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Structure of the origin recognition complex bound to DNA replication origin

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Supplementary Information

Supplementary Discussion

Configurations of the ATPase centres

ORC recognizes and binds to origin DNA in an ATP dependent manner¹. Orc1-5 subunits each contains AAA+ or AAA+-like domains, but only Orc1, 4 and 5 contain functional ATPase-related motifs^{2,3}. As expected, we identified three ATP γ S molecules and their associated Mg²⁺ at their corresponding interfaces ([Extended Data Fig. 4a-c](#)). However, each of the bound ATP γ S is uniquely coordinated. Most notably, in the Walker A motif of Orc4, the yeast-specific replacement of the conserved glycine by a bulky tyrosine (Tyr107) ([Extended Data Fig. 4f](#)) results in the flipping of the base moiety of the bound ATP γ S⁴ ([Extended Data Fig. 4b, d and e](#)) that likely weakens the affinity of Orc4 for ATP binding. As for the nucleotide binding pocket of Orc5, Tyr45 immediately downstream of the Walker A motif provides additional stabilization of nucleotide binding through ring-stacking ([Extended Data Fig. 4c](#)). Indeed, biochemical studies showed that Orc5 has the highest affinity for ATP binding^{3,5}. Although Orc1, Orc4 and Orc5 each binds ATP nucleotide, only ATP binding by Orc1 is essential for ORC to bind origin DNA³.

The ATPase site of Orc5:Orc3 appears to be inactive for ATP hydrolysis because the basic residues of Orc3 that could serve as Arginine Finger are too far from the nucleotide, due to the presence of a gap between these two subunits ([Extended Data Fig. 4e](#)), which is also true in the crystal structure of DmORC⁶. As for the Orc4:Orc5 centre, the equivalent Arginine Finger (Arg178 from Orc5) is also too far from ATP γ S. Instead, Orc5-Lys151 is the only basic residue less than 4-Å from the oxygen of the γ -phosphate, and could be a potential functional replacement ([Extended Data Fig. 4b](#)). In contrast, the Orc1 centre appears to be well situated for ATPase activity with Arginine Finger (Arg267 of Orc4) around 3-Å from the oxygen of the γ -phosphate ([Extended Data Fig. 4a](#)). This is in sharp contrast to the inhibitive structure of DmORC⁶, where the Orc1:Orc4 centre is not formed. Together with our apoORC structure in which Orc1-AAA+ appears highly

flexible, these findings suggest that origin DNA binding likely drives the activation of ORC through regulating the conformations of Orc1.

It has been shown that ATPase activity of Orc1, but not Orc4 or Orc5, is essential for ORC to function *in vivo* and for the viability of yeast cells^{3,7}. However, the exact role of ATP hydrolysis by Orc1 is not clear. Further investigations are required to identify the precise roles of ATP hydrolysis by Orc1:4 and other centres in regulating replication initiation.

Supplementary Video 1. Structure of the ORC-DNA complex

Segmented density of each ORC subunit is shown in transparent surface representation with atomic model superimposed. Interactions between DNA and ORC subunits are highlighted in zoom-in views. Next, the organization of ORC subunits and the potential DNA entry between Orc1 and Orc2 are shown. Last, the minor-groove inserting motif of Orc1-BP is highlighted in close-up views.

Supplementary Table 1. ACS sequences used to generate the position weight matrix of the ORC binding consensus.

All the ACS sequences used in this study were produced by Eaton et al.⁸

121 predicted ACS elements strictly matching to the ACS motif with their positions at 7, 9, and 11-13 as Ts						
chr	start	end	name	score	strand	seq
1	734	766	1_766_-	17.04	-	TATTTTATGTTTAGGTGATTTTGTGGGGATT
1	70402	70434	1_70434_-	7.19913	-	ATTTTATGTTTAGAAACAAATTTCCCGAG
1	124497	124529	1_124529_-	13.4856	-	ATTTTATATTTAAGTCTTGATTAAGTCTTT
1	159951	159983	1_159951_+	11.5248	+	TTTATTTATTTAGTGGGAGCAAAACAGTTTA
2	6541	6573	2_6573_-	16.9789	-	AATTTTATGTTTAGGTGATTTAGTGGTAATT
2	93537	93569	2_93537_+	8.51814	+	AGATATTATTTATGTAAGAATTAATAATA
2	170191	170223	2_170223_-	10.3217	-	CAGTTTATTTAGTGAACATATGGGCAATTC
2	255015	255047	2_255047_-	13.2524	-	TTTATTTATTTTATGTTTGTATTGGATTTT
2	407972	408004	2_408004_-	9.93797	-	TTTATTTATTTTGTCTGGAAGCTCTTACA
2	591418	591450	2_591418_+	15.8285	+	ATAGTTTATGTTTACTATAAAATTTAATTTT
2	704298	704330	2_704298_+	11.887	+	TATATATATTTAGGTAAATCATTTACACTTT
2	792022	792054	2_792054_-	8.99777	-	TTTATTTTATTTTGTATTTCAAAGGACATT
3	11254	11286	3_11254_+	13.8235	+	TTTTTTATGTTTTTTAAACATTAAGTTTT
3	39560	39592	3_39592_-	14.4454	-	TTTTATATGTTTGTATGTATTGTTATTTT

3	292648	292680	3_292680_-	17.6194	-	ATTTTTTATATTTAGGTATTA AATTGCGATTTA
3	315811	315843	3_315811_+	16.1916	+	TATTTTTATGTTTAGGTGATTTTAGTGGTGATT
4	86093	86125	4_86125_-	9.82279	-	GATTTTTATGTTTGGGCGCAGAAAACAAGCTA A
4	212562	212594	4_212594_-	11.7088	-	TTTTTTTATATTTTGTTGTTGGTTTCAGGAAAA
4	329671	329703	4_329671_+	12.4104	+	GGTGTTTATATTTAGGTAGGGCATAAGGATTT A
4	427865	427897	4_427865_+	11.8123	+	AAGTTTTATATTTAGGTGCTGCTCCGGTACTT
4	462573	462605	4_462605_-	13.4929	-	AGATTTTATGTTTAGATCTTTTATGCTTGCTTT
4	484003	484035	4_484035_-	12.2431	-	TTTTTTTATATTTATGTAGCTTTTTGTATATTC
4	505485	505517	4_505517_-	10.4526	-	TTTTTTTATATTTTGCCTATATTCTTCTTTTT
4	555365	555397	4_555397_-	9.48338	-	AAAGTTTATGTTTTTCTACTGGAGGCGTCATTT
4	913856	913888	4_913856_+	13.2807	+	TATTTTTATATTTGTTTCTTGCGTGGAGTTTT
4	1057887	1057919	4_1057887_+	13.9859	+	ATTTTTTATGTTTATTCCATATATACACTTATA
4	1240919	1240951	4_1240919_+	11.0904	+	TTGATTTATATTTAGTCCAAATATTACAGAAAA
4	1276277	1276309	4_1276277_+	8.901	+	TTTTTTTATGTTTCCCCCCAAAGTTCTGATTT
4	1302724	1302756	4_1302756_-	9.91521	-	CAAATATATATTTAGTTAATGAAAATGGAATTA
4	1404322	1404354	4_1404322_+	9.09136	+	TCTTTTTATATTTTGAATGTTTTGTGCTAAA
4	1447471	1447503	4_1447471_+	14.4494	+	AAATTTTATGTTTAGTTAGGTTTTACCTTGAAT
4	1462047	1462079	4_1462047_+	11.547	+	ATAATTTATGTTTAGCTCTTACTTTAATCCCAA
4	1502756	1502788	4_1502788_-	13.6392	-	TATAATTATGTTTTGTGAGAAATTTAGCTTT
4	1524641	1524673	4_1524641_+	15.1604	+	TATTTTTATGTTTAGGTGATTTTGGTGGTGATT
5	6406	6438	5_6438_-	15.4549	-	TATTTTTATGTTTAGGTGATTTTGATGGTGATT
5	94055	94087	5_94055_+	10.3628	+	CAAGTTTATATTTTGTTGCTAGCGTTACGGTTA
5	145682	145714	5_145714_-	12.4964	-	CAGTTTTTGTGTTAGTTTTTAATCTGGATATT
5	173776	173808	5_173808_-	12.3658	-	TAATTTTATATTTTGCCTTGAAATTTAATCATG
5	212454	212486	5_212454_+	8.83164	+	TAAAATTATGTTTAGGTAATGAAAAATAGTA A
5	287565	287597	5_287565_+	13.9654	+	TTTATTTATGTTTTGTTCCAGCGGGCATCTTT
5	498884	498916	5_498884_+	13.1378	+	CATATTTATGTTTAGTTTCCGAATGCTTTTGTA
5	569629	569661	5_569629_+	16.1916	+	TATTTTTATGTTTAGGTGATTTTAGTGGTGATT
6	5463	5495	6_5495_-	16.1916	-	TATTTTTATGTTTAGGTGATTTTAGTGGTGATT
6	118718	118750	6_118750_-	6.54157	-	TGCTTTTATATTTTTTATAGATCATTTTCAAAC
6	199401	199433	6_199401_+	11.8539	+	CTTGTTTATATTTAGTTACGTTGGGATCAAGTT
6	256343	256375	6_256375_-	13.3688	-	TTTTTTTATGTTTTTCCGGAATTGGCTAAATT
7	485082	485114	7_485114_-	14.3557	-	TTTATTTATGTTTTGCCGTAAGATCGATACTTT
7	574701	574733	7_574701_+	12.0302	+	AGTATTTATGTTTGTCTATTCTTTCTACATAA
7	659970	660002	7_660002_-	13.9741	-	ATATTTTATGTTTACTTATGTTAACCTGCATTA
7	1083674	1083706	7_1083674_+	16.0858	+	TATTTTTATGTTTAGGTGATTTTGATGATATT
8	5437	5469	8_5469_-	16.1916	-	TATTTTTATGTTTAGGTGATTTTAGTGGTGATT
8	7723	7755	8_7755_-	16.0466	-	TATTTTTATATTTAGGTGATTTTAGTGGTTATT
8	116382	116414	8_116414_-	8.42479	-	AAATAGTATGTTTTGGTGTTAAAGAAGAACAT T

8	447761	447793	8_447793_-	15.0713	-	TATGTTTATGTTTTGTGAGTAAAGTCAAGAATT
9	136276	136308	9_136308_-	7.666	-	AAGTTTTATCTTTGGTTGAAGCAGTTTATGTTT
9	175170	175202	9_175170_+	10.365	+	ATGTTTTATGTTTTGTCTGGAAAAACATATAGT
9	214732	214764	9_214732_+	9.92163	+	TTAATTTATGTTTTGTAAAGAATAAAATGAGTA
9	357222	357254	9_357222_+	8.60296	+	AATTTTTATATTTTGTTGCTTCAAAAACAGTGC
9	439100	439132	9_439100_+	17.3807	+	TATTTTTATGTTTAGGTGATTTTAGTGGTAATT
10	67663	67695	10_67663_+	7.70191	+	AAATTATATGTTTTGTCTGGGCGCGACATTC
10	99585	99617	10_99617_-	12.9205	-	TTTATTTATGTTTTGTTAACTGACGGTGTTTT
10	113712	113744	10_113744_-	10.822	-	TAAATATATATTTAGTTATGGAAATCAATAAA
10	228543	228575	10_228575_-	11.2455	-	AATATTTATATTTATGTACAGTTTACATTGTA
10	337048	337080	10_337048_+	13.1864	+	TTTTTTTATGTTTAGCTAAGTAAAGCAGCTTG
10	417058	417090	10_417090_-	13.5021	-	ATTTTTTATATTTAGTTTACTTTCCAGTCAATT
10	442392	442424	10_442424_-	13.5194	-	TAAATTTATATTTTGTTTCGTAAAAAGAAAAATT
10	612741	612773	10_612773_-	14.6221	-	TTTTTTTATCTTTAGTTGCCTAAATACTATTTA
11	741	773	11_773_-	16.2472	-	TATTTTTATGTTTAGGTAATTTTAGTGGTGATT
11	98385	98417	11_98385_+	11.7706	+	TTTTTTTATGTTTAGGTATATTTGCTAGAAAG
11	325956	325988	11_325988_-	8.92001	-	GAATATTATTTTTATTTATTTATTTATATTATT
11	329468	329500	11_329500_-	14.6252	-	TTTTTTTATGTTTTTTTACGTTTTGAGATCATA
11	388662	388694	11_388662_+	14.9652	+	CTTGTTTATGTTTATTTGTAAATTACATTATT
11	447805	447837	11_447837_-	12.8834	-	CCTTTTTATGTTTTGTTCTTGATTTTAATACTA
11	612014	612046	11_612046_-	9.9857	-	TTTTTTTATGTTTTTGCTCCTAGAGGTGAATA
11	642412	642444	11_642412_+	13.5507	+	TGATTTTATATTTAGTTGGCGAACTAGCTCATC
11	665568	665600	11_665568_+	15.1604	+	TATTTTTATGTTTAGGTGATTTTGGTGGTGATT
12	5918	5950	12_5918_+	14.6469	+	TTATTTTATGTTTACTTTTTATAGATTGTCTTT
12	373297	373329	12_373329_-	12.1529	-	TTTTTTTATATTTTCTCCGTATTTATGAAATT
12	412822	412854	12_412854_-	13.7762	-	ATGTTTTTGTGTTTGTGTAGTATTCGAGCATT
12	450506	450538	12_450506_+	12.4963	+	CGTTTTTATGTTTATTCGCTAAACCCTTCTTA
12	460369	460401	12_460401_-	7.09017	-	TTTTTTTTTTTTTTTTTAAAGTAAATGGCAGTTT
12	513054	513086	12_513086_-	12.7984	-	TTTATTTATGTTTTTGTACAAACGCGCACATG
12	659892	659924	12_659892_+	13.7201	+	GCTTTTTATGTTTATTTTCATGGATTACGAAATT
12	822089	822121	12_822089_+	11.0262	+	TATTTTTATGTTTAAAGAAAGGATTAAGAACAAT
12	888709	888741	12_888741_-	14.1212	-	GTTTTTTATGTTTAGATGTAAAAATTAATTTTT
12	1064312	1064344	12_1064312_+	16.1916	+	TATTTTTATGTTTAGGTGATTTTAGTGGTGATT
13	137321	137353	13_137321_+	12.4515	+	AATATTTATGTTTTGTTAATCTCCTCTACCCTT
13	159046	159078	13_159046_+	12.9155	+	TGTTTTTATGTTTAGACCTCGTACATAGGAATA
13	263126	263158	13_263126_+	7.70008	+	ATTTTTTATATTTGTGATAAAGGGATAACTCG
13	286914	286946	13_286946_-	10.1486	-	AGGATTTATGTTTTTTGTGCTTTGGAACTTT
13	535738	535770	13_535770_-	15.4832	-	TTAATTTATATTTAGTTTAGGATATAGATTATC
13	611317	611349	13_611317_+	13.7591	+	ATTGTTTATGTTTATGTTCTTTATACTCAAAAT
13	688902	688934	13_688902_+	5.3524	+	TAATTTTTTTTTTTGATGTTTCGACATCATTATT
13	758385	758417	13_758417_-	10.0205	-	AAATTTTATGTTTTTTTCTTCGTTTTGCGAAAA

13	805162	805194	13_805162_+	12.8451	+	TATTTTGTATTTAGTCTTTGTTTCGAACTTT
13	815391	815423	13_815391_+	11.4708	+	AAATTCTATGTTTTGTTCTGAAATCTCGATAT
13	897945	897977	13_897977_-	12.2572	-	TTTTTTATGTTTGGTCTTGTTATTGAACAAA
14	250461	250493	14_250493_-	8.32188	-	ACAATTTGTATTTAGTTGGTGTGACCTCAAATT
14	412407	412439	14_412439_-	7.02431	-	TTTTTTATATTTCTGCCCAAAAAACGTAGTTC
14	499037	499069	14_499037_+	10.6476	+	TTCTTTATGTTTAGCTCTTTTTCATCACTTC
14	500650	500682	14_500682_-	4.70867	-	TATTTTATGTTTTCATTTGAAACTTGCTGGT
14	738714	738746	14_738714_+	12.5092	+	CGCATTTATATTTAGTTAAATTATGTGAAATT
14	764321	764353	14_764353_-	9.03008	-	ACATTTTTATTTTGTTTCATCTTTGTGATTTT
15	780	812	15_812_-	16.1916	-	TATTTTATGTTTAGGTGATTTTAGTGGTGATT
15	10926	10958	15_10926_+	11.0754	+	TAATTATATGTTTAGGTGATTGCTTAGGTTTGT
15	85328	85360	15_85360_-	11.2805	-	TATATTTATGTTTATGTTCCATCATGTAGAAAA
15	167002	167034	15_167002_+	12.3119	+	TTTATTTATGTTTTCGTTATATTTTCAACATTT
15	277701	277733	15_277733_-	12.3309	-	GTTGTTTATCTTTGTTATTAAGCTCTACTTT
15	309233	309265	15_309265_-	8.2573	-	GAAAATTATATTTTGTCATGAAGTAATCTATTC
15	908306	908338	15_908306_+	14.1055	+	TTTGTTTATGTTTAGGTTAACGATAGACATATT
16	43131	43163	16_43163_-	14.6897	-	TATTTTATGTTTTGTTTATATTTTGAATTT
16	74102	74134	16_74134_-	8.05888	-	TATCTTTTTTTTTGTTACTATTAGTCATGTTT
16	116593	116625	16_116593_+	12.83	+	TATTTTATGTTTTGTTCCATACTAAATGCAGT
16	384592	384624	16_384592_+	13.3105	+	AAAATTTATGTTTATGTGGCGTAAAAATCTTT
16	511704	511736	16_511704_+	13.2688	+	TATTTTATGTTTTTGAGATATTTTCGAGCTTT
16	563877	563909	16_563877_+	9.6204	+	GTCTTTATATTTAGTCCGCTTTACACCGAAAA
16	695465	695497	16_695465_+	14.692	+	AATTTTATATTTGGTTGAAAATTATGACATT
16	777063	777095	16_777095_-	12.5663	-	TTTATTTATATTTGGCATTACTCTTCATCATT
16	819308	819340	16_819340_-	14.6098	-	AATTTTATATTTATTCATGATATATTAATATT
16	880905	880937	16_880905_+	14.8631	+	ATATTTATGTTTAGGTTAATAACTTTGGTAAT
16	942425	942457	16_942425_+	14.7587	+	AATTTTATGTTTAGGTGATTTTGGTGGTGATT

46 predicted ACS elements matching to the ACS motif with their positions at 11-13 as Ts but either (or both) positions at 7 or 9 as adenine

chr	start	end	name	score	strand	seq
1	31002	31034	1_31002_+	12.2805	+	TATTTTAAAGTTTTGTTGGGTCTCTGAGAACTT
2	63339	63371	2_63371_-	12.8086	-	TTTTTTAATTTTGTACGAAATCCTGGTATT
4	46198	46230	4_46230_-	7.99865	-	AAATTTAATATTTTGGATGAAAAAACCATTTT
4	253839	253871	4_253839_+	9.05184	+	TTTTTATAGTTTGCTTTGAATCTTTGTGTTT
4	316862	316894	4_316862_+	11.6583	+	TAATTTAAATTTGTTCTTTCTAAACAATT
4	435160	435192	4_435160_+	8.39184	+	GAAATAAATATTTAGTTGAGAAAGTTTGTTTA
4	629293	629325	4_629325_-	10.054	-	GAAATTAATGTTTAGCGATCTAATAGTGATCTT
4	640030	640062	4_640062_-	9.58996	-	TTTTTAAAGTTTGGTCGTTGAAAAAGGATTC
4	702924	702956	4_702924_+	14.9705	+	ATAATTAATGTTTGGTCTGAATTTTATTTT
4	806099	806131	4_806099_+	9.91679	+	ATTTTAAATTTAGCTGGGGTGGGTAACAA G

4	1353573	1353605	4_1353573_+	6.11805	+	CAAATTAATATTTATGAACGTTATGATGTCAAG
5	353582	353614	5_353582_+	12.3455	+	AATATTTACTTTTTGGTGCGGAAATCTGTAATA
5	439070	439102	5_439102_-	11.4315	-	ATTTTTTAAGTTTTGCGCCTTTAGCTCATGTTT
5	549650	549682	5_549682_-	11.8415	-	TAATTTAATATTTTTTTCCGAATTACAACAAT
7	64426	64458	7_64458_-	11.8331	-	ATTTTTAATATTTTGTTTCTCGTTTTGCTTAT
7	421252	421284	7_421284_-	11.1803	-	TAAATTATTGTTTAGTTTTGATTAGCTTTACTT
7	508877	508909	7_508909_-	12.2059	-	CATTTTAATGTTTGGTTGTGAATTGAAAGAATA
7	834635	834667	7_834667_-	8.16946	-	TTGTATATAGTTTAGTTACCATTTCCTACTTT
7	888414	888446	7_888414_+	14.2661	+	TATTTTAATATTTTGTTCTTTAGTTTTAAAAAT
8	45762	45794	8_45794_-	11.1276	-	AAAGTTAATATTTAGTACCGATACTATACATTA
8	64299	64331	8_64299_+	10.4645	+	TAATTTTAATTTTAGTTATTGATTTCATGAAA
9	73937	73969	9_73969_-	7.62169	-	CAAATTTAAGTTTCTTTATATATTCCTTACTTT
9	245848	245880	9_245880_-	16.4437	-	TTTTTTAATGTTTGTCTTTATAACGCGACTTA
9	341997	342029	9_342029_-	11.6559	-	TTTTTTAATGTTTAGCTTTCAAAAAGCTAAAA
9	411969	412001	9_412001_-	9.17527	-	AATTTTAATGTTTGTCTGGAAGAAGAAGAAG T
10	23920	23952	10_23920_+	11.4884	+	AAATTTTGTAGTTTGTATAATAAACGACTTTT
11	55835	55867	11_55867_-	10.4706	-	TTCATTAATGTTTAGTTCCGAGCGTGACGTTAC
11	213277	213309	11_213309_-	14.2299	-	TTTTTAAATATTTAGTTATTGAATGATTAAATT
11	416878	416910	11_416878_+	7.60058	+	GAAGTTTAATTTTAGGTGTCTGGGAGAAACATT T
11	462614	462646	11_462646_-	10.0913	-	GCTTTTAATGTTTAGGTAGTTACAGACCTTTTG
12	243727	243759	12_243727_+	16.4875	+	TAAATTAATGTTTAGTTCTGATATTTCAATTTT
12	289390	289422	12_289422_-	6.87921	-	AAAATTAATGTTTGTCTGCTTTTACTGTCGCGT
12	603078	603110	12_603110_-	11.3523	-	TTTTTTAATGTTTATGTTCAACATACCCGAAAC
12	794176	794208	12_794208_-	11.1448	-	AAAGTTTAAGTTTAGTTACGGGGTTTAATGTAA
12	928285	928317	12_928285_+	11.8356	+	AATATTATAGTTTTGTTAGTAATGTTGAACTTT
13	39493	39525	13_39493_+	10.6645	+	TAATTTTAAGTTTTGGGATGGATCTTTCATTTT
13	183842	183874	13_183874_-	12.0689	-	ATATTTAATGTTTAGAAGTTGTTTACATATTT
13	371019	371051	13_371019_+	11.204	+	AATTTTATTGTTTAGTTTCATGATAAAAACTTC
14	61825	61857	14_61857_-	12.5437	-	TTTATTTAAATTTTGCCATTTTATATGTACATT
14	89723	89755	14_89755_-	11.9634	-	TATTTTAAAGTTTTGTTGTTTTTTTTATTGTT
14	635799	635831	14_635831_-	12.7948	-	TTTTTTAATTTTAGTTAAGTTTTCTCTAATT
15	436837	436869	15_436869_-	9.61833	-	TTGATTAATATTTGTTGAAAAGTAAAGTTTTT
15	783386	783418	15_783386_+	12.6323	+	TATTTTAACTTTTGGTTTTGAAGCTCGTAATT
16	73173	73205	16_73205_-	10.5161	-	GTCTTTATTGTTTAGTCTCAATAATCGCAATTA
16	289530	289562	16_289530_+	11.9875	+	ATAATTAATGTTTACTTCAGACAATAAAACATT
16	633921	633953	16_633921_+	10.6151	+	GTTTTTATAGTTTAGTTGGTTTTGTTTAATTC

Supplementary Reference

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- 3 Klemm, R. D., Austin, R. J. & Bell, S. P. Coordinate binding of ATP and origin DNA regulates the ATPase activity of the origin recognition complex. *Cell* **88**, 493-502 (1997).
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