Development of chimeric molecules that degrade the estrogen receptor using decoy oligonucleotide ligands

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ABSTRACT: Targeted protein degradation using chimeric small molecules, such as proteolysis-targeting chimeras (PROTACs) and specific and nongenetic inhibitors of apoptosis protein [IAP]-dependent protein erasers (SNIPERs), has attracted attention as a method to degrade intracellular target proteins via the ubiquitin-proteasome system (UPS). These chimeric molecules target a variety of proteins using small molecules that can bind to the proteins. However, it is difficult to develop such degraders in the absence of suitable small molecule ligands for the target proteins, such as for transcription factors (TFs). Therefore, we constructed the chimeric molecule **LCL-ER(dec)**, which consists of a decoy oligonucleotide that can bind to the estrogen receptor α (ERα) and an IAP ligand, LCL161 (LCL), in a click reaction. **LCL-ER(dec)** was found to selectively degrade ERα via the UPS. These findings will be applicable to the development of other oligonucleotide-type degraders that target different TFs.

The identity of many target proteins that are involved in the pathogenesis of various diseases has been elucidated, and various drug discovery techniques have been developed to target these proteins.[1, 2] In particular, the use of targeted protein degradation has recently been attracting attention. This technology uses chimeric molecules called proteolysis-targeting chimeras (PROTACs) or specific and nongenetic inhibitors of apoptosis protein [IAP]-dependent protein erasers (SNIPERs) to degrade target proteins in cells via the ubiquitin-proteasome system (UPS).[3, 4] These chimeric molecules consist of a ligand for the target protein (protein of interest, POI) and an E3 ligand. The proximity of the POI and E3 ligase acts as a molecular mediator, thereby promoting the ubiquitination and subsequent degradation of the POI.[2] Small molecules, such as LCL161 (LCL) for IAPs, VH032 (VH) for von Hippel-Lindau protein (VHL), and pomalidomide (POM) for cereblon (CRBN) are often used as ligands for E3 ligases.[3] A small molecule that is known to bind to a POI can be used to develop chimeric molecules, and many chimeric degraders using small molecules as POI ligands have been developed to date.[3] Because the only activity required for the ligand is for it to be able to bind to the POI, this technology can target proteins that have no enzymatic activity (i.e., for which inhibitors cannot be developed). However, it is difficult to develop small molecule-based degraders against a POI in the absence of appropriate ligands. An alternative approach is to use molecules, such as peptides, that can bind to the protein surfaces as POI ligands. Several groups have recently reported peptide-based degraders that target transcriptional factors (TFs), such as the estrogen receptor α (ERα)[5] and neurogenic locus notch homolog protein 1 (NOTCH1),[6] by introducing an oligopeptide that interacts with the surface of the POI. This peptide-based protein knockdown strategy is also applicable to several types of POIs that have no specific small-molecule ligands.

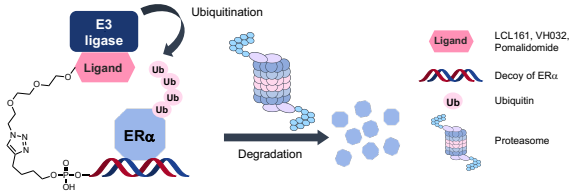

Figure 1. Decoy-type PROTACs degrade the ERα via the UPS.

Other molecules that can bind to protein surfaces include oligonucleotides, such as aptamers[7] and decoys[8]. If such oligonucleotides can be used as POI ligands in the development of chimeric degraders, the number of target proteins that can be degraded would be expanded. It is particularly advantageous to use a decoy as the ligand when targeting TFs, because the decoy can use the known DNA-binding sequence of the target TF, making it easy to design the ligand. In the present study, we developed decoy-based chimeric degraders that target the ERα

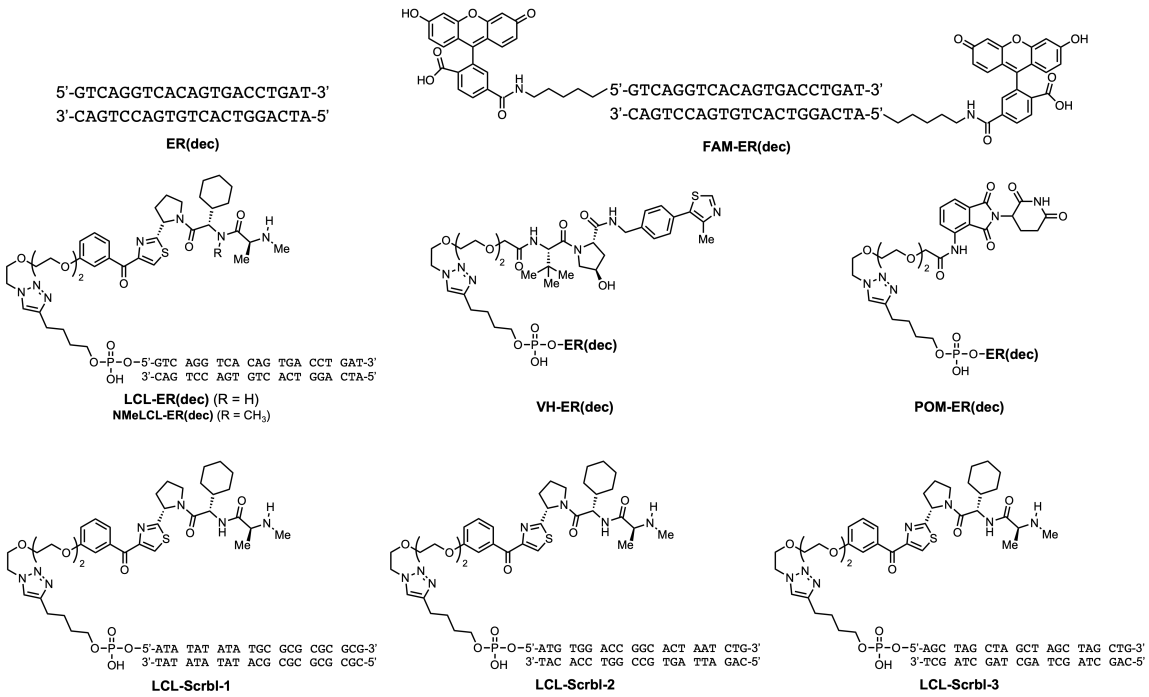

Figure 2. Molecules synthesized in this study.

as a model TF (**Figure 1**). The ERα is a member of the nuclear hormone receptor superfamily[9] and can bind directly to DNA to act as a TF.[10] In addition, ERα homodimers can form transcriptional complexes on the DNA response sequence and regulate the expression of target genes by recruiting co-regulators.[10] We have previously developed small molecule-based chimeric degraders against ERα[11, 12] using the ERα antagonist 4-hydroxytamoxifen (4-OHT), and peptide-based ERα degraders[5] using a coactivator motif that interacts with the ERα surface. Therefore, we chose ERα, as a model TF, as the target for the development of oligonucleotide-type chimeric degraders. Specifically, we designed a thermodynamically stable double-stranded decoy, **ER(dec)**, based on the sequence of the estrogen-responsive element (ERE)[13] that is known to bind strongly to the ERα. This decoy was conjugated with three different E3 ligase ligands, LCL, VH, and POM, to construct the degraders **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)**, respectively. The structural properties, binding affinities, and ERα-degradation activities of these degraders were evaluated.

The ERα-binding decoy **ER(dec)** (21 residues) was designed using information from the DNA sequence and co-crystal X-ray structure of the ERα,[14] and an ERE from the Xenopus vitellogenin A2 gene.[13] The 5'-end of the sense strand 5'-GTCAGGTCACAGTGACCTGAT-3' of **ER(dec)** was modified with a hexynyl group. To construct the E3 ligase ligands, a PEG3 linker with an azide group was attached to LCL, VH[15], and POM[16]. Then, the above sense strand with the alkyne was conjugated to each azide-containing E3 ligase ligand by a copper-catalyzed click reaction. Subsequent hybridization with the antisense strand 5'-ATCAGGTCACTGTGACCTGAC-3' afforded the desired chimeric molecules **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)**. In addition, three ERα non-binding decoys were designed with the same base composition as **ER(dec)**: **Scrbl-1** with an AT repeat and GC repeat sequence; **Scrbl-2** with a completely randomized sequence; and **Scrbl-3** with an AGCT repeat sequence. The chimeric molecules **LCL-Scrbl-1**, **LCL-Scrbl-2**, and **LCL-Scrbl-3** were synthesized in a similar manner as **LCL-ER(dec)**. A non-degradable control **NMeLCL-ER(dec)** containing an *N*-methylated analog of LCL161, and the fluorescein (FAM)-labeled decoy **FAM-ER(dec)** for use in a competitive fluorescence polarization assay were also synthesized (Figure 2). The detailed synthetic protocols of these molecules are described in the supporting information.

The preferred higher-order structures of the synthesized **ER(dec)** and the chimeric molecules **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** were analyzed using CD spectra. Each decoy showed a negative maximum at approximately 240 nm and a positive maximum at approximately 280 nm, indicating that **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** formed typical right-handed B-type structures and the terminal modification of **ER(dec)** did not affect the higher-order structure (Figure S4). The melting temperature (T*m*) values of **ER(dec)**, **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** were 64.5, 64.3, 66.9, and 62.9 °C, respectively, which indicated that these molecules had similar conformational stability to **ER(dec)** (Figure S6).

The binding affinities of **ER(dec)**, **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** to the ERα were evaluated by a competitive fluorescence polarization assay. For the evaluation, the compounds were added to a buffer system containing ERα and **FAM-ER(dec)**, and the inhibitory concentration was calculated as the IC_{50} value. The IC_{50} values were 83.2 nM for **ER(dec)**, 37.9 nM for **LCL-ER(dec)**, 39.3 nM for **VH-**

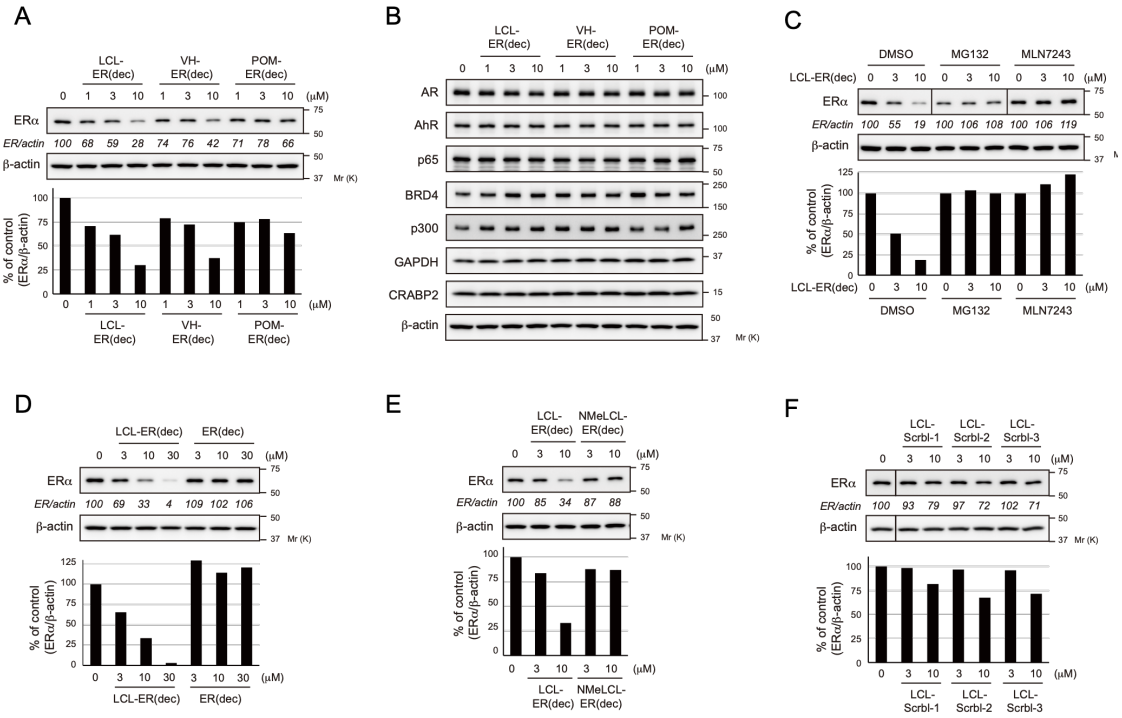

Figure 3. Degradation of the ERα via the UPS by the synthesized decoys. (A, B) The synthesized decoys selectively induced a reduction in the ERα protein level. MCF-7 cells were transiently transfected with the indicated concentrations of **LCL-ER(dec)**, **VH-ER(dec)**, or **POM-ER(dec)** for 24 h. (C) The effect of UPS inhibitors on the **LCL-ER(dec)**-induced reduction of ERα levels. MCF-7 cells were transiently transfected with the indicated concentrations of **LCL-ER(dec)** in the presence or absence of 10 μM MG132 or MLN7243 for 24 h. (D–F) Degradation of the ERα protein by **LCL-ER(dec)** is IAP-ligand and DNA-sequence dependent. MCF-7 cells were transiently transfected with the indicated concentrations of **LCL-ER(dec)**, **ER(dec)**, **NMeLCL-ER(dec)**, **LCL-Scramble-1**, **LCL-Scramble-2**, or **LCL-Scramble-3** for 24 h. Whole-cell lysates were analyzed by western blotting with the indicated antibodies; representative data are shown. The numbers below the ERα panels represent the ER/actin ratios, normalized by designating the expression using the vehicle control (condition without a decoy) as 100%. The changes in protein levels were reproducible between two independent experiments. The data in the bar graph are the mean of two results. Abbreviations; AR: androgen receptor, AhR: aryl hydrocarbon receptor, BRD4: bromodomain-containing protein 4, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, CRABP2: cellular retinoic acid binding protein 2.

ER(dec), and 50.5 nM for **POM-ER(dec)**. These results indicated that the binding activity of the decoy **ER(dec)** to the ERα was not weakened by the linking of **ER(dec)** to the E3 ligase ligand, and the compounds had sufficient binding ability to the ERα regardless of the type of the E3 ligase ligand (**Table 1**). The binding activities of **LCL-Scrbl-1**–**3** to the ERα were considerably weaker than that of **ER(dec)** composed of the consensus sequence, but some non-specific binding was observed at high concentrations (Figures S8 and S9).

Table 1. ERα binding affinity (IC_{50}) of ER(dec), LCL-ER(dec), VH-ER(dec), POM-ER(dec), LCL-Scrbl-1, LCL-Scrbl-2, and LCL-Scrbl-3.

Entry	Compound	IC_{50} (nM)
1	ER(dec)	67.0
2	LCL-ER(dec)	37.9
3	VH-ER(dec)	50.4
4	POM-ER(dec)	39.3
5	LCL-Scrbl-1	10.8×10^3
6	LCL-Scrbl-2	3.28×10^3
7	LCL-Scrbl-3	8.16×10^3

To investigate whether **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** have degradation activity against the ERα, the effect of these E3 ligand-decoy conjugates on the protein level of ERα was evaluated by western blotting analysis using MCF-7 breast cancer cells. All the decoys reduced the ERα protein level after 24 h of transfection, and **LCL-ER(dec)** had the most effect compared with the other decoys (Figure 3A). To investigate the selectivity for the target protein, the effect of these decoys on the levels of different proteins was examined (Figure 3B). None of the decoys effectively reduced the levels of other transcription factors (AR, AhR, and NF-κB p65), transcription-related factors (p300 and BRD4), or proteins not related to transcription (CRABP2, GAPDH, and β-actin), indicating that these decoys selectively reduced the protein level of ERα.

We next investigated the mechanism of the ERα reduction by focusing on **LCL-ER(dec)**, which showed the highest activity, as shown in Figure 3A. The **LCL-ER(dec)**-induced reduction of the ERα was abrogated by co-treatment with the

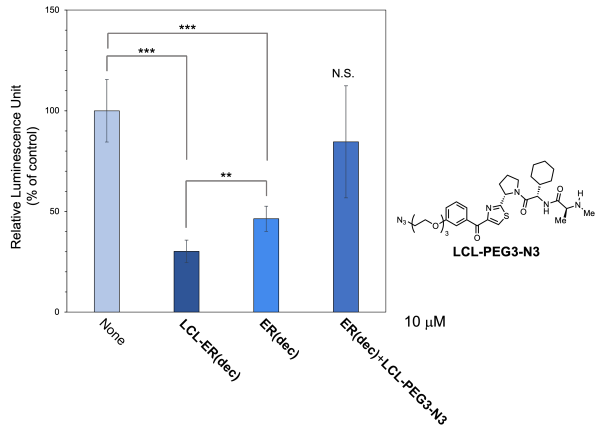

Figure 4. Inhibition of the estrogen-dependent transcriptional activity of ERα by **LCL-ER(dec)**. MCF-7 cells were transiently transfected with a luciferase reporter plasmid containing three tandem copies of the ERE and control Renilla luciferase plasmid-SV40. After 24 h, the cells were further transfected with 10 μM concentrations of the indicated decoys in the presence of 0.3 nM β-estradiol for 24 h. The ERα-dependent transcriptional activity was evaluated by a luciferase assay, and the relative luciferase activity was normalized by designating the activity of the non-treated control (column 1) as 100%. The data represent the mean ± S.D. (n = 4). *P* values were determined using the unpaired two-tailed Student's *t* test. N.S., not significant; **, *P* <

proteasome inhibitor MG132, and the ubiquitin-activating inhibitor MLN7243 (Figure 3C), suggesting that **LCL-ER(dec)** induced ubiquitin-proteasome system (UPS)-dependent degradation of the ERα. Unlike **LCL-ER(dec)**, **ER(dec)** did not induce degradation of the ERα protein (Figure 3D), indicating that conjugation of the LCL161 ligand is important for the degradation. In addition, the non-degradable control **NMeLCL-ER(dec)**, which contains an *N*-methylated analog of the LCL161 ligand, did not induce ERα degradation (Figure 3E), suggesting that the ability to bind IAPs is critical for the degradation activity. To examine whether target recognition by the decoy ligands was DNA-sequence dependent, we synthesized LCL161 ligand-decoy chimeras using several different decoys composed of scrambled DNA sequences as the target ligands. These decoy chimeras did not show significant ERα-degradation activity (Figure 3F), which correlated with their weak binding affinity to the ERα (Table 1). These results suggested that decoy oligonucleotides can be used in the development of chimeric molecules that induce DNA sequence-dependent degradation of target proteins.

Because the ERα plays an essential role in estrogen signaling, we examined the effect of **LCL-ER(dec)** on the estrogen-dependent transcriptional activity of the ERα. In a luciferase assay using an ERE reporter, **LCL-ER(dec)** inhibited ERα-dependent transcriptional activation by β-estradiol more effectively than **ER(dec)**, which was in good agreement with the ERα degradation activity (Figure 4). A mixture of the decoy ligand **ER(dec)** and **LCL-PEG3-N3** did not effectively decrease the transcription, indicating that the linking of the two ligands, **ER(dec)** and **LCL-PEG3-N3**, is crucial for effective inhibition. These results suggested that degradation of the ERα by **LCL-ER(dec)** leads to effective suppression of estrogen signaling.

In summary, we synthesized **LCL-ER(dec)** with the aim of developing a chimeric degrader using a decoy ligand that can be applied to a variety of TFs. For the target protein, we selected the ERα, which has previously been shown to be degraded by chimeric molecules containing small molecules or peptides. The three chimeric molecules **LCL-ER(dec)**, **VH-ER(dec)**, and **POM-ER(dec)** were synthesized by conjugating the ERα decoy **ER(dec)** with LCL161, VH032, and POM, E3 ligase ligands commonly used in PROTACs and SNIPERs. Among these three chimeric molecules, **LCL-ER(dec)** showed the highest ERα degradation-inducing activity as assessed by western blotting. In contrast, the ERα-non-binding chimeric molecules, **LCL-Scrbl-1–3**, did not reduce the protein levels of ERα, suggesting that **LCL-ER(dec)** binds to the ERα in a sequence-specific manner to induce the degradation. In addition, the non-degradable control, **NMeLCL-ER(dec)**, did not induce ERα degradation, suggesting that the ability to bind IAPs is critical for the degradation activity. Studies using UPS inhibitors suggested that **LCL-ER(dec)** degraded the ERα via the UPS. Recently, TF-PROTACs[16] (O′ PROTACs[17]) targeting TFs using double-stranded decoy ligands have been reported, indicating that decoy-type PROTACs are also useful as a new type of POI inducer. In the future, we aim to apply the methods developed in this study to the design of degradation inducers for transcription-related factors that are difficult to target.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

The synthetic procedures for all compounds listed in this manuscript and the protocols for the *in vitro* assays (binding and protein degradation assays) (PDF).

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Author Contributions

Miyako Naganuma, N.O., G.T., and H.T. performed the experiments and analyzed results. Miyako Naganuma, N.O., T.I., Mikihiko Naito, and Y.D. designed the research and wrote the paper. All authors discussed the results and commented on the manuscript.

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ABBREVIATIONS

PROTACs, proteolysis targeting chimeras; IAP, inhibitor of apoptosis protein; SNIPERs, specific and non-genetic IAP-dependent protein erasers; UPS, ubiquitin proteasome system; TF, transcription factor; ERα, estrogen receptor α; POI, protein of interest; VHL, von Hippel-Lindau protein; NOTCH1, neurogenic locus notch homolog protein 1; 4-OHT, 4-hydroxytamoxifen; ERE, estrogen-responsive element; FAM, fluorescein; CD, circular dichroism; T_m, melting temperature.

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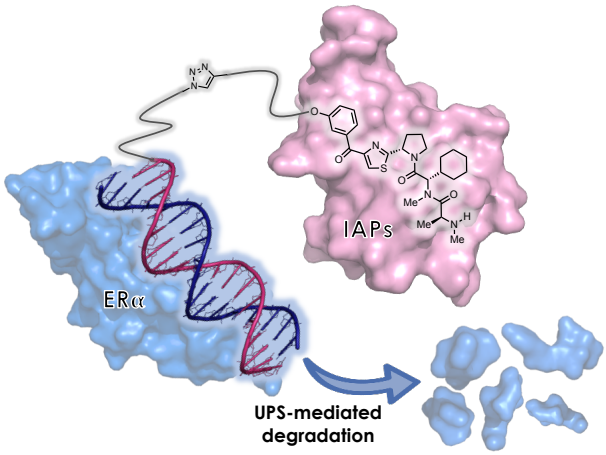

Lay Summary

Protein degradation technology using hybrid small molecules (known as PROTACs and SNIPERs) is an emerging drug development strategy for use in drug discovery and biological research. In this study, a decoy ligand-based estrogen receptor α (ERα) degrader LCL-ER(dec) was designed and synthesized and the binding affinity and degradation activity toward the ERα were evaluated. LCL-ER(dec) was revealed to selectively degrade the ERα via the ubiquitin-proteasome system. Because we were able to show that decoys were able to be used as the ligands for protein degraders, we expect that this concept will lead to the expansion of the number of proteins that can be targeted.