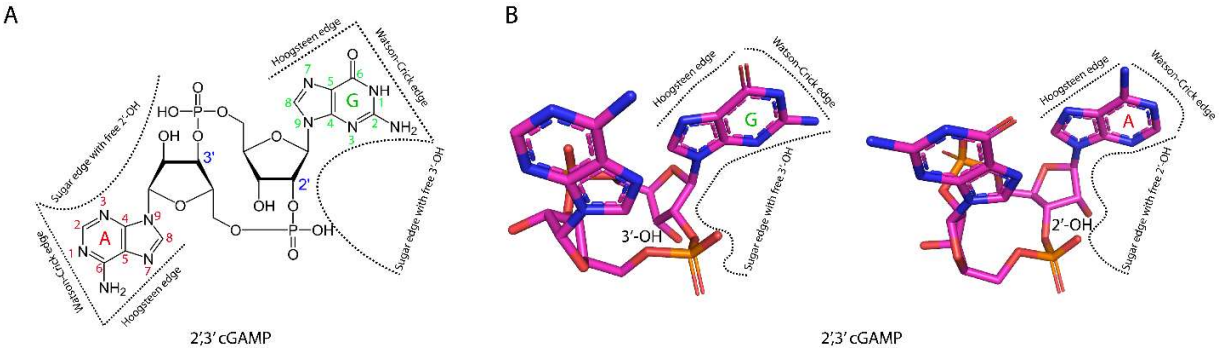
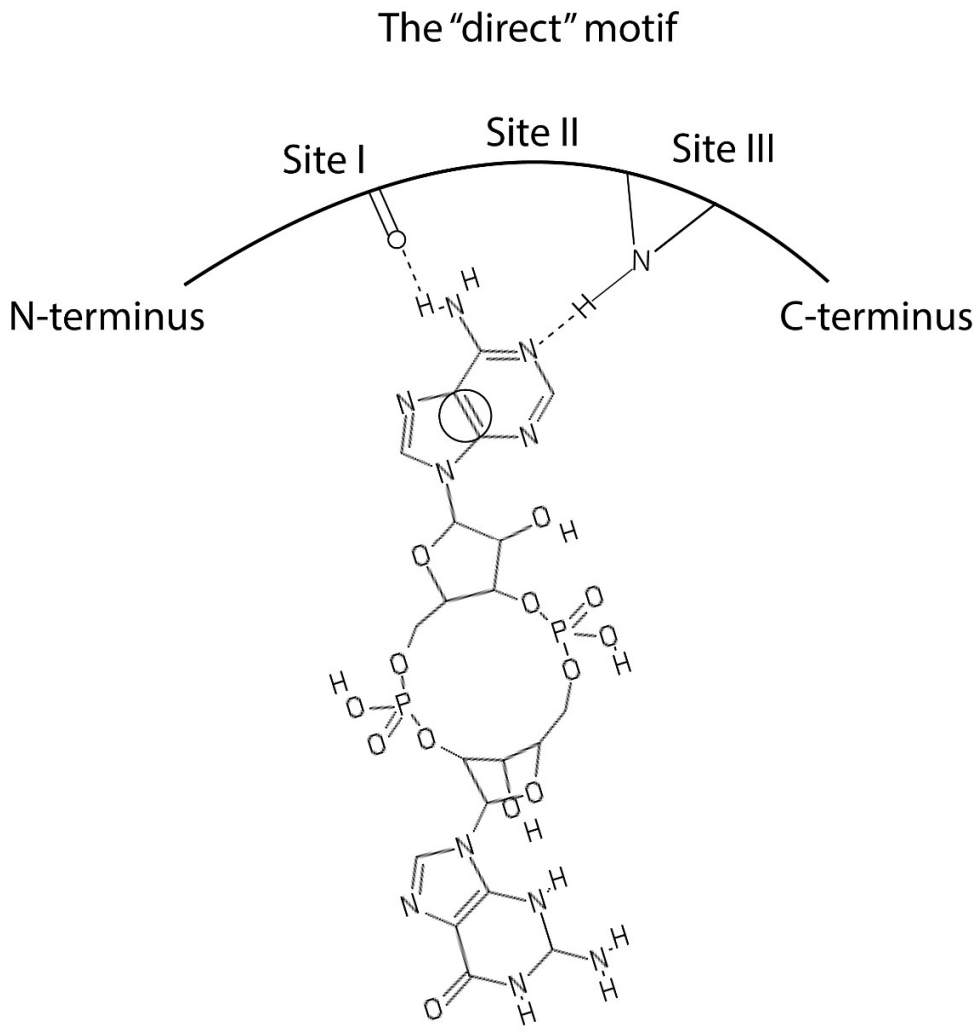



Supplementary figure 1. The sketch of interaction edges of 2',3' cGAMP.




Supplementary figure 2. Sketch of the “direct” (Site I at the N-terminus and site II at the C-terminus of the recognition loop) adenine-binding motif. The adenine moiety is recognized by the adenine binding loop with two hydrogen bonds and stacks with one hydrophobic residue (black circle).

## Supplementary table 1. Interactions between porcine STING$^{CBD}$ and CDNs

| | 2',3' cGAMP(6A06) | c-di-GMP(6A04) | 3',3' cGAMP(6A05) | c-di-AMP (6IYF) | c-di-AMP(6A03) |
|---|---|---|---|---|---|
| **Hydrogen bonds(≤3.2 Å)** | | | | | |
| R238(NH2) | N7 (Guanine) | N7 (Guanine) | N7 (Guanine) | N7 (Adenine) | |
| R238'(NH2) | N7 (Adenine) | | | | |
| T263(OG1) | N3 (Guanine) | N3 (Guanine) | | | |
| T263(OG1) | NH2(N2,Guanine) | 3' hydroxyl | 3' hydroxyl | 3' hydroxyl | |
| V239'(carbonyl) | NH2(N6, Adenine) | | NH2(N6, adenine) | NH2(N6, adenine) | |
| R238'(NH1) | O19(phosphate) | O21(phosphate) | OAI(phosphate) | O2P(phosphate) | |
| R238'(NH2) | O19(phosphate) | O21(phosphate) | | | |
| R238(NH1) | O29(phosphate) | O2(phosphate) | OAH(phosphate) | O2P1(phosphate) | O2P1(phosphate) |
| R238(NH2) | O29(phosphate) | | | O2P1(phosphate) | |
| S162(OG) | | | | | O5(phosphate) |
| S162'(OG) | | | | | O1P(phosphate) |
| **Water-mediated Hydrogen bonds (≤3.2 Å)** | 11 | 9 | 6 | 8 | 7 |
| **Charge-charge interaction** | 2 | 2 | 2 | 2 | 2 |
| **Stacking** | 6 | 6 | 6 | 6 | 6 |
| **Bad contact (bumps) ( ≤3.2 Å)** | | | | | |
| V239'(carbonyl) | | O(C6, Guanine) | | | |
| Y240'(CD1) | | O6 (Guanine) | | | NH2(N6,adenine) |
| Y240'(CE1) | | N7(Guanine) | NH2(N6,adenine) | | |
| Y240(CD1) | | | | | NH2(N6, adenine) |
| Y167(CE1) | | N3(Guanine) | | | |
| I235(CG1) | | NH2(N2, Guanine) | | | |

| | | | | | |
|---|---|---|---|---|---|
| T263(OG1) | | | | C2 (ribose) | |
| T263’(CB) | | 3’ hydroxyl | 3’ hydroxyl | | |
| P264(CD) | | | 3’ hydroxyl | | 3’ hydroxyl |
| P264’(CD) | | | | | 3’ hydroxyl |