The tumor suppressor p53 recruits the cellular coactivator CBP/p300 to mediate the transcriptional activation of target genes. In this study, we identify a novel p53-interacting region in CBP/p300, which we call CR2, located near the carboxyl terminus. The 95- amino acid CR2 region (amino acids 2055–2150) is located adjacent to the C/H3 domain and corresponds precisely with the minimal steroid receptor coactivator 1 (SRC1)-interacting domain of CBP (also called IIBD). We show that the region of p53 that participates in the CR2 interaction resides within the first 107 amino acids of the protein. p53 binds strongly to the CR2 domain of both CBP and the highly homologous coactivator p300. Importantly, an in-frame deletion of CR2 within the full-length p300 protein strongly compromises p300-mediated p53 transcriptional activation from a chromatin template in vitro. The identification of the p53-interacting CR2 domain in CBP/p300 prompted us to ask if the human T-cell leukemia virus (HTLV-I) Tax protein, which also interacts with CR2, competes with p53 for binding to this domain. We show that p53 and Tax exhibit mutually exclusive binding to the CR2 region, possibly contributing to the previously reported Tax repression of p53 function. Together, these studies identify and molecularly characterize a new p53 binding site on CBP/p300 that participates in coactivator-mediated p53 transcription function. The identity of the p53-CR2 interaction indicates that at least three distinct sites on CBP/p300 may participate in mediating p53 transactivation.

CBP and the highly related protein p300 are very large, highly conserved coactivator proteins that serve to mediate the regulation of gene expression in metazoans. Many transcriptional regulatory pathways converge at CBP and p300 (1–4). These include pathways that are required for development and differentiation, response to hormonal stimulation, apoptosis, and tumor suppression. A significant number of transcription factors, such as Mdm2, BRCA1, HTLV-I Tax, and SRC1,1 have been demonstrated to interact with CBP/p300, with several binding at multiple sites on the coactivators (5). The functional significance of these multivalent activator/coactivator interactions is currently unknown.

p53 is a sequence-specific, DNA-binding transcription factor that induces apoptosis or cell cycle arrest in response to genotoxic stress, thus blocking the transmission of DNA mutations to progeny cells (6). Loss of p53 activity has been identified in 60% of the human malignancies examined (7, 8), consistent with its critical role in the suppression of malignant transformation. The tumor suppressor functions of p53 are directly linked to its ability to mediate transcriptional activation. To stimulate transcription, p53 binds as a tetramer to specific response elements located in the transcriptional control regions of p53 target genes (6, 9). This step initiates the assembly of the complex transcriptional apparatus that initiates RNA synthesis. This critical early step in transcriptional activation is believed to be facilitated by the ability of p53 to simultaneously bind the specific DNA sequences and recruit CBP/p300 to the p53-responsive promoters. CBP/p300 recruitment appears to concomitantly bring RNA polymerase II to the target promoters (10), increasing the rate of preinitiation complex assembly (11). There is also evidence that, following promoter association, CBP/p300 may also recruit or stabilize components of the general transcription machinery, including TFIIIB and TBP (12, 13). CBP/p300 also facilitates transcriptional activation through nucleosome and transcription factor acetylation. The coactivators have been shown to directly acetylate lysine residues present within the amino-terminal tails of the four core histones (14). Acetylation appears to increase the accessibility of the nucleosomal DNA to transcription factor binding, a critical step in gene activation (15, 16). Interestingly, CBP and p300 have also been shown to acetylate p53 at lysine residues 373 and 382 (17). Although acetylated p53 binds short fragments of DNA with a higher affinity than the unacetylated form, this modification does not appear to significantly affect p53 DNA binding activity on chromatin assembled templates (18).

These observations serve to illustrate a prominent role for CBP/p300 in mediating the tumor suppressor functions of p53. However, the molecular details of the physical interaction between the activator and coactivator remain elusive. Several previous studies have indicated that p53 specifically binds to multiple sites on the coactivator, including the KIX domain (19), and an ill-defined carboxyl-terminal region of CBP/p300 (20–23). The amino-terminal activation domain of p53 has been shown to participate in each of these coactivator interactions (19, 24). In studies that attempted to elucidate the precise carboxyl-terminal region of CBP/p300 involved in p53 binding, only the C/H3 domain of CBP (approximate aa 1764–1850; also called TAZ2 and TRAM) has emerged as a site of p53 interaction (25). However, a recent study using heteronuclear NMR...
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GST Pull-down Assay—All GST pull-down experiments were performed as previously described (19). Anti-p53 (DO-1 (epitope corresponding to aa 11–25), Santa Cruz Biotechnology), anti-Tax (epitope corresponding to the 13 carboxy-terminal amino acids), and anti-His6 (H-15, Santa Cruz Biotechnology) antibodies were used in the GST pull-down experiments.

Electrophoretic Mobility Shift Assay—The single-end-labeled p53 consensus site double-stranded oligonucleotide probe (0.4 μM) was incubated with purified His6-p53 (0.15 μM) and increasing amounts of GST-CR1 (aa 1514–1994), GST-CR2 (aa 2055–2193), GST-CR3 (aa 2212–2441), or GST-KIX (aa 588–663) protein (0.20 μM, 0.50 μM, 0.65 μM) for 45 min on ice as previously described (35). Protein/DNA complexes were resolved by electrophoresis on a 5% non-denaturing polyacrylamide gel.

Transcription Template—The p53-responsive Mdm2 P2 G-less plasmid DNA used in the assembly reactions carried the two p53 response elements from the Mdm2 P2 intragenic promoter (39). Briefly, a 567-bp fragment carrying the p53 response elements, TATA sequence, and start site was PCR-amplified and cloned immediately upstream of a 190-bp G-less cassette. The identity of the Mdm2 P2 G-less construct was confirmed by restriction analysis.

Cloning, Expression, and Purification of Recombinant Proteins—The expression and purification of GST-C-HKXaa302-GST-KIIaa588-GST-Msb2-His6 (weight) (33) and GST-CR2 (aa 1514–1994), GST-CR3 (aa 2212–2441) have been previously described (19). The GST-CR2 deletion and point mutants and the CR2 region from human p300 (encompassing aa 1970–2150) and p300 (aa 1970–2193) were also previously described (29). These purified proteins were dialyzed against TM buffer (50 mM Tris-HCl (pH 7.9), 100 mM KCl, 12.5 mM MgCl2, 1 mM EDTA (pH 8.0), 1 mM dithiothreitol, 0.1% (v/v) Tween-20, 20% (v/v) glycerol) and stored at −70 °C. Purification of the Mdm2 promoter assembled into chromatin using GST-yNAP-1, Acf1/ISWI, and FLAG-tagged ISWI and p300 from Drosophila melanogaster (aa 12–42), prepared from CEM cells (a mutant p53 human T lymphocyte cell line) was immediately following the addition of the activator and/or coactivator. Following a 60-min preincubation reaction at 30 °C, RNA synthesis was initiated by the addition of 250 μM ATP, GTP, CTP, and 12 μM UTP plus 0.8 μM [α-32P]UTP (3000 Ci/mmol, PerkinElmer Life Sciences). Transcription reactions were processed and analyzed as previously described (20). The [35S]methionine (100 pmol, 57 mCi/mmol, United States Biochemical) was added to the transcription/translation products (6 μl modified Dulbecco’s medium) and samples were incubated at 30 °C for 60 min. The reactions were stopped with 10% SDS-PAGE and acetylated. Protein/DNA complexes were resolved by electrophoresis on a 5% non-denaturing polyacrylamide gel.

Mammalian Expression Plasmids, Cell Culture, and Transient Co-transfection Assays—Jurkat T-cells (a p53-negative human T lymphocyte cell line) were cultured in Iscove’s modified Dulbecco’s medium supplemented with 10% fetal bovine serum, 2 mm t-glutamine, and penicillin-streptomycin. For transient cotransfection assays, cells were transfected with a pRL-TK vector (Promega), which encodes the Renilla luciferase from the HSV-TK promoter, as an internal control.

RESULTS

Identification of the p53-interacting CR2 Region of CBP by GST Pull-down Assay—We began this study by testing three large regions of CBP spanning the carboxy-terminal half of the coactivator (Fig. 1A). Each of these CBP regions were cloned and expressed as GST fusion proteins and tested in GST pull-
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down assays with purified, recombinant, full-length p53. p53 binding to the KIX domain (aa 588–683) served as a positive control (Fig. 1B, lane 6). We found that p53 bound strongly to only one of the three carboxyl-terminal regions of CBP (Fig. 1B, lane 4). This region, which we call carboxyl-terminal region 2 (CR2), encompasses CBP amino acids 1894–2221. Consistent with previous studies (24, 25), we found that p53 also bound to CBP/p300 (aa 1894–2193) (20 pmol each), p53 was detected using an anti-p53 antibody. On input p53 (5%) is shown (lane 1). Bound p53 and protein molecular weight standards are indicated. On lane 1 we tested p53 binding to CBP (aa 2003–2212) or p300 (aa 1970–2193) (20 pmol each). p53 was detected using an anti-p53 antibody. On input p53 (5%) is shown (lane 1). Bound p53 is indicated.

Preliminary yeast two-hybrid studies suggested that the site of CBP interaction resides within the first 112 amino acids of p53 (data not shown). Based on this observation, we performed GST pull-down assays using an amino-terminal fragment of p53. In vitro transcribed-translation 35S-labeled full-length p53 and a 35S-labeled amino-terminal truncation of p53 (aa 1–107) were tested for their ability to bind the CR2 domain of CBP. Glutathione beads were bound with GST-CR2aa1894-2221 or GST-C/H1-KIXaa302–683 and then incubated with the 35S-labeled in vitro translation products, and the resulting protein-protein interactions were detected by PhosphorImager analysis. Fig. 3A shows that both the full-length and the amino-terminal p53 fragment binds to CR2 (lanes 5 and 8). Although the binding of the amino-terminal truncation fragment to CR2 is clearly specific, the binding appears to be reduced relative to the full-length protein, possibly because the amino-terminal domain in isolation is not structurally identical to the analogous region in the full-length protein. This result is consistent with the observation that amino and carboxyl-ter-

Fine Mapping and Mutational Analysis of the Minimal p53-interacting Region of CR2—We were next interested in mapping the minimal region of CR2 competent for p53 interaction. For these studies, we analyzed p53 binding to a series of deletion mutants of CR2 using the GST pull-down assay. Progressive carboxyl-terminal deletions of GST-CR2 revealed that amino acid 2150 represents the carboxyl-terminal border competent for wild type interaction with p53 (GST-CR2aa2003–2212) (Fig. 2A, lanes 3–6). Progressive amino-terminal deletions of CR2 revealed that amino acid 2055 represents the amino-terminal border competent for wild type interaction with p53 (GST-CR2aa2055–2150) (Fig. 2A, compare lane 3 with lanes 7–10). These data show that the minimal region of CR2 competent for interaction with p53 resides within a 95-amino acid fragment, bordered by residues 2055 and 2150 (Fig. 2A, lane 10). This region precisely overlaps with the minimal CBP sequence (aa 2058–2130) required for interaction with SRC-1 (28).

To identify critical amino acids within CR2 responsible for interaction with p53, we prepared and characterized a series of double point mutations. The amino acids targeted for mutagenesis were chosen based on conservation between CBP and p300 as well as conservation between the mouse and human CBP. We targeted specific leucine residues within a region that forms amphipathic α-helices (and thus, possibly, protein-protein contacts). The selected residues were changed to alanines, to minimize effects on secondary and tertiary structure. Four CR2aa2003–2212 constructs were prepared, each carrying two point mutations as follows: F2101A/I2102A; L2068A/L2071A; L2072A/L2075A; L2140A/L2143A. Fig. 2B shows that only the double point mutant L2068A/L2071A, which resides within the first of the three α-helices, had a significant effect on p53 binding (lane 5). These data provide further evidence for the specificity of the p53-CR2 interaction. A summary of the p53 interactions with the various CR2 constructs from CBP and p300 is shown in Fig. 2C.
minal interactions in p53 are important for p53 function (50).

To determine whether a previously characterized minimal activation domain of p53 may be involved in the interaction with CR2, we introduced a double point mutation (L22Q/W23S) into this region (19) and tested the ability of the purified mutant protein to bind the minimal CR2 domain (aa 2055–2150). Mutation of these residues has previously been shown to have a dramatic effect on p53 transcription function (51). Fig. 3B shows the results of a GST pull-down assay where we tested the binding of purified wild type and mutant p53 proteins to both CR2 and KIX. Surprisingly, the double point mutation in this minimal p53 activation domain did not have a significant effect on p53 binding to the CR2 domain (Fig. 3B, lanes 7 and 8). As we have previously reported, the double point mutations did significantly reduce p53 binding to the KIX domain (Fig. 3B, lanes 5 and 6) (19). These data suggest that other amino acids in the p53 tripartite activation domain likely participate in CR2 binding.

**EMSA Studies on the p53-CR2 Interaction**—As an alternate method to characterize the p53-CR2 interaction, we utilized the electrophoretic mobility shift assay (EMSA). We were interested in determining whether CR2 aa2055–2150 could form a ternary complex with p53 bound to its consensus DNA recognition element. Fig. 4 shows that titration of the purified CR2 domain into p53-containing binding reactions decreased the mobility of the p53/DNA complex (lanes 5–7 and 12–14). The change in mobility suggested that CR2 was stably incorporated into the complex. Interestingly, we did not observe a change in the mobility of the p53/DNA complex in the presence of increasing amounts of the C/H3-containing CR1 domain (Fig. 4, lanes 2–4). The CR3 domain also had no effect on the migration of the p53/DNA complex, consistent with our previous observations (Fig. 4, lanes 8–10). As a positive control, we titrated the KIX domain of CBP into the p53/DNA binding reactions, and compared the ternary complex formation with that observed with CR2. Fig. 4 shows that both CR2 and KIX similarly decreased the mobility of the p53/DNA complex (lanes 12–17). The specificity of the DNA binding activity of p53 was confirmed by competition assays using the p53 consensus sequence and antibody supershift assays (data not shown). Finally, CR2, as well as the other CBP domains, did not bind DNA in the absence of

**Fig. 2. Identification of the minimal region of CR2 competent for p53 binding.** A, p53 interacts with amino acids 2055–2150 of CBP in vitro. Purified p53 (10 pmol) was incubated with GST alone (lane 2) or the indicated GST-CR2 deletion mutants (10 pmol) (lanes 4–10). As a positive control, p53 binding to full-length GST-CR2 aa1894–2221 was also tested (lane 3). p53 was detected using an anti-p53 antibody. Onput p53 (5%) is shown (lane 1). Bound p53 and protein molecular weight standards are indicated. B, p53 is defective for an interaction with the CR2 double point mutant L2068A/L2071A. Purified p53 (25 pmol) was assayed for its ability to bind to GST alone or the GST-CR2 aa2003–2212 double point mutants: F2101A/I2102A, L2068A/L2071A, L2072A/L2075, or L2140A/L2143A. (25 pmol). p53 binding to wild-type GST-CR2 aa2003–2212 was tested as a positive control (lane 3). Onput p53 (5%) is shown (lane 1). Bound p53 and protein molecular weight standards are indicated. C, summary of the p53-CR2 interactions.
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Functional Significance of the p53-CR2 Interaction in Vitro and in Vivo—To test whether the p53-CR2 interaction participated in CBP/p300-mediated p53 transcriptional activation, we examined p53 transcription function in the presence of exogenous wild type p300 or a mutant form of p300 that carries a deletion of the SRC1 domain (26). We selected p300 for these studies, because p53 interacts similarly with the CR2 region of both CBP and p300, and p300 coactivator function has been well characterized in vitro (18, 26, 41, 52, 53). To measure coactivator-mediated p53 transcriptional activation, we used a DNA template containing a 567-bp fragment from the Mdm2 intragenic P2 promoter, driving synthesis of a 190-nucleotide guanine-less transcript. This Mdm2 P2 fragment carries two p53 binding sites upstream of the core promoter (54). We chose to analyze transcription in a chromatin context, because several studies have found that analysis of p300 coactivator function in vitro requires nucleosomal templates (18, 41, 52, 53). Chromatin assembly of the p53-responsive G-less template was performed using the recombinant Drosophila assembly proteins Acf1/ISWI, GST-nNAP-1, and purified Drosophila core histones, as previously described (38). These assembly proteins are sufficient for the ATP-dependent formation of evenly spaced nucleosomal arrays (38, 55). Fig. 5A shows a DNA topological analysis demonstrating the assembly of native Drosophila core histones onto the p53-responsive G-less template (lanes 3–9). In the presence of the assembly factors, increasing ratios (w/w) of the core histones to the DNA produced a concomitant increase in DNA supercoiling, indicating that nucleosomes were deposited on the template. The figure shows that a histone/DNA ratio of 1:1.1:0.0 (w/w) fully assembled the DNA template into chromatin (lane 9); this ratio was used in subsequent in vitro transcription assays. Micrococcal nuclease digestion of the reconstituted chromatin template indicated the presence of evenly spaced nucleosomes on the DNA (data not shown).

We performed in vitro transcription assays on this p53-responsive chromatin template using nuclear extracts from CEM cells (a mutant p53 human T lymphocyte cell line) as a source of basal transcription factors and RNA polymerase. All experiments were performed in the presence of acetyl CoA and in the presence or absence of exogenous p53 and/or p300 or p300ΔSRC. The activator, coactivators, and nuclear extract were added following chromatin assembly. We used unacetylated p53 in this experiment, because a recent study has shown that the unacetylated form of p53 is sufficient for in vitro transcription from a chromatin-assembled template (18). Fig. 5B shows that the addition of purified recombinant p53 alone did not activate transcription from the Mdm2 promoter (lane 3). However, addition of purified recombinant p300 together with p53 produced a significant increase in RNA synthesis from the Mdm2 promoter (18-fold, Fig. 5B, lane 4). Under these same conditions, addition of p300ΔSRC, which carries an in-frame deletion of CR2 (aa 2042–2157), activated transcription only 5-fold from these templates; a 3.6-fold reduction in p300 coactivator function (Fig. 5B, lane 5). The absence of p53 reduced both wild type and mutant p300-stimulated transcription, indicating that optimal coactivator function required the presence of p53 (Fig. 5B, lanes 6 and 7). Fig. 5C demonstrates that both the wild type and mutant p300 proteins similarly acetylate p53, confirming that both proteins were equivalently functional with respect to acetyltransferase activity. Furthermore, p300ΔSRC is fully functional for acetylation of free histones as well as nucleosomal core histones (26).

Finally, to determine the functional role of the p53-CR2
interaction in vivo, we examined p53 transcription activity in transient transfection assays in p53-negative Jurkat T-cells in the presence of an expression plasmid for CR2 (CMV-CR2). Because CR2 does not have intrinsic activation properties, p53 binding to free CR2 should block the p53 interaction with endogenous (or transfected) CBP/p300 and, therefore, have a dominant negative effect on p53 transcriptional activity. The left panel of Fig. 5D shows that titration of the expression plasmid for CR2 repressed p53 transcriptional activation in a dose-dependent manner (lanes 3–5). We also measured the effect of CR2 on p53 transcriptional activation in the presence of an expression plasmid for CBP. The right panel shows that, in the presence of cotransfected full-length CBP, CR2 again repressed p53-mediated transcription. As expected, the presence of the CBP expression plasmid partially rescued the observed CR2 repression (Fig. 5D, compare lanes 8 and 10). Addition of either the CR2 or the CBP expression plasmids in the absence of p53 had no effect on pG13-Luc reporter activity (lane 11 and data not shown). These data support a role for the CR2 domain of CBP/p300 in p53 transcription function in vivo.

**HTLV-I Tax and p53 Compete for CR2 Binding in Vitro—**

Several studies have previously reported that the human T-cell leukemia virus Tax protein represses p53 transcription function (19, 31–33). Several recent studies suggest that this transcriptional repression may occur as a consequence of direct competition for binding to common regions of CBP/p300, thus compromising p53 promoter recruitment of the coactivator (19, 56–58). Recently, we reported that the HTLV-I Tax protein binds to the CR2 domain of CBP and p300, and identified CBP aa 2003–2212 as the minimal region competent for interaction with Tax (29). Based on these observations, we hypothesized that the binding of Tax and p53 to CR2 might be mutually exclusive. To directly test this hypothesis, we examined whether increasing concentrations of purified recombinant p53 can displace Tax from CR2 in vitro. Glutathione beads were bound with GST-CR2aa2003–2212 then incubated with a constant amount of Tax and increasing amounts of p53. The resulting protein–protein interactions were detected by Western blot analysis using a solution containing antibodies against both Tax and p53. Fig. 6 shows that increasing amounts of p53 reduced Tax binding to CR2, with a concomitant increase in p53 binding (lanes 3–5). This observation was corroborated in the reciprocal experiment, where increasing concentrations of Tax similarly displaced p53 from CR2 (Fig. 6, lanes 7–9). This
result is consistent with our observations that both Tax (29) and p53 bind to a similar, overlapping minimal domain of CR2 (aa 2003–2212 and aa 2055–2150, respectively), and that the CR2 double point mutant L2068A/L2071A reduces interaction with both proteins.

**DISCUSSION**

In this report, we show that p53 interacts strongly with the carboxyl-terminal region 2 (CR2) of CBP, located between amino acids 2055 and 2150. We also demonstrate that p53 interacts with the corresponding CR2 region of p300, located between amino acids 1970 and 2193. The CR2 region is distinct from the C/H3 domain, the only previously identified region within the carboxyl-terminal half of CBP that has been shown to interact with p53 (24, 25). In our assays, p53 interacted more strongly with CR2 than with the region of CBP that encompasses the C/H3 domain (CR1; aa 1514–1894). We mapped the minimal CR2 region of CBP required for strong interaction with p53 to amino acids 2055–2150. This 95-amino acid minimal CR2 sequence corresponds precisely with the SRC1-interacting domain of CBP, which has been mapped to amino acids 2058–2130 (28). This domain also corresponds to the CBP region involved in binding to IRF-3 and HTLV-I Tax (29, 30). We show that a CR2 double point mutation (L2068A/L2071A), which specifically disrupts the first of the three α-helices that resides within this region (30), reduces interaction with p53.

The amino-terminal 107 amino acids of p53 at least partially participate in protein-protein interaction with CR2. This is consistent with our observation that CR2 binds well to full-length p53 DNA complexes, suggesting that the DNA binding and tetramerization domains are not involved in CR2 recognition. Previous studies have indicated that the p53 activation domain participates in binding to the KIX domain (19) and C/H3 domain of CBP (20, 23). We tested whether a minimal region of the p53 activation domain might interact with CR2 using a double point mutant of p53 (L22Q/W23S). Although we did not observe a significant decrease in the CR2-p53 interaction using this mutant, the activation domain of p53 is tripartite, and extends through the first 100 amino acids of the protein. Therefore, other amino acids that reside within this amino-terminal region of p53 likely participate in CR2 complex formation.

Our *in vitro* transcription studies clearly show that p53 interaction with the p300 CR2 domain is relevant to p53 transcription function. The addition of p300 and p53 strongly stimulated RNA synthesis from the p53-responsive Mdm2 P2 promoter assembled into chromatin. However, the p300 deletion mutant p300Δ5RSC was significantly reduced in its ability to mediate coactivator function. Our observation that p300Δ5RSC retained partial coactivator function in p53-mediated transcription may reflect the ability of p53 to recruit CBP/p300 to the Mdm2 promoter via interaction with other coactivator domains (such as KIX and/or C/H3) (19, 20, 23, 25, 59, 60). The *in vitro* transcription result was corroborated using transient transfection assays, confirming a functional role for the CR2 domain in mediating p53 transcription function *in vivo*.

Previous studies have shown that the HTLV-I Tax protein inhibits many of the tumor suppressor functions of p53 (31–33, 61–63). Several recent studies suggest that this may occur through competition for CBP/p300 (19, 56–58). We have recently shown that, like p53, Tax also recognizes the CR2 region of CBP/p300 (29), raising the possibility that both Tax and p53 bind mutually exclusively to this region. Using a competition binding assay, we directly show that Tax specifically disrupts the p53-CR2 interaction, providing further evidence for coactivator competition between these two proteins. It appears that both proteins recognize the same surface structure of CR2, because p53 and Tax are unable to bind to the CR2 domain that harbors the double point mutation (L2068A/L2071A) (shown in Fig. 2B, and Ref. 29). Together, these data provide further evidence for a model of Tax repression of p53 transcription function mediated through direct competition, at multiple sites, for CBP/p300. This coactivator competition between Tax and p53 may contribute to the molecular mechanism of HTLV-I-associated malignant transformation.

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Jill A. Livengood, Kirsten E. S. Scoggin, Karen Van Orden, Steven J. McBryant, Rajeswari S. Edayathumangalam, Paul J. Laybourn and Jennifer K. Nyborg

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