[Cell Cycle 7:4, 449-452; 15 February 2008]; ©2008 Landes Bioscience

Perspective

Cell biology of cancer

BRCA1 and sister chromatid pairing reactions?

Robert V. Skibbens

Lehigh University; Department of Biological Sciences; Bethlehem, Pennsylvania USA

Key words: chromosome, BRCA1, BARD, BASC, CTF7/ECO1, RFC, PCNA, sister chromatid cohesion, cohesion establishment, chromosome segregation

A significant portion of familial breast/ovarian cancer patients harbors a mutation in Breast Cancer Associated gene 1 (BRCA1). Cells deficient for BRCA1 exhibit chromosome aberrations such as whole chromosome duplications, translocations, inter-sister gaps and gene mis-regulation. Here, new evidence is reviewed that defects in sister chromatid cohesion may contribute directly to cancer cell phenotypes—especially those of BRCA1 mutant cells. Linking cohesion to BRCA1-dependent tumorigenesis are reports that BRCA1-associated components (DNA helicase, RFC, PCNA and genome surveillance factors) are required for efficient sister chromatid cohesion. Other cohesion factors (WAPL, EFO2/ESCO2 and hSecurin) are tightly correlated with various cell-type specific carcinogenesis, in support of a generalized model for cohesion in cancer. Recent findings further reveal that a reciprocal relationship exists in that DNA damage induces new Ctf7/Eco1-dependent sister chromatid pairing reactions that, in turn, are required for efficient DNA repair. Future research into sister chromatid pairing mechanisms are likely to provide critical new insights into the underlying causes of cancer.

Introduction

Breast and ovarian cancers dramatically impact the lives of affected women and further place a significant economic burden on both their families and the health care system. Roughly 25% of familial breast and breast/ovarian cancer patients harbor a mutation in Breast Cancer Associated gene 1 (BRCA1). Long-term prospects for BRCA1-dependent basal-type breast cancer patients are poor,[1] mandating that elucidation of BRCA1 pathways remain a prominent research priority. BRCA1 is a tumor suppressor protein comprised in part of a N-terminal RING finger domain, two NLS motifs and a C-terminal BRCT domain. A significant source of information regarding BRCA1 function is predicated on its binding partners. For instance, BRCA1 associates with BARD1 (E3 ubiquitin ligase), BASC (DNA replication-associated repair), MRN (DNA damage sensor complex), BACH1/BRIP/FANCJ (DNA helicase), CBP/p300-RNA polymerase II holoenzyme (acetyltransferase transcription activator) and many other factors.[2,3] While this abundance of BRCA1-interactions reveals a plethora of subcomplexes and functions, it simultaneously complicates BRCA1 analyses. What is clear is that BRCA1-deficient cells exhibit chromosome aberrations that include whole chromosome duplications, translocations, chromosome breaks, elevated sister chromatid exchange rates and inter-sister gaps.[4-7] Linking pleiotropic chromosomal effects to a singular underlying mechanism will provide critical new insights into the molecular basis of cancer and to BRCA1-dependent tumorigenesis in particular.

Fundamental for high fidelity chromosome segregation is the pairing of sister chromatids from DNA replication until anaphase onset. The pairing of sister chromatids, termed cohesion, requires the coordination of four activities (cohesins, deposition, regulators and establishment)—all of which are highly conserved through evolution.[8-10] Cohesins (Smc1, Smc3, Irr1/Scc3/Psc3/SA1/SA2 and Mcd1/Scc1/Rad21) maintain sister pairing from S phase until anaphase onset and resist poleward-pulling forces produced by the mitotic spindle (nomenclature indicative of either yeast, human, Drosophila, frog or worm). At least a subset of cohesins comprise a soluble ring-like complex that is thought to encompass each sister chromatid.[9-14] Scc2/Mis4/Nipped-B/NIPBL and Scc4 function as a cohesin deposition complex that load cohesin ring-like complexes onto chromosomes. Cohesin deposition can occur throughout the cell cycle, but loading at least must occur in S phase with some evidence that loading prior to S phase also may be important.[11,15-19] Regulating cohesin dynamics is accomplished by the antagonistic functions of Pds5/Spo76/BimD and WAPL/Rad61. Pds5 family members promote cohesion establishment during S-phase and antagonize cohesin proteolysis during M-phase.[20-23] WAPL/Rad61 promotes cohesin removal early during M phase. WAPL-dependent cohesin release occurs prior to and independent from Esp1-directed cohesin proteolysis at anaphase onset.[24,25] Ctf7 establishes cohesion between nascent sister chromatids during S-phase.[26,27] Ctf7 establishment family members (Ctf7/Eco1/Eso1/Deco/EFO1,2/ESCO1,2) do not maintain sister pairing nor promote cohesin deposition.[26-31] Instead, a likely scenario is that these factors catalyze cohesin associations that tether together sister chromatids.[11,32] Ctf7 binds numerous DNA replication factors including the DNA

*Correspondence to: Robert V. Skibbens; Lehigh University; Department of Biological Sciences; 111 Research Dr.; Bethlehem, Pennsylvania 18015 USA; Tel.: 610.758.6162; Email: rvs3@lehigh.edu

Submitted: 12/12/07; Accepted: 12/13/07

Previously published online as a *Cell Cycle* E-publication: http://www.landesbioscience.com/journals/cc/article/5435

helicase Chl1 (BACH1 homolog), RFCs and PCNA—all of which are critical for cohesion establishment.[26,33-39] More recent evidence reveals that Ctf7p activity can be induced outside of S phase in response to DNA double-strand breaks.[16,17,40,41]

Linking Sister Chromatid Cohesion to Tumorigenesis

Studies from a number of model organisms establish that defects in sister chromatid cohesion result in massive chromosome mis-segregation, aneuploidy and gene mis-expression—all hallmarks of cancer progression.[8-10] In many ways, the link between sister chromatid pairing defects and cancer is conceptually satisfying (Fig. 1). Properly paired sister chromatids supply a repair template required in response to DNA damage and may further provide structural fortification to resist chromosome breakage.[7,42] Thus, defects in sister chromatid pairing eradicate high-fidelity DNA repair pathways and may serve as fragile sites that promote chromosomal translocations, truncations and subsequent gene mis-expression (as observed in BRCA1-deficient cells). Global loss of sister chromatid pairing produces whole chromosome duplications via mis-segregation. Finally, cohesion factors participate in higher-order heterochromatic complex formation. These complexes function as boundary elements of transcriptionally repressed domains and may further sequester factors important for enhancer-promoter activation, providing for additional mechanisms of gene mis-regulation.[43]

There is now compelling evidence that cohesion is a critical factor in many forms of cancer. Human securin (a Pds1-like regulator of cohesin dissolution at anaphase onset) is the human proto-oncogene pituitary tumor-transforming gene (PTTG). PTTG exhibits tumor transforming activity in culture and is highly upregulated in human cancer cell lines.[44,45] The establishment factor EFO2/ESCO2 is one of only ~12 cell cycle control genes that are highly upregulated in aggressive melanoma cells.[46] WAPL was characterized in drosophila as a heteochromatin regulator with subsequent studies revealing a role in pre-anaphase cohesin release. WAPL expression correlates tightly with oncogenesis in cervical malignancies. NIH3T3 cells expressing elevated WAPL levels produced tumors in 100% of injected nude mice, identifying WAPL as a potent oncogene.[24,25] Thus, a significant body of evidence links mutations in cohesion pathways to a variety of cancers.

Linking BRCA1-Dependent Tumorigenesis to Cohesion

Is there evidence that BRCA1-dependent tumorigenesis operates through sister chromatid pairing reactions? While speculative, numerous studies suggest just such a link.[8] For instance, several BRCA1-binding partners play critical roles in sister chromatid cohesion. In a first example, BRCA1 binds to the DNA helicase BACH1 (also called FANCJ and BRIP1) which is required for BRCA1-dependent double strand break repair.[47-50] In one study, a small number of breast cancer patients were found that harbor mutations in BACH1, but not mutations in either BRCA1 or BRCA2. This and other studies suggest that loss of BACH1 helicase activity is itself sufficient to predispose affected individuals to tumorigenesis.[49,50] BACH1 mutations pre-dispose affected individuals not only to breast and ovarian cancer but also to Fanconi anemia.[51] At the cellular level, diminished BACH1 function results in chromosome aberrations that include inter-sister gaps (localized cohesion defects) similar to those found in cells deficient for BRCA1.[4,52] Mutations

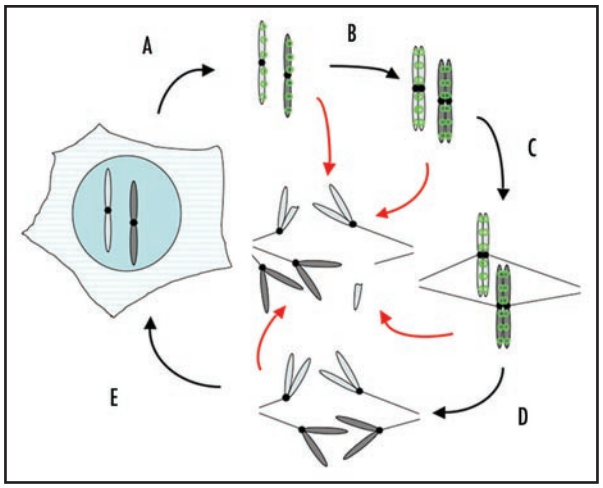

Figure 1. Schematic illustrating chromosome cycle and sister chromatid pairing defects that produce aneuploidy and gene mis-expression. Prototypical cell containing two chromosomes (light and dark gray) highlight multiple cohesin-based processes. The nucleus (blue) and cell contents are absent from subsequent stages of the chromosome cycle for simplicity. (A) Cohesins (green rings) become chromatin-associated or deposited prior to DNA replication. (B) DNA replication is coupled to sister chromatid pairing activities—termed cohesion establishment. (C) Assembly of the mitotic spindle (spindle microtubules = lines captured by kinetochores = black balls placed midway along each chromosome) generates pulling forces across sister chromatids that must be resisted by cohesion structures (shown as paired rings). (D) Cohesin dissolution marks anaphase onset and allows each chromatid to segregate away from its sister and into the newly forming daughter cell (not shown). Red arrows indicate defects in any one of the cohesion pathways (deposition, maintenance, establishment, regulation) that result in cell aneuploidy, chromosome duplication, fragmentation and gene mis-expression.

in BACH1 homologs such as yeast Chl1 are entirely sufficient to produce sister chromatid cohesion defects and aneuploidy.[33-35] Moreover, the BACH1 yeast homolog Chl1 interacts both physically and genetically with the cohesion establishment factor Ctf7.[33] That mutation of a single DNA helicase results in cohesion-related cell aneuploidy is confirmed in a number of model organisms.[4,33-35,53-55] Knock-out mice homozygous null for RecQL4 (the helicase responsible for Rothmund-Thomson Syndrome or RTS) recapitulate RTS phenotypes including skin abnormalities, skeletal defects, aneuploidy and a pre-disposition to cancer. Significantly, cells from recql4$^{-/-}$ mice exhibit dramatic cohesion defects—providing a clear and singular cohesion-based tumorigenic mechanism.[55]

Other lines of evidence support the model that BRCA1-dependent tumorigenesis may act through sister chromatid pairing reactions. BRCA1 binds and functionally interacts with the human DNA repair MRN complex comprised of Mre11, Rad50 and Nbs1.[56,57] A mutation in any one of the MRX complex component homologs (human Nbs1 is termed Xrs2 in yeast) produced significant cohesion defects that result in chromosome mis-segregation and aneuploidy.[54,58] BLM (Bloom syndrome helicase) is another BRCA1-associated component that, when mutated, results in hypermutability, elevated rates of somatic recombination and predisposition to cancer.[56,59] Analyses of the yeast homologs of BACH1, BLM and WRN helicases (Werner mutations results in premature aging) all confirm that homologs of BRCA1-associated DNA helicases play key roles in sister chromatid pairing mechanisms.[4,33-35,53,54] In combination, BRCA1 associates with many factors that function in sister chromatid pairing.

It is worth speculating that BRCA1-tumorigenesis may involve Ctf7 family members. First, human BRCA1 participates in complexes that contain the DNA helicase BACH1 and RFC subunits and BRCA1 is recruited to PCNA/RFC foci upon DNA damage.[4,49,50,60-62] In all model organisms tested to date, Ctf7 exhibits multiple interactions with Chl1 (homolog of human BACH1), PCNA and all RFC complexes—including those implicated in DNA repair.[26,33,36,37] Second, BRCA1 is part of CBP/p300 and SWI/SNF chromatin remodeling complexes that exhibit acetyltransferase activity.[63-65] Ctf7 family members are all acetyltransferases, lending indirect support for a model that this conserved activity may play a role in BRCA1-dependent functions.[28-31,66,67] Third, cells harboring mutations in either BRCA1- or EFO/ESCO-related pathways exhibit inter-sister gaps and cohesion defects especially along heterochromatic and centromeric regions.[8,11] That BRCA1 and Ctf7 family members share overlapping partners, exhibit similar activities in complex and, when mutated, produce aberrant chromosomal phenotypes provide for intriguing parallels.

Coming Full Circle—DNA Repair Induces Cohesion

In an unusual twist, recent evidence reveals that a reciprocal relationship exists between DNA repair and sister chromatid cohesion. Early evidence indicated that cohesion establishment only occurs during S phase.[26,27] Subsequent studies indicated that DNA double strand breaks re-activate cohesion establishment pathways outside of S-phase.[16,17] More recently, the Koshland and Sjogren labs provided evidence that DNA double strand breaks specifically re-activate Ctf7-dependent cohesion establishment activity and that this pairing occurs independent of the replication/repair fork.[40,41] DNA damage-induced re-activation of Ctf7 requires Mec1/ATR (ataxia telangiectasia and Rad3 related) PI kinase checkpoint activity. Thus, a chicken and egg scenario emerges: cohesion is required for DNA repair and DNA damage induces new rounds of Ctf7-dependent cohesion establishment which in turn promotes efficient DNA repair.

Cohesion in Developmental Abnormalities

Sister chromatid pairing reactions are not just cancer-related. For instance, mutations in any one of the cohesion-related processes (cohesins, deposition, regulators and establishment) produce developmental manifestations.[43] Mutation of either human Scc2/NIPBL or Smc1 results in Cornelia de Lange Syndrome.[68-70] Cornelia de Lange Syndrome (CdLS) presents with developmental defects in multiple cell systems that result in heart defects, hearing impairments, microcephaly, missing digits and often severe mental retardation. Mutations in cohesion establishment factors such as EFO2/ESCO2 result in Roberts Syndrome—a recessive malady in which afflicted individuals exhibit severe growth retardation, craniofacial abnormalities, mental deficiencies and tetraphocomelia. EFO2/ESCO2 mutations also produce the related SC phocomelia which mimics thalidomide fetal effects but typically allows survival into adulthood.[31] Solving the mystery of whether cohesion defects will produce developmental abnormalities or tumors probably will require elucidating the roles of numerous factors including the cell type involved, mutation consequence (loss-of-function versus gain-of-function), or timing of mutagenesis (embryogenesis or in adult tissue).

Conclusions

In summary, a growing body of evidence suggests that altered sister chromatid pairing activities are integral to a number of human disease states including developmental abnormalities, pre-mature aging and cancer. Moreover, I speculate here that BRCA1 pathways are intimately linked to sister chromatid pairing reactions to affect a variety of chromosomal phenotypes. Thus, while BRCA1 associates with numerous complexes and participates in a number of activities, it may be that one underlying mechanism may indeed fit all.

Acknowledgements

RVS is supported by an award from the Susan G. Komen for the Cure Foundation (BCTR0707708). Any opinions, conclusions or recommendations expressed in this Commentary are those of the author and does not necessarily reflect the views of the Susan G. Komen for the Cure Foundation.

References

1. Tischkowitz MD, Foulkes WD. The basal phenotype of BRCA1-related breast cancer: past, present and future. Cell Cycle 2006; 5:963-7.
2. Boulton SJ. Cellular functions of the BRCA tumour-suppressor proteins. Biochem Soc Trans 2006; 34:633-45.
3. Deng C-X. BRCA1: Cell cycle checkpoint, DNA damage response and cancer evolution. Nuc Acids Res 2006; 34:1416-26.
4. Deming PB, Cistulli CA, Zhao H, Graves PR, Piwnica-Worms H, Paules RS, Downes CS, Kaufmann WK. The human decatenation checkpoint. Proc Natl Acad Sci USA 2001; 98:12044-9.
5. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, Akslen LA. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003; 95:1482-5.
6. Eyfjord JE, Bodvarsdottir SK. Genomic instability and cancer: networks involved in response to DNA damage. Mutat Res 2005; 592:18-28.
7. Arlt MF, Durkin SG, Ragland RL, Glover TW. Common fragile sites as targets for chromosome rearrangements. DNA Repair (Amst) 2006; 5:1126-35.
8. Skibbens RV. Unzipped and loaded: The role of DNA helicases and RFC clamp-loading complexes in sister chromatid cohesion. J Cell Biol 2005; 169:841-6.
9. Huang CE, Milutinovich M, Koshland D. Rings, bracelet or snaps: fashionable alternatives for Smc complexes. Phil Trans R Soc 2005; 360:537-42.
10. Losada A, Hirano T. Dynamic molecular linkers of the genome: the first decade of SMC proteins. Genes Dev 2005; 19:1269-87.
11. Skibbens RV, Maradeo M, Eastman L. Fork it over: the cohesion establishment factor Ctf7p and DNA replication. J Cell Sci 2007; 120:2471-7.
12. Nasmyth K. How might cohesin hold sister chromatids together? Philos Trans R Soc Lond B Biol Sci 2005; 74:483-96.
13. Gruber S, Haering CH, Nasmyth K. Chromosomal cohesin forms a ring. Cell 2003; 112:765-77.
14. Haering C, Lowe J, Hochwagen A Nasmyth K. Molecular architecture of SMC proteins and the yeast cohesin complex. Mol Cell 2002; 9:773-88.
15. Uhlmann F, Nasmyth K. Cohesion between sister chromatids must be established during DNA replication. Curr Biol 1998; 8:1095-101.
16. Strom L, Lindroos HB, Shirahige K, Sjogren C. Postreplicative recruitment of cohesin to double-strand breaks in required for DNA repair. Mol Cell 2004; 16:1003-15.
17. Unal E, Arbel-Eden A, Sattler U, Shroff R, Lichten M, Haber JE, Koshland D. DNA damage response pathway uses histone modification to assemble a double-strand break-specific cohesin domain. Mol Cell 2004; 16:991-1002.
18. Ciosk R, Shirayama M, Shevchenko A, Tanaka T, Toth A, Shevchenko A, Nasmyth K. Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4. Mol Cell 2000; 5:243-54.
19. Lengronne A, McIntyre J, Katou Y, Kanoh Y, Hopfner K-P, Shirahige K, Uhlmann F. Establishment of sister chromatid cohesion at the *S. cerevisiae* replication fork. Mol Cell 2006; 23:787-99.
20. Hartman T, Stead K, Koshland D, Guacci V. Pds5p is an essential chromosomal protein required for both sister chromatid cohesion and condensation in *Saccharomyces cerevisiae*. J Cell Biol 2000; 151:613-26.
21. Panizza S, Tanaka T, Hochwagen A, Eisenhaber F, Nasmyth K. Pds5p cooperates with cohesin in maintaining sister chromatid cohesion. Curr Biol 2000; 10:1557-64.
22. Stead K, Aguilar C, Hartman T, Drexel M, Meluh P, Guacci V. Pds5p regulates the maintenance of sister chromatid cohesion and is sumolyated to promote the dissolution of cohesion. J Cell Biol 2003; 163:729-41.
23. Noble D, Kenna MA, Dix M, Skibbens RV, Unal E, Guacci V. Intersection between the regulators of sister chromatid cohesion establishment and maintenance in budding yeast indicates a multi-step mechanism. Cell Cycle 2006; 21:2528-36.

24. Oikawa K, Ohbayashi T, Kiyono T, Nishi H, Isaka K, Umezawa A, Kuroda M, Mukai K. Expression of a novel human gene, *Human Wings Apart-Like* (hWAPL), is associated with cervical carcinogenesis and tumor progression. Cancer Res 2004; 64:3545-9.
25. Kueng S, Hegemann B, Peters BH, Lipp JJ, Schleiffer A, Mechtler K, Peters J-M. Wapl controls the dynamic association of cohesin with chromatin. Cell 2006; 127:955-67.
26. Skibbens RV, Corson LB, Koshland D, Hieter P. Ctf7p is essential for sister chromatid cohesion and links mitotic chromosome structure to the DNA replication machinery. Genes Dev 1999; 13:307-19.
27. Toth A, Ciosk R, Uhlmann F, Galova M, Schleffer A, Nasmyth K. Yeast cohesin complex requires a conserved protein, Eco1p(Ctf7), to establish cohesion between sister chromatids during DNA replication. Genes Dev 1999; 13:320-33.
28. Bellows AM, Kenna MA, Cassimeris L, Skibbens RV. Human EFO1p exhibits acetyltransferase activity and is a unique combination of linker histone and Ctf7p/Eco1p chromatid cohesion establishment domains. Nucleic Acids Res 2003; 31:6334-43.
29. Williams BC, Garrett-Engele CM, Li Z, Williams EV, Rosenman ED, Goldberg ML. Two putative acetyltransferases, san and deco, are required for establishing sister chromatid cohesion in Drosophila. Curr Biol 2003; 13:2025-36.
30. Hou F, Zou H. Two human orthologues of Eco1/Ctf7p acetyltransferases are both required for proper sister-chromatid cohesion. Mol Biol Cell 2005; 16:3908-18.
31. Vega H, Waisfisz Q, Gordillo M, Sakai N, Yanagirhara I, Yamada M, van Gosliga D, Kayserilii H, Xu C, Ozono K, Jabs EW, Inui K, Joenje H. Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. Nat Genet 2005; 37:468-70.
32. Skibbens RV. Holding your own: Establishing sister chromatid cohesion. Genome Research 2000; 10:1664-71.
33. Skibbens RV. Chl1p, a DNA helicase-like protein in budding yeast, functions in sister chromatid cohesion. Genetics 2004; 166:33-42.
34. Mayer ML, Pot I, Chang M, Xu H, Aneliunas V, Kwok T, Newitt R, Aebersold R, Boone C, Brown GW, Hieter P. Identification of protein complexes required for efficient sister chromatid cohesion. Mol Biol Cell 2004; 15:1736-45.
35. Petronczki M, Chwalla B, Siomos MF, Yokobayashi S, Helmhart W, Deutschbauer AM, Davis RW, Watanabe Y, Nasmyth K. Sister chromatid cohesion mediated by the alternative RF-CCtf18/Dcc1/Ctf8, the helicase Chl1 and the polymerase-alpha-associated protein Ctf4 is essential for chromatid disjunction during meiosis II. J Cell Sci 2004; 117:3547-59.
36. Kenna MA, Skibbens RV. Mechanical link between cohesion establishment and DNA replication: Ctf7p/Eco1p, a cohesion establishment factor, associates with three different Replication Factor C Complexes. Mol Cell Biol 2003; 23:2999-3007.
37. Moldovan G-L, Pfander B, Jentsch S. PCNA controls establishment of sister chromatid cohesion during S-phase. Mol Cell 2006; 23:723-32.
38. Hanna JS, Kroll ES, Lundblad V, Spencer FA. *Saccharomyces cerevisiae* CTF18 and CTF4 are required for sister chromatid cohesion. Mol Cell Biol 2001; 21:3144-58.
39. Mayer ML, Gygi SP, Aebersold R, Hieter P. Identification of RFC (Ctf18p, Ctf8p, Dcc1p): An alternative RFC complex required for sister chromatid cohesion in *S. cerevisiae*. Mol Cell 2001; 7:959-70.
40. Strom L, Karlsson C, Lindroos HB, Wedahl S, Katou Y, Shirahige K, Sjogren C. Postreplicative formation of cohesion is required for repair and induced by a single DNA break. Science 2007; 317:242-5.
41. Unal E, Heidinger-Pauli JM, Koshland D. DNA double-strand breaks trigger genome-wide sister-chromatid cohesion through Eco1 (Ctf7). Science 2007; 317:245-8.
42. Lowndes NF, Toh GW. DNA repair: the importance of phsophorylating histone H2AX. Curr Biol 2005; 15:99-102.
43. Dorsett D. Roles of the sister chromatid cohesion apparatus in gene expression, development, and human syndromes. Chromosoma 2007; 116:1-13.
44. Cohen-Fix O, Peters JM, Kirschner MW, Koshland D. Anaphase initiation in Saccharomyces cerevisiae is controlled by the APC-dependent degradation of the anaphase inhibitor Pds1p. Genes Dev 1996; 10:3081-93.
45. Zou H, McGarry TJ, Bernal T, Kirschner MW. Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tumorigenesis. Science 1999; 285:418-22.
46. Ryu B, Kim DS, Deluca AM, Alani RM. Comprehensive expression profiling of tumor cell lines identifies molecular signatures of melanoma progression. PLoS ONE 2007; 2:594.
47. Kerr P, Ashworth A. New complexities for BRCA1 and BRCA2. Curr Biol 2001; 11:668-76.
48. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002; 108:171-82.
49. Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, Wahrer DC, Sgroi DC, Lane WS, Haber JA, Livingston DM. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. Cell 2001; 105:149-60.
50. Cantor S, Drapkin R, Zhang F, Lin Y, Han J, Pamidi S, Livingston DM. The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. Proc Natl Acad Sci 2004; 101:2357-62.
51. Cantor SB, Andreassen PR. Assessing the link between BACH1 and BRCA1 in the FA pathway. Cell Cycle 2006; 5:164-7.
52. Bridge WL, Vandenberg CJ, Franklin RJ, Hiom K. The BRIP1 helicase functions independently of BRCA1 in the Fanconi anemia pathway for DNA crosslink repair. Nat Genet 2005; 37:953-7.
53. Franchitto A, Oshima J, Pichierri P. The G_2-phase decatenation checkpoint is defective in Werner syndrome cells. Cancer Res 2003; 63:3289-95.
54. Warren CD, Eckley DM, Lee MS, Hanna JS, Hughes A, Peyser B, Jie C, Irizarry R, Spencer F. S-phase checkpoint genes safeguard high-fidelity sister chromatid cohesion. Mol Biol Cell 2004; 15:1724-35.
55. Mann MB, Hodges CA, Barnes E, Vogel H, Hassold TJ, Luo G. Defective sister chromatid cohesion, aneuploidy and cancer predisposition in a mouse model of Type II Rothmund-Thomson syndrome. Hum Mol Genet 2005; 14:813-25.
56. Wang Y, Cortez D, Yazdi P, Neff N, Elledge S, Qin J. BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes Dev 2000; 14:927-39.
57. Kobayashi J, Antoccia A, Tauchi H, Matsuura S, Komatsu K. NBS1 and its functional role in the DNA damage response. DNA Repair 2004; 3:855-61.
58. Grenon M, Gilbert C, Lowndes NF. Checkpoint activation in response to double-strand breaks requires the Mre11/Rad50/Xrs2 complex. Nat Cell Biol 2001; 3:844-7.
59. Franchitto A, Pichierri P. Bloom's syndrome protein is required for correct localization of RAD50/MRE11/NBS1 complex after replication fork arrest. J Cell Biol 2002; 157:19-30.
60. Scully R, Chen J, Ochs RL, Keegan K, Hoekstra M, Feutneun J, Livingston DM. Dynamic changes of BRCA1 subnuclear location and phosphorylation state are initiated by DNA damage. Cell 1997; 90:425-35.
61. Bochar DA, Wang L, Beniya H, Kinev A, Xue Y, Lane WS, Wang W, Kashanchi F, Shiekhattar R. BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer. Cell 2000; 102:257-65.
62. Ward IM, Chen J. Histone H2AX is phosphorylated in an ATR-dependent manner in response to replication stress. J Biol Chem 2001; 276:47759-62.
63. Cui JQ, Shao N, Chai Y, Wang H, Reddy ES, Rao VN. BRCA1 splice variants BRCA1a and BRCA1b associate with CBP co-activator. Oncol Rep 1998; 5:591-5.
64. Pao GM, Janknecht R, Ruffner H, Hunter T, Verma IM. CBP/p300 interact with and function as transcriptional coactivators of BRCA1. Proc Natl Acad Sci USA 2000; 97:1020-5.
65. Fan S, Ma YX, Wang C, Yuan RQ, Meng Q, Wang JA, Erdos M, Goldberg ID, Webb P, Kushner PJ, Rosen EM. p300 modulates the BRCA1 inhibition of estrogen receptor activity. Cancer Res 2002; 62:141-51.
66. Ivanov D, Schleiffer A, Eisenhaber F, Mechtler K, Haering CH Nasmyth K. Eco1 is a novel acetyltransferase that can acetylate proteins involved in cohesion. Curr Biol 2002; 12:323-8.
67. Brands A, Skibbens RV. Ctf7p/Eco1p exhibits acetyltransferase activity—but does it matter? Current Biol 2005; 15:50-1.
68. Tonkin ET, Wang TJ, Lisgo S, Bamshad MJ, Strachan T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat Genet 2004; 36:636-41.
69. Krantz ID, McCallum J, DeScipio C, Kaur M, Gillis LA, etc. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of Drosophila melanogaster Nipped-B. Nat Genet 2004; 36:631-5.
70. Musio A, Selicorni A, Focarelli ML, Gervasini C, Milani D, Russo S, Vezzoni P, Larizza L. X-linked Cornelia de Lange syndrome owing to SMC1L1 mutations. Nat Genet 2006; 38:528-30.