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Sororin is tethered to Cohesin SA2

Comment on: Zhang N, Debananda P. C-terminus of Sororin interacts with SA2 and regulates sister chromatid cohesion. Cell Cycle 2015; 2015;14(6):820-6; http://dx.doi.org/10.1080/15384101.2014.1000206

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To produce euploid progeny with equal chromosome complements and identical genomes, cells must achieve accurate chromosome segregation during mitosis. Many cellular processes contribute to this fidelity of genome transmission, including the fundamental principle that the identical sister chromatids, produced via DNA replication, must remain physically connected until just before their segregation in anaphase. There are 2 overarching mechanisms that account for the cohesion that is maintained between the sisters.[1] Firstly, the nascent DNA molecules emerge from the replicative machinery as physically entwined, or catenated, entities. These cannot be resolved from each other without coupled DNA breakage and re-ligation, known as strand passage reactions, that are completed by Type II topoisomerases in preparation for chromatid segregation. The second cohesive mechanism is broadly defined as protein-mediated cohesion, and involves the activity of numerous proteins, including a protein complex named Cohesin whose ability to tether sister DNA molecules has been the subject of intense study. In this issue of Cell Cycle, Zhang and Pati[2] describe a key role for the C-terminus of Sororin, a Cohesin regulatory sub-unit required for maintenance of cohesion in human cells.[3,4] This discovery promises to stimulate a new understanding of how Cohesin is regulated by Sororin.

The core of the Cohesin complex consists of 4 subunits (Smc1, Smc3, Rad21 and SA1/SA2) that can arrange as a ring via strong protein-protein interactions. Cohesin function can be disrupted by binding of the negative regulator Wapl. Sororin promotes sister chromatid cohesion by antagonizing Wapl activity, but the mechanism remains unknown. One model is that the Sororin-Wapl antagonism is largely a matter of competition for binding with the Cohesin-regulator Pds5. That is, binding of Sororin to Pds5 blocks the binding site on the Cohesin complex for Wapl, and thus serves to maintain the function of Cohesin. To remove Cohesin from chromosomes in mitosis, Wapl needs to associate with Cohesin-bound Pds5. This is achieved through the action of mitotic kinases (CDK1 and Aurora B) that phosphorylate Sororin with the result that Sororin is displaced from Pds5, allowing recruitment of Wapl. Conversely, crystallographic analysis of the Rad21-SA2 binding interface revealed a conserved site that interacts with Wapl.[5] Interestingly, Wapl binding to Rad21-SA2 at this site is also subject to competition by another Cohesin protector, the centromeric protein Sgo1.[5] Furthermore, it has been shown that Sgo1 promotes Sororin function through dephosphorylation by the PP2A phosphatase, a Sgo1 binding partner, which counteracts Sororin phosphorylation by CDK1 and Aurora B during mitosis. As well as the key role of Sororin phosphorylation, antagonizing the function of Cohesin in promoting sister tethering requires phosphorylation of the SA2 Cohesin sub-unit by the Plk1 kinase. Interestingly, evidence also indicates that phosphorylated Sororin recruits Plk1 to SA2.[6] These results indicate a complex regulatory network between Cohesin, its protectors Sororin and Sgo1, and the inhibitor Wapl.

The study by Zhang and Pati[2] provides evidence that Sororin associates with the SA2 sub-unit of the Cohesin complex and that this interaction is crucial for sister chromatid tethering. The data confirm previous work that the C-terminus of Sororin is required for its role as a protector of Cohesin and that residues within this region facilitate the interaction with Cohesin.[7] Moreover, Zhang and Pati identify 12 conserved amino acids at the extreme C-terminus as being necessary for interaction with SA2 and for the function of Sororin in sister tethering.[2] This evidence provokes an intriguing model for Cohesin function, where multiple regulators bind the SA2 sub-unit or perhaps the Rad21-SA2 interface. Although the C-terminus of Sororin interacts with SA2, how this interaction is regulated and how Sororin binding functionally impacts SA2 will be questions of great interest.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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