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Garcinolic Acid Distinguishes Between GACKIX Domains and Modulates Interaction Networks

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Natural products are often uniquely suited to modulate protein-protein interactions (PPIs) due to their architectural and functional group complexity relative to synthetic molecules. Here we demonstrate that the natural product garcinolic acid allosterically blocks the CBP/p300 KIX PPI network and displays excellent selectivity over related GACKIX motifs. It does so via a strong interaction (K_D 1 μM) with a non-canonical binding site containing a structurally dynamic loop in CBP/p300 KIX. Garcinolic acid engages full-length CBP in the context of the proteome and in doing so effectively inhibits KIX-dependent transcription in a leukemia model. As the most potent small-molecule KIX inhibitor yet reported, garcinolic acid represents an important step forward in the therapeutic targeting of CBP/p300.

Introduction

The protein-protein interactions (PPIs) mediated by transcriptional coactivators are particularly challenging to inhibit with typical small molecules due to the large surface area of the interactions and the amphipathic nature of binding surfaces.[1–3] The master coactivator CBP/p300, for example, contains at least five structural motifs that mediate PPI networks with transcriptional activators, all of which use amphipathic peptide sequences comprised of hydrophobic and negatively charged/polar amino acids to recognize the binding surfaces within the domains.[4–9] An emerging molecular recognition model for such activator binding domains (ABDs) suggests that dynamic loops

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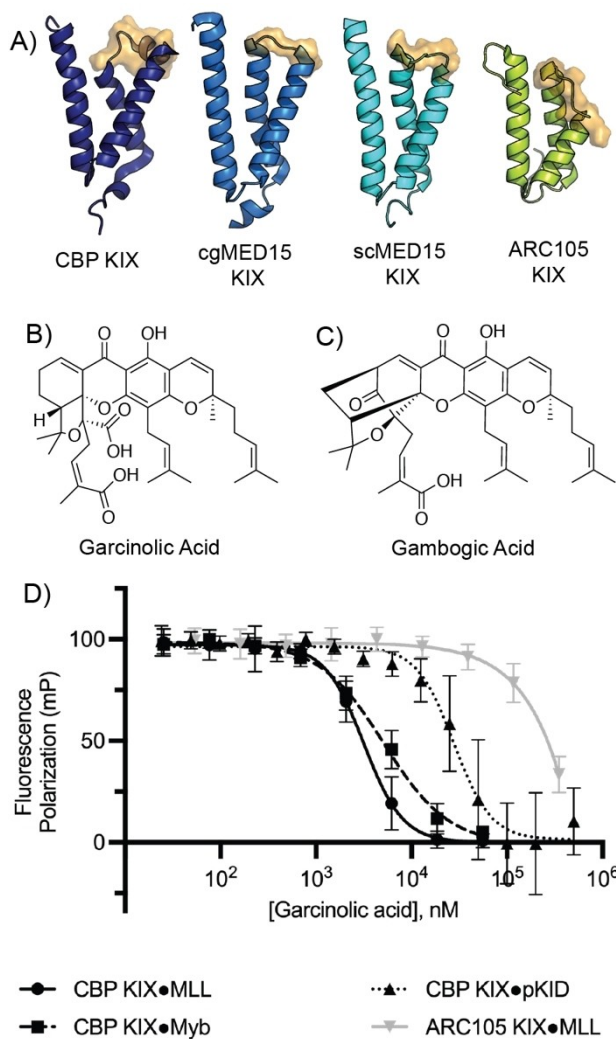
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flanking the canonical binding surfaces play a critical role in recognition and in allosteric regulation.[10–12] Thus, the dynamic loops are desirable targets for probe discovery.

The GACKIX family of ABDs are small, independently folding 3-helix bundles (Figure 1A).[13] The KIX ABDs within CBP/p300 and ARC105 are high-value targets for pharmacological modulators due to the dysregulation of their PPI networks in a number of disease states.[1,9,14] c-Myb-dependent leukemias, for example, often rely upon a PPI between c-Myb and one of the two binding sites with CBP/p300 KIX to activate critical gene circuits, and genetic or pharmacological blocking of the PPI arrests leukemogenesis.[15–17] Nonetheless, the c-Myb binding site is a challenging one for small molecules, as it is large (> 1200 Å^2) and lacks significant topography.[1,13,18,19] We previously demonstrated that Tethering covalent fragments adjacent to a flexible loop within the KIX ABD of CBP/p300 produced effective allosteric modulators of KIX conformation and binding at both activator binding sites.[20] Here we report the identification of a natural product, garcinolic acid, that reversibly engages a binding site comprised of the flexible loop and the adjoining α2 and α3-helices, and in doing so functions as an effective allosteric inhibitor of CBP/p300 KIX PPI networks with selectivity over other KIX ABDs. Further, with a K_D of 1 μM and low micromolar IC$_{50}$s in several cell lines, garcinolic acid is the most potent small molecule inhibitor of this motif to date and comparable to larger, native binding partners of CBP/p300 KIX.

Results and Discussion

Garcinolic acid was first identified from a screen of three GACKIX family members: *C. glabrata* MED15 KIX, *S. cerevisiae* MED15 KIX, and CBP KIX (Figure 1A). A library of 5916 compounds comprised of natural products, FDA-approved drugs, and known bioactive molecules was screened in a competitive inhibition binding assay of two KIX-transcriptional

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Figure 1. A) Structure of GACKIX domains tested in this study; CBP KIX, cgMED15 KIX, scMED15 KIX, and ARC105 KIX derived from Protein Data Bank entries 2AGH, 4D7X, 2K0N, and 2GUT respectively. Flexible loop between α1 and α2 is highlighted in each domain. Structures of B) garcinolic and C) gambogic acid. D) Garcinolic acid inhibition of CBP KIX binding to the MLL (black circles), Myb (black squares), and pKID (black triangles) Transcriptional Activation Domains (TADs) and ARC105 KIX binding to the MLL (gray) TAD as measured by competitive fluorescence polarization. Error bars are standard deviation of the mean as measured from three independent experiments.

activation domain (TAD) pairs, *C. glabrata* Med15 KIX·Pdr1 and *S. cerevisiae* Med15 KIX·Pdr1[21] (for full screen details see Supporting Information). This initial screen produced only modest hits against either target, but counterscreening identified garcinolic acid (Figure 1B),[22] as an effective inhibitor of the CBP KIX·MLL complex. Further testing found garcinolic acid potently inhibits CBP and p300 KIX PPIs at both binding surfaces (Figure 1D, S1). Garcinolic acid is a caged xanthone natural product that is a minor component of resin (gamboge) from *Garcinia hanburyi* trees. Gamboge has been used in Eastern traditional medicine to treat a variety of ailments,[23] and more recently, garcinolic acid has been explored as an inhibitor of viral nsP1.[24,25] Garcinolic acid is selective for the CBP/p300 KIX motif, as it only modestly inhibits the Med15 KIX complexes

used in the original screen (Figure S2) and, further, does not interact with the ARC105 KIX domain at concentrations up to 200 μM (Figure 1D). Notably, gambogic acid, a structurally similar caged xanthone that is the major component of gamboge,[26] has little effect on CBP/p300 KIX PPIs (Figure 1C, S1).

Several lines of evidence indicate that garcinolic acid interacts with CBP/p300 KIX reversibly but in a manner distinct from known protein partners of CBP/p300 KIX (Figure 2). Mass spectrometric analysis of CBP KIX samples incubated with garcinolic acid for up to 12 hours detected no adducts, ruling out a covalent mechanism (Figures S3, S4). Additionally, data from transient kinetic experiments support a reversible binding mechanism. For these experiments a previously reported
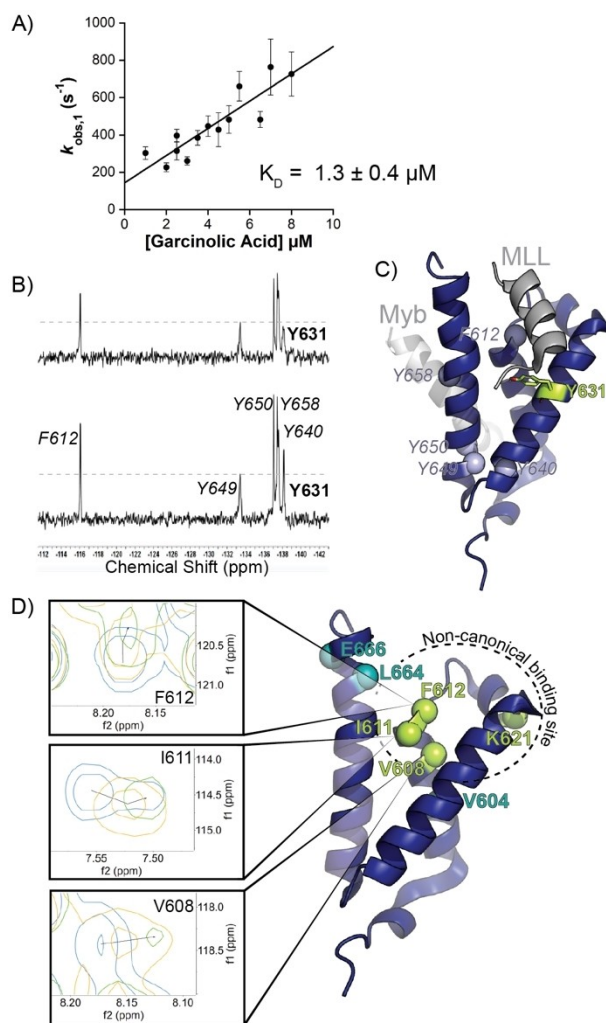

Figure 2. A) Stopped-flow fluorescence association data between Y631W CBP KIX and garcinolic acid. All data points are averaged from 35–40 individual traces with the indicated error (SD). B) ^{19}F-NMR data of 3FY/4FF-labeled CBP KIX (15 μM, bottom) exhibiting lowering of fluorine-labeled Y631 residue signal upon garcinolic acid (30 μM, top) binding as measured by PrOF NMR. C) Schematic of CBP KIX (dark blue) highlighting unaffected fluorine-labeled phenylalanine and tyrosine residues (light blue) and perturbed Y631 residue (lime green) as measured by PrOF NMR. See Figures S10–S15 for additional details. D) ^{1}H-^{15}N HSQC NMR data exhibiting perturbation of CBP KIX (100 μM) residues V608, I611, and F612 in the presence of 0 (blue), 0.25 (yellow) and 0.5 eq of garcinolic acid (green).

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Y631W CBP KIX mutant was utilized as this provides an excellent fluorescent reporter to monitor binding reactions using a stopped-flow fluorescence apparatus and does not affect TAD binding to KIX.[27] Mixing of excess garcinolic with fixed concentrations of KIX[Y631W] produced two distinct kinetic phases: a large amplitude fast step and a small amplitude slow step. The observed rate constants measured for the fast step ($k_{obs,1}$) had a linear dependence on garcinolic acid concentration, indicating a bimolecular binding step with association rate constant $k_{on} = 68 \pm 10 \times 10^6\ M^{-1} s^{-1}$ (Figure 2A). The identity of the second phase could not be confidently assessed due to a lack of significant concentration-dependent changes; however, consideration of several mechanistic possibilities indicates that it does not significantly contribute to affinity (see Supplementary Information for additional details). Finally, we performed dissociation kinetic experiments to quantitate k_{off} by mixing an excess of unlabeled wild-type KIX with a preformed complex of KIX[Y631W]·garcinolic acid, giving a k_{off} value of $88 \pm 21\ s^{-1}$ allowing estimation of an equilibrium dissociation constant ($K_d = k_{off}/k_{on}$) of $1.3 \pm 0.4\ \mu M$. This value is consistent with the Ki from the previous competitive inhibition assays with wild-type CBP KIX. Thus, garcinolic acid has an affinity for CBP KIX comparable to the native transcriptional activator binding partners, whose affinities range from 1–20 μM.[27–32]

Garcinolic acid inhibits the binding of both the MLL and c-Myb transcriptional activation domain peptides with similar IC_{50} values. Several lines of NMR-based evidence indicate that garcinolic acid engages a previously-described non-canonical binding site adjacent to the MLL binding surface composed of the dynamic loop connecting the $\alpha 1$ and $\alpha 2$ helices (Figure 1A).[33] Most revealing was data obtained in Protein-Observed ^{19}F (PrOF) NMR experiments with 3FY/4FF-labeled CBP KIX (CBP KIX in which all tyrosine residues were replaced with 3-fluorotyrosine (3FY) and F612 is replaced by 4-fluorophenylalanine (4FF)).[33–35] As garcinolic acid was titrated into a solution of 3FY/4FF-labeled CBP KIX only a single residue was perturbed, Y631, located on $\alpha 2$ of CBP KIX. Notably, garcinolic acid titration did not lead to perturbations within the canonical MLL binding site (F612) nor in the cMyb binding surface (Y658, Y650) (Figure 2B, C;). Consistent with the PrOF data, titration of garcinolic acid into ^{15}N-labeled CBP KIX and analysis of the resulting complex by ^{1}H, ^{15}N-HSQC NMR showed perturbation of residues adjacent to the canonical MLL binding site (Figures S7, S8, S9). Specifically, residues V608, I611, F612, and K621 experience a chemical shift change of greater than two standard deviations in the presence of garcinolic acid (Figure 2D). Three other residues (V604, L664, and E666) exhibit a chemical shift change greater than one standard deviation (Figure 2D, S9). Collectively, the HSQC and PrOF NMR experiments are consistent with previously published structural and computational data on small molecules shown to bind a non-canonical site adjacent to the flexible loop region of CBP/p300 KIX.[33]

Based on garcinolic acid's engagement of the flexible loop region, we next examined if garcinolic acid would stabilize the KIX domain. Using a SYPRO Orange probe, we employed differential scanning fluorimetry (DSF) to assess the thermal stability of CBP KIX in the presence of garcinolic acid as well as Myb and MLL peptides (Figure 3A). While all complexes of CBP KIX showed an increased melting temperature relative to free CBP KIX, garcinolic acid increased the temperature ($\Delta T_m = 2.1 \pm$
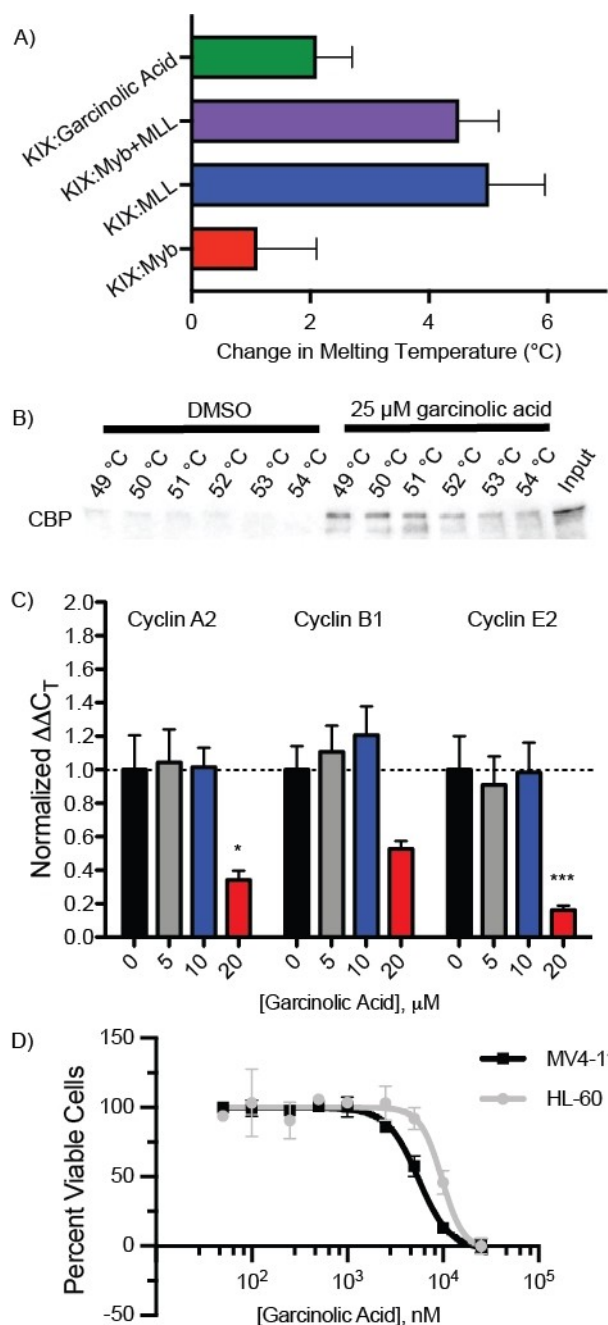
Figure 3. A) DSF data for CBP KIX complexed with garcinolic acid and MLL and Myb peptides. All complexes of CBP KIX had an increased melting temperature over free CBP KIX. Error bars are the standard deviation as calculated from three replicates. B) Thermal shift of endogenous CBP in MV4-11 nuclear extracts treated with 25 μM garcinolic acid. A Western blot of the input and treated samples were probed with anti-CBP antibody. C) Impact of garcinolic acid on CREB-dependent cyclin genes in MV4-11 acute myeloid leukemia cells over 8 h. Error bars are standard deviation calculated from technical triplicates of biological duplicate experiments. D) Garcinolic acid decreases viability of MV4-11 (black) and HL-60 (grey) acute myeloid leukemia cells over 48 h. Error bars are standard deviation calculated from biological triplicates.

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0.6) more than the native binding partner Myb ($\Delta T_m = 1.1 \pm 1.0$). In addition to a shift in T_m, the CBP KIX melting curve displays an increased fluorescence intensity and notable deviation in slope when bound with garcinolic acid (Figure S16). These changes are not due to interactions between the fluorescent probe and garcinolic acid, and they are not seen with the native ligands Myb and MLL. This indicates that a unique CBP KIX conformation(s) is stabilized by garcinolic acid and supports the model that garcinolic acid binds to a non-canonical binding site on CBP KIX. With the correlation between thermal and conformational stability, the effective change in KIX thermal stability implies that garcinolic acid has an effect on the flexible loop between the α_2 and α_3 helices of this domain that induces conformational malleability.[12] To assess if garcinolic acid would stabilize the full-length CBP protein we used cellular thermal shift assays (CETSA) to analyze CBP from MV4-11 nuclear extracts treated with 25 µM garcinolic acid. As seen in Figure 3B, almost no full-length CBP is found in the DMSO treated samples, but intact CBP is still observed in the garcinolic acid treated samples, supporting that garcinolic acid engages the KIX domain in the context of the full-length protein. Taken together, these data demonstrate the binding of garcinolic acid alters the stability of both the isolated CBP KIX domain and CBP in cellular proteomes. In certain leukemic cell lines CBP/p300 KIX-activator PPIs regulate cyclin expression and cell cycle progression. To test if garcinolic engagement of CBP/p300 KIX inhibits its PPI network in cells, MV4-11 (AML) and Hap1 (CML) cells were dosed with garcinolic acid and downregulation of Cyclin A2, B1, and E2 transcripts was observed (Figure 3C, Figure S18). Additionally garcinolic acid impacts the viability of MV4-11 ($IC_{50} = 5.5 \pm 0.5$ µM) and HL-60 ($IC_{50} = 10 \pm 2$ µM) AML cell lines (Figure 3D).

Conclusions

Garcinolic acid is a potent small-molecule inhibitor of CBP/p300 KIX interactions and appears to function through binding to a previously reported third binding site on KIX. The disruption of MLL, Myb, and CREB binding to CBP/p300 KIX in the presence of garcinolic acid supports the existing evidence that the flexible loop region between the $\alpha1$ and $\alpha2$ helices has a large impact on the behavior of CBP/p300 KIX. We hypothesize that structural differences in this loop region also contribute to garcinolic acid's selectivity for CBP/p300 KIX over other KIX domains. The subsequent inhibition of downstream processes and cellular viability of cells dependent on the Myb·KIX interactions further emphasizes the importance of the dynamic loop region of CBP/p300 KIX and the large-scale effects that targeting this region can have.

Supporting Information

The authors have cited additional references within the Supporting Information.[36–42]

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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RESEARCH ARTICLE

Garcinolic acid is a topologically complex natural product derived from *Garcinia hanburyi*. It engages the KIX domain in the master coactivator CBP/p300 selectively over other closely related motifs and in doing so disrupts CBP/p300 KIX protein-protein interactions. In the cellular context this enables downregulation of transcriptional circuits essential for cMyb-dependent leukemias.

Garcinolic acid

Garcinia hanburyi

MLL

Myb

CBP KIX
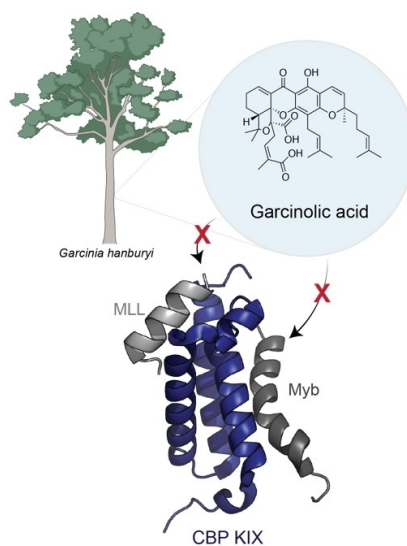
Dr. M. E. Breen, Dr. S. T. Joy, O. J. Baruti, M. S. Beyersdorf, M. J. Henley, S. N. De Salle, P. D. Ycas, A. Croskey, Prof. Dr. T. Cierpicki, Prof. Dr. W. C. K. Pomerantz, Prof. A. K. Mapp*

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