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Meiosis-like Functions in Oncogenesis: A New View of Cancer

Ramsay J. McFarlane[1] and Jane A. Wakeman[1]

Abstract

Cancer cells have many abnormal characteristics enabling tumors to grow, spread, and avoid immunologic and therapeutic destruction. Central to this is the innate ability of populations of cancer cells to rapidly evolve. One feature of many cancers is that they activate genes that are normally associated with distinct developmental states, including germ cell–specific genes. This has historically led to the proposal that tumors take on embryonal characteristics, the so called embryonal theory of cancer. However, one group of germline genes, not directly associated with embryonic somatic tissue genesis, is the one that encodes the specific factors to drive the unique reductional chromosome segregation of meiosis I, which also results in chromosomal exchanges. Here we propose that meiosis I–specific modulators of reductional segregation can contribute to oncogenic chromosome dynamics and that the embryonal theory for cancer cell growth/proliferation is overly simplistic, as meiotic factors are not a feature of most embryonic tissue development. We postulate that some meiotic chromosome-regulatory functions contribute to a soma-to-germline model for cancer, in which activation of germline (including meiosis) functions drive oncogenesis, and we extend this to propose that meiotic factors could be powerful sources of targets for therapeutics and biomonitoring in oncology. *Cancer Res; 1–5. ©2017 AACR.*

Introduction

Organogenesis, tissue growth/repair, and the maintenance of gametogenic germ cell pools are driven by mitotic cell proliferation, where the homologous chromosomes of diploid cells divide equationally, ensuring that maternal/paternal allelic heterozygosity is maintained, as uniparent disomy can cause oncogenic loss of heterozygosity (LOH). Cancers can arise through dysregulation of the normal regulatory constraints that ensure high fidelity chromosome segregation during development and tissue homeostasis (1). These chromosomal segregation events differ considerably to those of the first meiotic division during gametogenesis, where homologous chromosomes of a diploid germline progenitor cell conjoin via programmed genetic recombination intermediates to form a bivalent, which is ultimately resolved, culminating in a reductional chromosome segregation event and "shuffled" genetic material (2, 3). There is now solid emerging evidence to support the concept that the inappropriate activation of meiotic chromosome regulator genes in mitotically dividing somatic cells results in deviations in mechanisms controlling chromosome maintenance and segregation (4–9).

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Activation of Meiotic Functions in Cancer Cells

In human males, meiosis is an integral part of spermatogenesis, which occurs in the seminiferous tubules of the testes (10). Many genes that are silent in healthy somatic tissue are specifically activated during the spermatogenic program, providing functions that modulate cellular morphologic changes and meiosis. These genes are known as cancer/testis (CT) genes (or cancer germline genes) when they become aberrantly activated in cancerous tissue (11–13). The proteins encoded by these genes have garnered interest in the field of clinical oncology as they can potentially serve as targets for immune therapies and expression of CT genes can be applied to patient stratification (for examples, see refs. 14–16). However, there is emerging evidence that they play a functional role in initiating and maintaining oncogenesis. The requirement for tumor initiation is eluded to by the finding that l (3)mbt brain tumor formation in *Drosophila* required the activation of germline genes (17), a gene activation profile that is also found in many human cancers (18). Indeed, this has led to the proposal that a key feature of oncogenesis is the cellular switch from a specific somatic designation to the acquisition of a germline cell–like state, the so called "soma-to-germline transition," which reflects the functional activation of germline-specific genes to meet the needs of the evolving oncogenic process in a stage- and environment-specific context (18).

Following on from this, a number of CT genes have been demonstrated to play a role in various aspects of tumor development, maintenance, and spread (for examples, see refs. 19–30), including the fostering of genome instability, a driver of cancer evolution (24). However, given that the normal function of many CT genes in spermatogenesis is unknown, it remained unclear whether proteins that normally specifically orchestrate meiotic chromosome segregation events (such as interhomolog

association/recombination and sister centromere monopolarity) contribute to maintenance and/or development/progression of cancers. A screen for a subclass of CT genes that are specifically associated with mammalian meiotic spermatocytes revealed a few genes encoding functions associated with meiotic chromosome dynamics, such as the gene encoding the meiotic recombination hotspot activator PRDM9 and the meiosis-specific cohesin genes *RAD21L1* and *SMC1β* (31, 32). Meiotic chromosome regulator genes have been previously reported as CT genes (4–7), but only now is robust evidence starting to emerge to indicate that these so called meiCT (meiotic cancer testis) genes (a specific subgroup of the CT gene family) have an important influence on cancer chromosome biology. Greenberg and colleagues found that two meiosis-specific factors, MND1-HOP2, which are normally required to bias meiotic recombination down an interhomolog pathway (instead of inter-sister chromatid repair), function in cancer cells to assist utilization of an alternative lengthening of telomeres (ALT) mechanism in the absence of telomerase reactivation (refs. 33, 34; Fig. 1A). This is dependent upon the inherent ability of these factors to stimulate non-sister chromosome interactions. The ALT pathway operates via a recombination-mediated mechanism in which, in the absence of normal telomerase-mediated elongation, telomeres behave like a broken chromosome end, serving to stimulate RAD51 recombinase-mediated strand invasion of an uncapped telomere into a non-sister telomere to enable the invading end to serve as a substrate for DNA replication–dependent *de novo* telomere elongation (35). This phenomenon can not only help drive tumor formation but also enables tumor cell proliferative activity and is likely to contribute to tumor cell evolutionary potential (36, 37), although this latter point requires experimental exploration.

The identification of the role of MND2-HOP1 in ALT was not the first demonstration of meiotic genes driving chromosomal dynamics in cancer cells. During meiosis in most eukaryotes (not all) a proteinaceous, ladder-like structure of poorly defined function, termed the synaptonemal complex (SC), forms between paired homologues to mediate synapsis (3). Miyagawa and colleagues demonstrated that, when aberrantly produce in mitotically dividing cells, the meiosis-specific SC protein SYCP3 impairs recombination by disrupting the function of the tumor suppressor recombination regulator BRCA2 (Fig. 1B; ref. 38); moreover, *SYCP3* expression in cancer cells drives ploidy changes and is thus a key example of a meiotic chromosome regulator directly influencing chromosomal segregation in cancer cells (38). SYCP3 is thought to form a component part of the SC lateral elements (linear substructures of the SC). Although the exact role of SYCP3/lateral elements is unclear (39), it is likely that they provide a structure-induced feature, such as chromosome compaction stress, needed for chromosomal cross over control (2, 3); this is direct evidence that a meiotic recombination–associated protein can modulate genome maintenance/segregation in cancer cells. Evidence for the modulation of homologous recombination repair in cancers by SC-associated factors is extended by the finding that elevated expression of the CT gene *HORMAD1* (40), which is required for SC formation and meiotic recombination control (41, 42), alters DNA repair pathways in triple-negative breast cancers, and sensitizes them to homologous recombination–associated therapies (43).

There are other examples of activation of meiotic recombination regulators contributing to cancer cell survival. The meiosis-specific RAD51 ortholog DMC1 is activated in glioblastoma and it contributes to proliferative potential and genotoxic stress recovery (44). In addition, during meiosis, interhomolog recombination is initiated by the type II topoisomerase-like activity of the SPO11–TOPVIBL complex, which generates a DNA double-strand break in one participating chromatid (45–48). Recent work in mice has demonstrated that the mammalian-specific gene *Tex19.1* is required to promote normal levels of these meiotic recombination–initiating events (49). The human ortholog, *TEX19*, normally has expression restricted to the testis and embryo stem cells, but is also widely activated in cancer cells (31); importantly, this expression is required in a number of distinct cancer cell types to mediate proliferation and cancer stem-like cell self-renewal (50). While the mechanism of action of TEX19 in

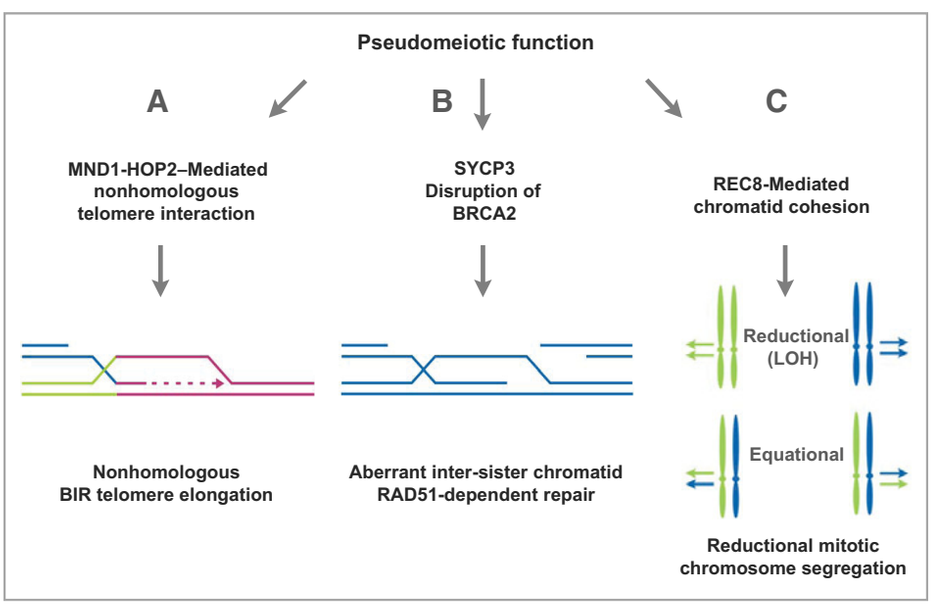

Figure 1.
Pseudomeiotic chromosome segregation functions drive oncogenic genomic dynamics. The schematic represents example models for proposed pseudomeiotic functions in mitotically diving cells that modulate chromosome dynamics to serve the oncogenic program. Activation of MND1-HOP2 (**A**; left; refs. 33, 34), SYCP3 (**B**; middle; ref. 38), and REC8 (**C**; right; 63, 64) drive alternative lengthening of telomeres, disrupt repair recombination, and generate loss of heterozygosity (LOH) by reductional segregation, respectively. BIR, break-induced replication.

cancer cells remains unknown, this work further demonstrates the functional requirements diverse meiotic chromosomal modulators, including regulators of meiotic recombination initiation, in oncogenesis.

This emerging field has now taken on a new player, the fission yeast. For many years, the fission yeast has provided an excellent experimental model in which to demonstrate key features of meiotic chromosome dynamics, from meiotic recombination hotspot activation (51, 52) through to the control of meiosis I centromeric monopolarity (53, 54). Normal meiosis in the fission yeast requires the induction and commitment of a number of "tightly" meiosis-specific genes following meiotic commitment (55); for example, *rec8*, a gene encoding a meiosis-specific cohesin component (56). During mitotic proliferation, these genes are suppressed at the transcriptional and posttranscriptional levels through an RNA interference- and exosome-dependent pathway controlled by the Mmi1 protein (57–62). Dysregulation of the Mmi1 pathway in mitotically dividing cells results in inappropriate levels of meiosis-specific transcripts such as *rec8* mRNA (59). Recently, Grewal and colleagues noticed that Mmi1-deficient mitotic cells (with aberrant levels of meiotic mRNAs) exhibited high levels of chromosome mis-segregation events in mitotically dividing diploid cells, including high levels of uniparent disomy (UPD; ref. 63). They extended this to demonstrate that UPD, which can drive LOH in oncogenesis, could also be induced by overexpressing only the *rec8* meiotic cohesin gene in mitotically dividing diploid cells (63). Rec8 is required in meiosis I for centromere monopolarity, which normally drives the reductional association of sister centromeres on the meiotic spindle (54). Grewal and colleagues demonstrated that the expression of *rec8* could generate high levels of UPD associated with mitotic reductional segregation of homologues in diploid cells. This indicated a direct meiosis-like (pseudomeiotic) behavior of chromosomes following activation of just a single meiotic cohesin gene (63) (Fig. 1C). While it has been previously suggested that oncogenesis might require, or be enhanced by, the activation of a wide scale soma-to-germline transcriptional program, this seminal finding in fission yeast opens up the possibility that the activation of only a single meiotic regulator can alter chromosome dynamics in such a fashion as to potentiate an oncogenic transformation. Extrapolating this observation to human cells might be speculative in nature, but the relevance of this finding in fission yeast to human cancers is an interesting and important question.

The work in fission yeast is not, however, the first inference of a function for this meiotic cohesin in cancer progression. Human REC8 has been shown to be present in endopolyploid *TP53*-deficient tumor cells induced by ionizing irradiation (64). It was previously proposed that REC8 functions in these cells to induce pseudomeiotic chromosome segregation events that enable them to survive genotoxic treatment, which might infer REC8 (and potentially other meiotic factors) can drive therapeutic resistance in tumors (64). A screen for human CT genes specifically associated with meiotic spermatocytes did not identify *REC8*, although it did identify other meiosis-specific cohesin genes, *RAD21L1* and *SMC1β* (31). Interestingly, however, that study found evidence for widespread expression of *REC8* in nonmeiotic somatic tissue (obtained post mortem; ref. 31). While it is unknown whether this *REC8* expression resulted in the production of REC8 protein in these somatic tissues, others have indicated REC8 is present in noncancerous cultured cells (9); this might suggest that terminally differentiated human cells do not have such a tight requirement to constrain expression of meiotic genes as actively dividing cells, such as cultured fission yeast cells (i.e., there is no need for a strict Mmi1-like system in terminally differentiated cells). Given that such cells are largely nonproliferative in adult somatic tissue, it is assumed that expression of genes such as *REC8* would have little/no influence on ploidy [although cohesins have been implicated in other processes, such as DNA damage recovery and transcriptional control; refs. 65, 66]. So, it might be the case that nonproliferative, terminally differentiated cells do not require an Mmi1-like activity to degrade meiotic transcripts as cells can tolerate these mRNAs due to them being functionally inert, possibly even remaining untranslated. This said, the meiosis-specific cohesion gene *RAD21L1* has expression tightly restricted to the testis in humans (31); interestingly, production of an ectopic GFP-fused Rad21L1 in mitotically dividing murine primary fibroblasts increases adjacency of homologous chromosomes, a clear pseudomeiotic activity with oncogenic and tumor evolutionary potential (67).

Pseudomeiotic Functions Distinguish the Soma-to-Germline Oncogenic Model from the Embryologic Model of Oncogenesis

Cancers, or at least the so called cancer stem-like cells within tumors, have long been thought of as being embryo-like, contributing to a long established embryologic theory of cancer, which espouses the view that tumors have extensive embryo-like characteristics (e.g., cellular self-renewal and differentiation capacity with some cancer cells capable of differentiating to give rise to the major germline cell layers; see ref. 8 and citations therein). CT genes contribute to a wide range of these embryonal cell–like processes, including an ability to migrate, extensive proliferative potential, and change cellular morphology (13). However, embryonic cells in normal embryo development execute these characteristics and developmental changes in a highly orchestrated and temporally controlled fashion, with cascades of gene expression regulation at the heart of this process. Importantly, during embryogenesis, all cells, from the zygote on, maintain ploidy and avoid mutational genetic change. Indeed, early embryo stem cells have evolved distinct genome maintenance pathways to ensure this, and to avoid excessive germline mutations (68, 69). Cancer cells differ considerably in these core features. For example, gene expression regulation does change, but it is not done in a programmed and preordained temporal fashion, as would be the case during embryogenesis. Rather, tumor cells have the capacity to undergo a relatively rapid genomic and epigenetic evolution over time in response to the immediate requirements and pressures of the tumor/tumor cells (36, 37, 70). Indeed, tumor cells deviate considerably from the normal cellular constraints that control embryogenesis, such as apoptosis and telomeric regulation. Therefore, the ability for tumor genomes to evolve is a fundamental distinguishing feature that differentiates these cells from all embryonic cells. The new findings that indicate key features of oncogenic genomic evolution, namely altered DNA repair, centromeric polarity control, and chromosomal end protection (Fig. 1), are all potentially modulated by pseudomeiotic functions, strongly suggesting that meiotic factors play a fundamental role in distinguishing oncogenesis from embryogenesis. This would mean that the embryologic theory of cancer, in which cancers mimic cellular behavior in embryogenesis, appears too restrictive. We postulate that a more

appropriate viewpoint is simply to state that cancers undergo a degree of soma-to-germline transition, which can encompass embryo development–like and gametogenic-like features, but does not mimic embryogenesis *per se*. The functions that become activated might be inter-related, but they are simply activated on the basis of the evolutionary drivers/requirements within a tumor/tumor cells located within distinct environmental contexts, and are not part of a rigid, defined embryo-like program for tumor development.

Concluding Remarks

We speculate that the importance of pseudomeiotic functions does not lie simply in conferring/enhancing the evolutionary capacity of a tumor/tumor cell, but that they can also potentially provide single event initiator capability, as illustrated by the finding that activation of SYCP3 can alter BRCA2-mediated DNA repair (38) and *rec8* activation (ref. 63; in fission yeast, at least) can drive abnormal reductional segregations. Thus, activation of pseudomeiotic functions/meiCT genes can not only serve in tumor evolution and maintenance, but might also be an important single first step oncogenic initiator that does not require a genetic change [i.e., can arise due to epigenetic/misregulated gene activation in the absence of genome sequence alteration (70)].

Importantly, the finding that these meiotic factors can contribute to tumor maintenance, and potentially to tumor cell therapeutic resistance by driving rapid tumor evolution, marks them as potential cancer-specific drug targets. This makes the study of meiosis and meiotic processes in a wide range of model organisms of importance not only for elevating our basic understanding of life on earth, but also because it could reveal new features of exceptional importance in clinical oncology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R.J. McFarlane, J.A. Wakeman

Writing, review, and/or revision of the manuscript: R.J. McFarlane, J.A. Wakeman

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