CELL REGENERATION

REVIEW Open Access

Cohesin complexes with a potential to link mammalian meiosis to cancer

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Abstract

Among multiple genes aberrantly activated in cancers, invariably, there is a group related to the capacity of cell to self-renewal. Some of these genes are related to the normal process of development, including the establishment of a germline. This group, a part of growing family of Cancer/Testis (CT) genes, now includes the meiosis specific subunits of cohesin complex. The first reports characterizing the *SMC1* and *RAD21* genes, encoding subunits of cohesin, were published 20 years ago; however the exact molecular mechanics of cohesin molecular machine in vivo remains rather obscure notwithstanding ample elegant experiments. The matters are complicated by the fact that the evolution of cohesin function, which is served by just two basic types of protein complexes in budding yeast, took an explosive turn in Metazoa. The recent characterization of a new set of genes encoding cohesin subunits specific for meiosis in vertebrates adds several levels of complexity to the task of structure-function analysis of specific cohesin pathways, even more so in relation to their aberrant functionality in cancers. These three proteins, SMC1β, RAD21L and STAG3 are likely involved in a specific function in the first meiotic prophase, genetic recombination, and segregation of homologues. However, at present, it is rather challenging to pinpoint the molecular role of these proteins, particularly in synaptonemal complex or centromere function, due to the multiplicity of different cohesins in meiosis. The roles of these proteins in cancer cell physiology, upon their aberrant activation in tumors, also remain to be elucidated. Nevertheless, as the existence of Cancer/Testis cohesin complexes in tumor cells appears to be all but certain, this brings a promise of a new target for cancer therapy and/or diagnostics.

Keywords: Spermatogenesis, Germline, Chromothripsis, CTCFL, BORIS, CTCF, SMC, Kleisin

Introduction

Cohesin is a protein complex that is essential for cell proliferation in all eukaryotic cells. Cohesin is the key activity that establishes sister chromatid cohesion (SCC) and then holds sister chromatids until the anaphase. The separation of sister chromatids in mitotic cell division requires the inactivation of SCC function by either proteolytic cleavage or stripping cohesin molecules from chromatin. The original ("mitotic" or "somatic") cohesin complex is postulated to have the shape of a "ring" that is potentially able to physically embrace two chromatids [1]. All cohesin complexes are composed of four essential subunits. The chromatid-embracing core of the ring-like structure is formed by two SMC proteins, SMC1 and SMC3, which belong to the family of SMC (Structural Maintenance of Chromosomes) ATP-binding proteins [2]. SMC1 and SMC3 heterodimerize by joining via their hinge domains [3]. The "locking" of the ring is achieved via binding of two ATP molecules at the ATP-binding domains of SMC1 and SMC3 [4]. Such a locking of the ring is facilitated by the third subunit that is known as RAD21/SCC1/MCD1 in a variety of systems [5-7]. This very subunit is the target of proteolytic cleavage by the separase/separin coincidental with anaphase initiation [8-10]. The forth core cohesin subunit is a HEAT repeat protein known as SCC3 in yeast [11], and represented in vertebrates by two paralogs, SA1/STAG1 and SA2/STAG2 [12,13]. The functionality of mitotic/somatic cohesin is well studied with respect to its involvement in SCC at the centromeres. The molecular role of cohesin at the chromosomal arms is more obscure, however it has been directly linked to DNA repair [14] and, albeit less conclusively, to many instances of

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gene expression regulation [15-18]. It is believed that cohesin, in yet to be uncovered fashion, facilitates the function of the multipurpose transcriptional regulator CTCF [19], at a subset of thousands of CTCF sites in the genomes of Metazoa where cohesin and CTCF colocalize [20,21]. However, as CTCF itself is a multifunctional protein, delineating the molecular pathway linking cohesin to gene expression regulation has proven rather difficult. Furthermore, while the differential functions of SA1/STAG1 and SA2/STAG2 are not well defined, the most recent data indicate that SA1/STAG1, but not SA2/STAG2, is somehow linked to cohesin colocalization with CTCF [22].

With the exception of still unclear mechanistic links to non-SCC mediated processes, such as transcription, the biggest splash since the characterization of cohesin in the 1990s was made with the discovery of the meiotic function of cohesin. Indeed, upon entering meiosis I, in the preparation for the reductional division, a meiosis-specific subunit REC8 de facto replaces RAD21/SCC1/MCD1 and makes mei-cohesin to behave rather differently with respect to timing of SCC1 release. Namely, REC8 protects SCC throughout the process of homologous recombination and then maintains the association of homologues after recombination is complete, up to the point when chromosomes are ready to segregate. At this point, REC8-mediated cohesion is released along the arms, but persists at the centromeres to ensure proper sister chromatid orientation in meiosis II [23-25]. In yeast, REC8 is known to have some functions in addition to SCC per se, including chromosomal restructuring leading to recombination: assembly of axial elements, pairing and synapsis of homologues. Yeast REC8 can easily take the place of SCC1/MCD1 in the SMC1/SMC3 complex in vitro [26], however in vivo studies in mice show that there is little, if any, exchange of REC8 once it becomes chromatin-bound [27]. In general, in metazoan systems, the rebuilding of cohesin for meiosis is much more complex, evidently due to the evolutionary emergence of the sophisticated germline development process. In addition to REC8 [28], there is a meiosis-specific paralog of SMC1α, SMC1β [29], as well as the meiosis-specific SA3/STAG3 subunit [30].

Making the sense of the multitude of cohesin subunits is becoming objectively more and more difficult. Recently, three groups characterized the RAD21L (RAD21-like) protein, which is yet another meiosis-specific cohesin subunit [31-33]. RAD21L is expressed strictly in germline, i.e. in spermatocytes and oocytes. The presence of putative RAD21L complexes in the repertoire of meiotic cohesins significantly increases the level of potential complexity in the task of defining separate types of cohesin complexes in meiosis. A recent review on the subject estimates that there are 18 potential cohesin complexes (Figure 1) that could be present in cells, based on purely combinatorial considerations [34]. However, RAD21L cohesin complexes appear to come in only two forms in vivo: with SMC3 and STAG3 complexed with either SMC1α or SMC1β [31,35,36].

Rad21L appears at chromosomes in germline lineage in a fashion coordinated with REC8, at the pre-meiotic S phase. It resides on chromosomes from the establishment of SCC, through pairing of homologues and the establishment of the synapsis. More specifically, RAD21L appears to colocalize with axial elements upon meiosis initiation. Then, when homologues synapse, RAD21L stays associated with the synaptonemal complex all the way to the end of pachytene, when it disappears from the still persisting synaptonemal complex, according to [31]. However, there is some disagreement on the exact time of RAD21L disappearance [35], which is not possible to resolve based on purely cytological data. It is quite possible that REC8 is actually trailing RAD21L in chromosome loading in leptotene, making RAD21L the chief interface between cohesin and the initiation of synapsis. Upon cohabitation with REC8 the two proteins appear to enrich chromosomes in an alternating pattern [32], although high-resolution chromatin mapping data is required to confirm that that pattern is truly mutually exclusive.

The release of RAD21L from synaptonemal complex also coincides with the emergence of MLH1 foci at crossover sites. Thus, after the genetic recombination is finished, RAD21L leaves chromosomes, parting its ways with REC8, which stays bound at the axes of recombined chromosomes. As a result, RAD21L is apparently absent or has only marginal presence on chromosomes when they commit to segregation in meiosis I. This prompted a speculation that the RAD21L-containing cohesin represents the first case of cohesin complex which, at large, is actually uninvolved with SCC per se. Such a conclusion is indirectly supported by the observation that some of RAD21L loading onto chromosomes, apparently via the replacement of RAD21, in late pachytene may be replication independent [31,32], i.e. happens after SCC establishment. However, if a direct exchange of RAD21 to RAD21L exists in situ, the situation becomes more complex to decipher. In any case, it would be premature to draw conclusions on any non-SCC function of RAD21L cohesin based solely on antibody staining data, without detailed molecular analysis and in the absence of mapping the distinct cohesin complexes in meiotic chromatin with high resolution.

RAD21L cohesin complexes are involved in homologue pairing

The peculiar dynamics of chromosomal associations of RAD21L indicates that it may have a direct molecular role in homologue pairing. Alternatively, RAD21L and