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RAD21L is a novel kleisin subunit of the cohesin complex

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Cohesin forms a ring-like complex that mediates cohesion between two sister chromatids during both mitosis and meiosis.[1] In mammals, the canonical cohesin complex consists of two structural maintenance of chromosomes (SMC) proteins, SMC1α and SMC3, and two non-SMC proteins, α-kleisin subunit RAD21 and SA/STAG. Two different SA subunits have been characterized in mitotic cells, namely SA1 and SA2. In addition, meiotic cells express at least three additional cohesin proteins, SMC1β (SMC1α paralog), STAG3 (SA1/SA2 paralog) and α-kleisin subunit REC8 (RAD21 paralog). Gutierrez-Caballero et al.,[2] and two other independent studies,[3,4] now report identification of a novel α-kleisin subunit, RAD21L.

Gutierrez-Caballero et al. performed in silico searches to identify paralogs of the mouse RAD21/REC8 and found a new protein, which was named RAD21L (RAD21-like protein).[2] RAD21L is predominantly expressed in mouse testis (and weakly in other tissues), indicating that this novel α-kleisin might play a role in mouse meiosis. Coimmunoprecipitation experiments revealed interactions with known cohesin subunits, suggesting that RAD21L is indeed a novel cohesin subunit. Based on the extensive coimmunoprecipitation assays carried out in all three studies,[2,3,4] the presence of at least four different meiotic cohesin complexes can be postulated (Table 1). What are the functions of these complexes? Mounting evidence suggests that the REC8-containing complexes mediate sister chromatid cohesion,[5] while the meiotic roles of cohesin complexes containing RAD21 or RAD21L are less clear. Localization studies showed that RAD21L binds to chromosomes at premeiotic S phase, and most of it disappears in the middle of the pachytene stage.[2,3,4] Interestingly, Ishiguro et al. noticed that a small fraction of RAD21L remains in the vicinity of centromere regions until metaphase I, and future studies should address the possible role of RAD21L in metaphase I cells.[4] Intriguingly, RAD21L and REC8 were detected along the axial/lateral elements of the synaptonemal complexes in a mutually exclusive manner.[3,4] Given this distinctive localization pattern, it is reasonable to propose that RAD21L might be required for the pairing and synapsis of homologous chromosomes. However, to test the proposed function of RAD21L, it will be essential to generate and analyze RAD21L-knockout mice.

It is becoming increasingly clear that cohesin, in addition to its canonical function in sister chromatid cohesion, also has other important functions, such as regulating gene expression and repairing damaged DNA.[6,7,8,9] Moreover, the presence of different cohesin complexes adds another level of complexity. The recently identified RAD21L-containing cohesin complex is the latest addition to this exciting field of research. In order to decipher molecular functions of the RAD21L, it will be important to determine whether RAD21L

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cohesin complexes form canonical tripartite rings and to identify interaction partners. Interestingly, the current studies revealed that, in addition to known cohesin proteins, RAD21L interacts with the synaptonemal-complex protein SYCP1 and the centromere protein CENP-C.[3,4] Given the unique localization pattern of RAD21L, it will be important to find out whether dissociation of RAD21L from chromosomes is important for meiosis and to identify molecules involved in the RAD21L removal. Finally, it will be crucial to determine what defines the RAD21L- and REC8-specific domains along chromosomes and whether these domains contribute to pairing of homologous chromosomes during meiotic prophase.

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Table 1

Proposed subunit composition of the cohesin complexes

	Mitosis	**Meiosis**			
SMC subunits	SMC3	SMC3	SMC3	SMC3	SMC3
	SMC1α	SMC1β	SMC1β	SMC1α	SMC1β
non-SMC subunits	SA1/SA2	STAG3	STAG3	STAG3	STAG3
	RAD21	RAD21	REC8	RAD21L	RAD21L

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