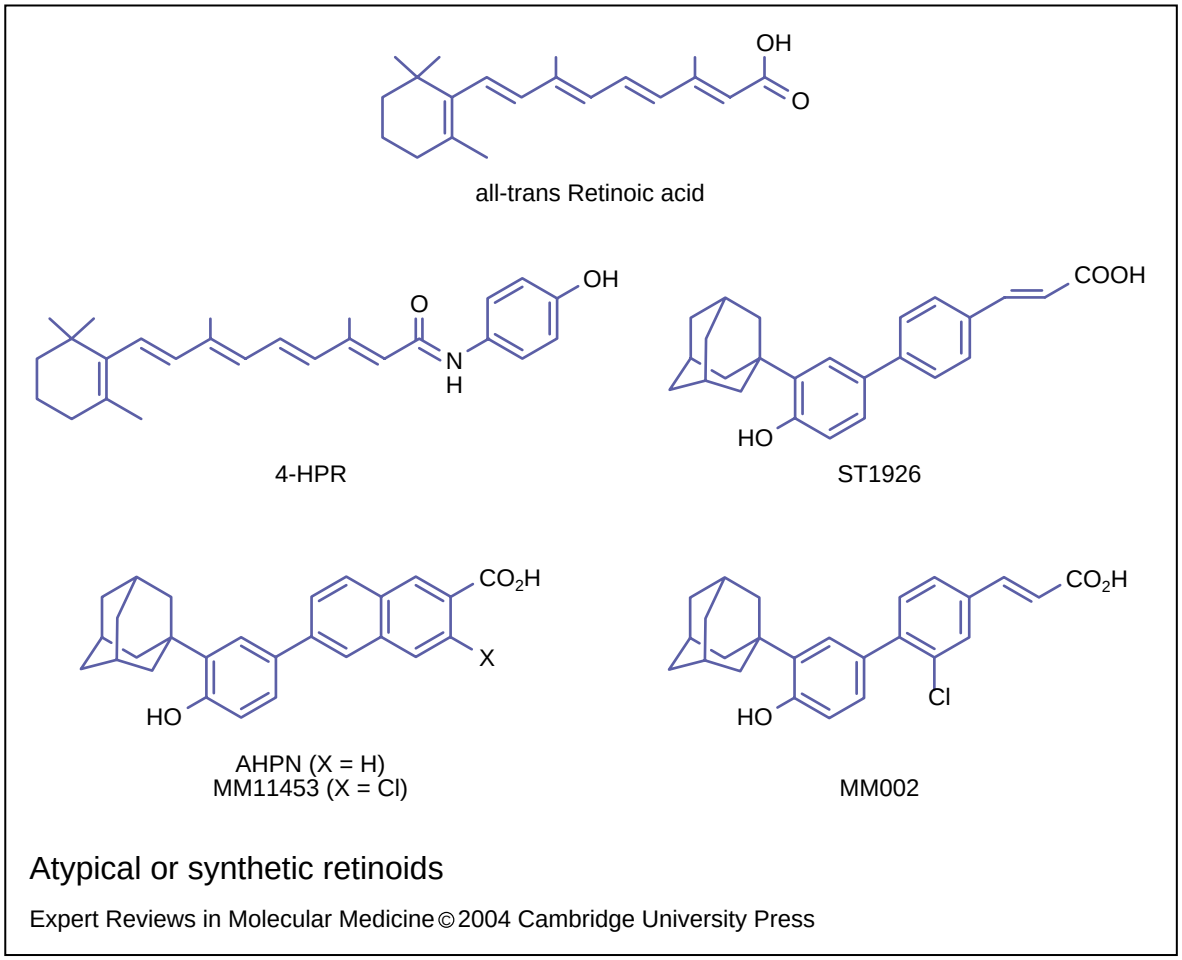

Figure 5. Atypical or synthetic retinoids. The structure of four atypical retinoids are given with the structure of the ligand all-trans retinoic acid as comparison. 4-HPR [N-(4-hydroxyphenyl) retinamide; 'fenretinide'], can induce antiproliferative effects and apoptosis in cells independently of the retinoid receptors but is also able to bind and activate the retinoid receptors. ST1926 [E-3-(4'-hydroxy-3'-adamantylbiphenyl-4-yl)acrylic acid; a synthetic heteroretinoid with some documented RARγ activity – see text], and MM11453 and MM002 {analogues of 6-[3-(1-admantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437), an atypical retinoid}, lack the ability to induce RAR transcriptional activity but have been found to have potent anticancer activity against several tumour cell types in vitro. Compared with classical retinoids, such as 13-cis retinoic acid, some of these retinoids might have lower toxicity, and be able to induce apoptosis in RA-resistant cells, suggesting future promise in clinical applications.

known as nur77) is a nuclear orphan receptor of the steroid/thyroid family and was reported to cause depolarisation of the mitochondrial membrane and release of cytochrome *c* (Ref. 93). Recently, TR3 action has been elucidated in more detail. TR3 interacts with the anti-apoptotic factor Bcl-2, which is localised to the mitochondria (Ref. 94). This interaction was shown to induce a conformational change in Bcl-2 to expose its BH3 domain, converting it into an apoptotic factor. This increased knowledge is valuable for the design of cocktails of different retinoids, such as combinations of at-RA and atypical retinoids, which could synergise by inducing the extrinsic pathway through TRAIL and death receptors as well as the intrinsic, mitochondrial pathway (Fig. 4).

Although mitochondria seem to play a central role in apoptosis induction by atypical retinoids, other pathways have also been shown to be important for their antiproliferative and apoptotic action. In this regard, another protein, CARP1 (for 'cell cycle and apoptosis regulatory protein 1'), has been shown to be induced by CD437 in cancer

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cells and to be involved in apoptosis induction by this atypical retinoid (Refs 95, 96). It is clear that much work is still required to understand the pathways involved in apoptosis induction by these novel retinoids.

Retinoid combination therapies

Several retinoid combinations show additive or synergistic antiproliferative effects on various cancer cell models in vitro and in vivo (see below), but many of the molecular actions of retinoid combinations are still awaiting elucidation. Here, we review one combination that has been more-extensively studied at the molecular level: the IFN–retinoid combination.

IFNs consist of two main subtypes: type I (IFNs α and β) and type II (IFN-γ) (Refs 97, 98, 99, 100, 101, 102). IFNs have profound antiproliferative, antitumour, antiviral and anti-angiogenic properties (Refs 103, 104, 105), and seem a natural partner for retinoids. Several genes involved in the antiproliferative and apoptotic effect of the retinoid–IFN-β combination have been identified in a genetic screen using a library of antisense cDNAs (Ref. 106). Antisense cDNAs that rendered breast cancer cells resistant to apoptosis by the RA–IFN combination were cloned and collectively termed GRIMs (for 'gene associated with retinoid–IFN-induced mortality'). It seems that none of the classical proteins involved in IFN responses was identified in this screen, including JAKs, STATs or IFN-regulatory factors (of which members of the latter two are known to have tumour-suppressive activity).

GRIM-12 and -19 have been characterised and their mechanism of action elucidated. GRIM-12 encodes thioredoxin reductase (TR), and its expression is increased at the post-transcriptional, rather than transcriptional, level by the IFN–RA combination (Ref. 106). TR has been shown to modulate cell death by regulation of the activity of caspase 8 (Ref. 107), as well as p53 activity and therefore p53-regulated genes (Ref. 108). In vivo, TR transgene expression in mouse xenografts inhibited tumour growth (Ref. 109). GRIM-19 was identified as a mitochondrial component that is essential for ATP synthesis (Ref. 110) but, more importantly, it was shown by two groups to inhibit the activity of the transcription factor STAT3 (Refs 111, 112). STAT3 is aberrantly activated in many cancers and has been shown to contribute to tumourigenesis (Ref. 113). Therefore, GRIMs are interesting factors to manipulate in order to promote antitumour activities in cancer cells.

In addition to the GRIMs, other factors are induced by IFNs that could act in a synergistic manner with RA. In breast cancer cells, IFN-γ induces the expression of caspase 8 through the action of IRF-1 (Ref. 114), and IFN-α and IFN-β induce XAF1 (X-linked inhibitor of apoptosis-associated factor 1) in various cell systems (Ref. 115). XAF1 is an antagonist of XIAP, a member of the IAP (inhibitors of apoptosis) family, which suppress apoptosis through the inhibition of caspases (Ref. 116). In light of the fact that TRAIL and the death receptor pathway is responsible for retinoid-induced death in certain systems, IFNs could potentiate the anticancer effect of retinoids by modulating factors that interact with or take part in this pathway, leading to cocktails that are more effective at killing cancer cells.

Clinical applications of retinoids in cancer prevention and therapy

Retinoids and PML

APL can be effectively eradicated by retinoid treatment combined with chemotherapy; this therefore forms the prototype for retinoid-based therapies. APL is of prime importance in cancer research, not only because retinoid therapy is one of the rare success stories in the fight against cancer, but also because we understand most of the molecular details that explain the oncogenic properties of the fusion proteins, as well as the events that contribute to the differentiation and apoptosis of APL blasts (see above). Although RA has dramatically changed the clinical course of APL from a highly lethal to a curable leukaemia, some patients relapse with disease that is often resistant to RA. Pharmacological and genetic mechanisms have been implicated in such acquired resistance. The pharmacological mechanism involves catabolism of RA through the P450 system or induction of cytoplasmic-binding proteins that sequester RA and prevent normal RA signalling, as reviewed in Ref. 117. The genetic mechanisms of RA resistance include intrinsic resistance, as found in the rare t(11,17) APL cases expressing the fusion protein promyelocytic leukaemia zinc finger (PLZF)–RARα, as well as the acquired resistance that occurs with the appearance of mutations in the LBD of the RARα portion of PML–RARα (Refs 117, 118, 119). Recently, an innovative type of treatment based on the use of PML–RARα vaccination and

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conventional at-RA therapy showed a protective immune response against leukaemia progression in mice and might provide a new approach to improve clinical outcome in human leukaemia (Ref. 120).

Retinoids and solid cancers

In addition to the efficacy of RA in APL, retinoids are preventative and therapeutic agents for other types of cancers and precancerous lesions. An impressive amount of data from in vitro and animal studies strongly support the notion that retinoids, either alone or in combination with other chemotherapeutic agents, are promising anticancer drugs (Refs 13, 118). Pan-agonists for RAR and RXR [e.g. at-RA, 9c-RA and 13-cis (13c)-RA] have shown potent antitumour activity when combined with agonist or antagonists for other members of the NR subfamily (e.g. vitamin D, PPARγ ligands and steroids). The anti-oestrogen tamoxifen, which has antiproliferative effects by itself, is more effective against breast carcinoma or hepatoma cells when used in combination with retinoids (Ref. 121). In fact, retinoids have been reported as promising in adjuvant therapy for hepatocarcinoma (Ref. 122) or for the reduction of secondary liver cancer, aerodigestive malignancies and for secondary breast cancer (Ref. 123). Together with vitamin D3 analogues, retinoids can effectively reduce breast tumour mass in nude mice (Ref. 124) and can inhibit cell growth and induce apoptosis in lung, prostate, breast and ovarian cancer cells. Recently, the combination of dexamethasone and at-RA has been shown to inhibit cell proliferation and induce differentiation in human osteosarcoma cells (Ref. 125).

Rexinoids, which are selective for RXRs, have been found to be effective for the treatment or chemoprevention of certain types of cancer. The rexinoid LGD1069 was shown to be a highly efficacious chemopreventive and therapeutic agent, either alone or in combination with tamoxifen, promoting complete regression of rat mammary tumours (Refs 126, 127). Furthermore, LGD1069/bexarotene is currently used as treatment for persistent or refractory cutaneous T-cell lymphoma (Refs 128, 129, 130) and is in Phase II clinical trials for the treatment of non-small-cell lung cancer (Ref. 131), whereas classical retinoids have not shown a benefit in reduction of primary or secondary lung cancer (Ref. 132). This aspect indicates the need to increase the number and selectivity of new retinoid compounds with reasonable anticancer effects and lower toxicity and side effects (Ref. 133).

The combination of RAR-selective retinoids (at-RA or 13c-RA) and IFNs (mostly IFN-α) has been extensively studied, both in vitro and in nude mice, with cells derived from ovarian, breast, head and neck, and cervical cancer, as well as chronic myelogenous leukaemia (CML) or advanced multiple myeloma (Ref. 134). The molecular mechanism underlying this synergistic effect is unclear but might be related to the induction of the extrinsic apoptosis pathway (see above). Recently, the combination of IFN-α and isotretinoin showed antitumour effects and was well tolerated in patients with lymphoid malignancies (Ref. 135). Previous clinical evidence suggests that the combination of retinoids and T-cell-based immunotherapy might have efficacy in treatment of neuroblastoma (Ref. 136).

Finally, atypical retinoids such as 4-HRP or CD437 have been shown either to have a synergistic antiproliferative effect when combined with other chemotherapeutic agents (e.g. cisplatin, etoposide, camptothecin, taxol, vinblastin, gencitabine and cytosine arabinoside) or to sensitise certain types of cancer to chemotherapy-induced apoptosis. In support of this, several clinical trials to test anticancer activities of 4-HPR – used alone or in combination – in neuroblastoma, ovarian cancer, prostate cancer, glioblastoma, or advanced solid tumours are ongoing at present (Ref. 96). Furthermore, it has been reported that selective agonists for RARα/β synergise potently with taxol, vinblastin and cisplatin in head and neck, breast and ovarian carcinoma cell lines (Ref. 137). Recently, it has been shown that melarsoprol, an organic arsenical for the treatment of trypanosomiasis, alone or with at-RA, markedly inhibited growth of human breast and prostate cancer in vitro and in vivo (Ref. 138), whereas other studies did not show evidence that retinoids (classical and synthetic) can be used in prostate cancer prevention (Refs 139, 140). Many of these retinoid combinations or atypical retinoids have shown great promise in vitro or in vivo and are currently being used in ongoing clinical trials (Refs 13, 96) (Table 2).

Retinoids and cancer prevention

Strong evidence supports the idea that retinoids can prevent cancer by inhibiting progression from

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Table 2. Ongoing clinical trials using retinoids alone or as part of combination therapies[a]

Compound	Receptor activity	Type of cancer	Combination	Phase
Isotretinoin (13c-RA)	Pan-RAR agonist	T-cell lymphoma	IFN-α	II
		StageIII/IV squamous cell carcinoma	IFN-α, vitamin E	III
			Vitamin E	II
		Non-small-cell lung cancer	IFN-α, paclitaxel	II
Tretinoin (at-RA)	Pan-RAR agonist	Stage I/II/III multiple myeloma	Dexamethasone	II
		Metastatic renal cell cancer	IFN-α2b	II
		AML, CML, myelodysplastic syndromes	Phenylbutyrate	I
		Hodgkin's disease		II
Fenretinide (4-HPR)	RARγ and RARβ agonist; additional unknown activities?	Stage II/III prostate cancer; metastatic/hormone-refractory prostate cancer; stage III/IV, recurrent malignant glioma; small-cell lung cancer; metastatic head/neck cancer; metastatic ovarian epithelial cancer; peritoneal cavity cancer; recurrent/resistant neuroblastoma; stage III/IV advanced renal cell carcinoma		II
		Refractory solid tumours	Paclitaxel, cisplatin	I
Bexarotene	RXR-selective	Cutaneous T-cell lymphoma	IFN-α	II
		Breast cancer		Prevention

[a] For further information, see http://clinicaltrials.gov.
Abbreviations: AML, acute myeloid leukaemia; CML, chronic myelogenous leukaemia; IFN, interferon.

premalignant to malignant stages – and blocking preneoplastic conversion might be more feasible than reversing cancer. Epidemiological studies and experiments that measure the susceptibility of vitamin-A-deficient animals to chemical carcinogens indicate that retinoids reduce cancer risk (see Refs 141, 142). As discussed above, retinoids inhibit the progression stage during chemical skin carcinogenesis, and RXRα seems to be required for this effect. Moreover, classical retinoids are effective for the treatment of three precancerous lesions – leukoplakia, actinic keratosis and cervical dysplasia – and can delay the development of skin cancer in individuals with xeroderma pigmentosum, an inherited predisposition to ultraviolet-induced cancers. Retinoids are now routinely used for the treatment of all these conditions. Further cancer-prevention trials are in progress, and increasing attention is being directed towards atypical retinoids because one of these – polyprenoic acid – was reported to prevent second primary hepatocarcinomas (Ref. 153). Treatment of premenopausal women at risk for breast cancer with another atypical retinoid, 4-HPR, in combination with tamoxifen, also reduced the frequency of contralateral disease (Ref. 154).

Research in progress and outstanding research questions

The continued successful use of retinoids in the clinic will depend on the ability to develop ways to: (1) overcome resistance to retinoids in patients; (2) decrease the side effects (toxicity) of existing retinoids and increase the level of delivery to target tissues; and (3) understand better the molecular pathways induced by individual retinoids and their corresponding receptors.

Retinoid resistance in AML subtypes and solid tumours (e.g. because of methylation and

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silencing of the RARβ gene) might be combatted by the use of epigenetic modifying agents such as HDAC or methylase inhibitors in combination with retinoids, some of which are already in use in clinical trials. In terms of toxicity and efficacy, liposomal retinoids are attractive for cancer therapeutics since many studies have shown that they have enhanced stability and efficacy and lower toxicity (Ref. 143). Also, the development of selective ligands might allow the dis-association of the unwanted side effects of conventional retinoids from the desired antiproliferative or anticancer signalling aspects of the retinoid receptors. The development of selective ligands for the receptors is ongoing and, in particular, RARβ-selective ligands will be of prime importance because of their potential tumour-suppressive activity. As the RARβ LBP differs by only one or two residues from that of RARα or RARγ LBP, respectively, the design of such selective molecules appears very difficult. Furthermore, whereas both RARα- and RARγ-selective ligands can be generated through a hydrogen bond between the ligand and Ser232 or Met272, respectively, no such bond can be established in the RARβ LBP. However, the recent definition of the crystal structure of the RARβ LBD revealed important features that distinguished it from the two other RARs, offering the opportunity to design RARβ-selective compounds (Ref. 144).

Lastly, an outstanding question in retinoid biology remains the elucidation of molecular pathways underlying the antiproliferative and anticancer activities of retinoids – in particular, understanding the reason for the loss of RARβ expression in many neoplastic tissues and its role in tumour suppression by RA. Recent work has begun to reveal a network of tumour-suppressive activities induced by retinoids, involving IRF-1 (Ref. 49) and TRAIL (Ref. 39). These data argue for the use of retinoid combination therapies (e.g. RA and IFNs – a combination already in use in clinical trials) that can eradicate tumour cells by targeting antitumour pathways such as TRAIL and its death receptors, and emphasise the need for better understanding of the underlying molecular mechanisms of the anticancer action of retinoids.

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Further reading, resources and contacts

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Features associated with this article

Figures

Figure 1. Structural and functional organisation of the nuclear receptor superfamily.
Figure 2. Subordination and synergy: model for RAR–RXR heterodimer function in the presence or absence of agonists.
Figure 3. Mode of action of RAR–RXR heterodimers.
Figure 4. Retinoids and apoptosis; induction of apoptosis by TRAIL.
Figure 5. Atypical or synthetic retinoids.

Table

Table 1. Retinoid receptors and their ligands.
Table 2. Ongoing clinical trials using retinoids alone or as part of combination therapies.

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