

Meiosis-like functions in oncogenesis: a new view of cancer.

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Perspectives

²/₃ Q1 Meiosis-like Functions in Oncogenesis: 4 Q2 A New View of Cancer №

5 AU Ramsay J. McFarlane¹ and Jane A. Wakeman¹

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6 Abstract

7Cancer cells have many abnormal characteristics enabling 8 tumors to grow, spread, and avoid immunologic and thera-9 peutic destruction. Central to this is the innate ability of populations of cancer cells to rapidly evolve. One feature of 10 11 many cancers is that they activate genes that are normally 12 associated with distinct developmental states, including germ 13cell-specific genes. This has historically led to the proposal that tumors take on embryonal characteristics, the so called embry-1415 Q5 onal theory of cancer. However, one group of germline genes, 16 not directly associated with embryonic somatic tissue genesis, is 17the one that encodes the specific factors to drive the unique reductional chromosome segregation of meiosis I, which also 18 32

results in chromosomal exchanges. Here we propose that mei-2021osis I-specific modulators of reductional segregation can contribute to oncogenic chromosome dynamics and that the 22embryonal theory for cancer cell growth/proliferation is overly 23simplistic, as meiotic factors are not a feature of most embry-2425onic tissue development. We postulate that some meiotic chromosome-regulatory functions contribute to a soma-to-26germline model for cancer, in which activation of germline 27(including meiosis) functions drive oncogenesis, and we extend 28this to propose that meiotic factors could be powerful sources 29 of targets for therapeutics and biomonitoring in oncology. 30 Cancer Res; 1-5. ©2017 AACR. 31

33 Introduction

34 Organogenesis, tissue growth/repair, and the maintenance 35of gametogenic germ cell pools are driven by mitotic cell 36 proliferation, where the homologous chromosomes of diploid 37 cells divide equationally, ensuring that maternal/paternal alle-38 lic heterozygosity is maintained, as uniparent disomy can 39 cause oncogenic loss of heterozygosity (LOH). Cancers can arise through dysregulation of the normal regulatory con-40 41straints that ensure high fidelity chromosome segregation 42during development and tissue homeostasis (1). These chro-43mosomal segregation events differ considerably to those of the 44 first meiotic division during gametogenesis, where homolo-45gous chromosomes of a diploid germline progenitor cell 46 conjoin via programmed genetic recombination intermediates 47to form a bivalent, which is ultimately resolved, culminating in 48a reductional chromosome segregation event and "shuffled" 49genetic material (2, 3). There is now solid emerging evidence 50to support the concept that the inappropriate activation of 51meiotic chromosome regulator genes in mitotically dividing 52somatic cells results in deviations in mechanisms controlling 53chromosome 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

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90 association/recombination and sister centromere monopolarity) 91 contribute to maintenance and/or development/progression of 92 cancers. A screen for a subclass of CT genes that are specifically 93 associated with mammalian meiotic spermatocytes revealed a few 94genes encoding functions associated with meiotic chromosome 95 dynamics, such as the gene encoding the meiotic recombination 96 hotspot activator PRDM9 and the meiosis-specific cohesin genes 97 RAD21L1 and SMC1B (31, 32). Meiotic chromosome regulator 98 genes have been previously reported as CT genes (4-7), but only 99 now is robust evidence starting to emerge to indicate that these so called meiCT (meiotic cancer testis) genes (a specific subgroup 100 101 of the CT gene family) have an important influence on cancer chromosome biology. Greenberg and colleagues found that 102103two meiosis-specific factors, MND1-HOP2, which are normally 104required to bias meiotic recombination down an interhomolog 105pathway (instead of inter-sister chromatid repair), function in 106 cancer cells to assist utilization of an alternative lengthening 107of telomeres (ALT) mechanism in the absence of telomerase 108 reactivation (refs. 33, 34; Fig. 1A). This is dependent upon the 109 inherent ability of these factors to stimulate non-sister chromo-110 some interactions. The ALT pathway operates via a recombina-111 tion-mediated mechanism in which, in the absence of normal 112 telomerase-mediated elongation, telomeres behave like a broken 113chromosome end, serving to stimulate RAD51 recombinase-114 mediated strand invasion of an uncapped telomere into a non-115sister telomere to enable the invading end to serve as a substrate for DNA replication-dependent de novo telomere elongation (35). 116 117 This phenomenon can not only help drive tumor formation but 118 also enables tumor cell proliferative activity and is likely to 119 contribute to tumor cell evolutionary potential (36, 37), although 120this latter point requires experimental exploration.

121 The identification of the role of MND2-HOP1 in ALT was not 122 the first demonstration of meiotic genes driving chromosomal 123 dynamics in cancer cells. During meiosis in most eukaryotes (not 124 all) a proteinaceous, ladder-like structure of poorly defined func-125 tion, termed the synaptonemal complex (SC), forms between 126 paired homologues to mediate synapsis (3). Miyagawa and colleagues demonstrated that, when aberrantly produce in mitot-128 ically dividing cells, the meiosis-specific SC protein SYCP3 129impairs recombination by disrupting the function of the tumor 130suppressor recombination regulator BRCA2 (Fig. 1B; ref. 38); 131 moreover, SYCP3 expression in cancer cells drives ploidy changes 132 and is thus a key example of a meiotic chromosome regulator 133directly influencing chromosomal segregation in cancer cells (38). 134SYCP3 is thought to form a component part of the SC lateral 135 elements (linear substructures of the SC). Although the exact role 136 of SYCP3/lateral elements is unclear (39), it is likely that they 137 provide a structure-induced feature, such as chromosome com-138 paction stress, needed for chromosomal cross over control (2, 3); 139this is direct evidence that a meiotic recombination-associated 140protein can modulate genome maintenance/segregation in cancer 141cells. Evidence for the modulation of homologous recombination 142repair in cancers by SC-associated factors is extended by the 143finding that elevated expression of the CT gene HORMAD1 144 (40), which is required for SC formation and meiotic recombi-145nation control (41, 42), alters DNA repair pathways in triple-146 negative breast cancers, and sensitizes them to homologous 147recombination-associated therapies (43). 148

There are other examples of activation of meiotic recombination regulators contributing to cancer cell survival. The meiosisspecific 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 doublestrand 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



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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.

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167 cancer cells remains unknown, this work further demonstrates the
 168 functional requirements diverse meiotic chromosomal modula 169 tors, including regulators of meiotic recombination initiation, in
 170 oncogenesis.

171This emerging field has now taken on a new player, the fission 172yeast. For many years, the fission yeast has provided an excellent 173experimental model in which to demonstrate key features of 174meiotic chromosome dynamics, from meiotic recombination 175hotspot activation (51, 52) through to the control of meiosis I 176centromeric monopolarity (53, 54). Normal meiosis in the fission yeast requires the induction and commitment of a number of 177 178 "tightly" meiosis-specific genes following meiotic commitment 179(55); for example, rec8, a gene encoding a meiosis-specific cohesin 180 component (56). During mitotic proliferation, these genes are 181 suppressed at the transcriptional and posttranscriptional levels 182through an RNA interference- and exosome-dependent pathway controlled by the Mmi1 protein (57-62). Dysregulation of the 183 184 Mmi1 pathway in mitotically dividing cells results in inappro-185 priate levels of meiosis-specific transcripts such as rec8 mRNA 186 (59). Recently, Grewal and colleagues noticed that Mmi1-defi-187 cient mitotic cells (with aberrant levels of meiotic mRNAs) 188 exhibited high levels of chromosome mis-segregation events in 189 mitotically dividing diploid cells, including high levels of uni-190 parent disomy (UPD; ref. 63). They extended this to demonstrate 191 that UPD, which can drive LOH in oncogenesis, could also be 192induced by overexpressing only the rec8 meiotic cohesin gene in 193 mitotically dividing diploid cells (63). Rec8 is required in meiosis 194I for centromere monopolarity, which normally drives the reduc-195tional association of sister centromeres on the meiotic spindle 196 (54). Grewal and colleagues demonstrated that the expression of 197rec8 could generate high levels of UPD associated with mitotic 198reductional segregation of homologues in diploid cells. This 199 indicated a direct meiosis-like (pseudomeiotic) behavior of chro-200mosomes following activation of just a single meiotic cohesin 201gene (63) (Fig. 1C). While it has been previously suggested that 202 oncogenesis might require, or be enhanced by, the activation of a 203wide scale soma-to-germline transcriptional program, this sem-204 inal finding in fission yeast opens up the possibility that the 205activation of only a single meiotic regulator can alter chromosome 206 dynamics in such a fashion as to potentiate an oncogenic trans-207formation. Extrapolating this observation to human cells might be speculative in nature, but the relevance of this finding in fission 208209 yeast to human cancers is an interesting and important question. 210The work in fission yeast is not, however, the first inference of a

211function for this meiotic cohesin in cancer progression. Human 212REC8 has been shown to be present in endopolyploid TP53-213deficient tumor cells induced by ionizing irradiation (64). It was 214previously proposed that REC8 functions in these cells to induce 215pseudomeiotic chromosome segregation events that enable them 216to survive genotoxic treatment, which might infer REC8 (and 217potentially other meiotic factors) can drive therapeutic resistance 218in tumors (64). A screen for human CT genes specifically asso-219ciated with meiotic spermatocytes did not identify REC8, although it did identify other meiosis-specific cohesin genes, 220 221RAD21L1 and SMC1 β (31). Interestingly, however, that study 222 found evidence for widespread expression of REC8 in nonmeiotic 223somatic tissue (obtained post mortem; ref. 31). While it is 224unknown whether this REC8 expression resulted in the produc-225tion of REC8 protein in these somatic tissues, others have indi-226cated REC8 is present in noncancerous cultured cells (9); this 227might suggest that terminally differentiated human cells do not

229have such a tight requirement to constrain expression of meiotic genes as actively dividing cells, such as cultured fission yeast cells 230231 (i.e., there is no need for a strict Mmi1-like system in terminally 232differentiated cells). Given that such cells are largely nonproliferative in adult somatic tissue, it is assumed that expression of 233 genes such as REC8 would have little/no influence on ploidy 234235[although cohesins have been implicated in other processes, such 236as DNA damage recovery and transcriptional control; refs. 65, 66]. So, it might be the case that nonproliferative, terminally differ-237entiated cells do not require an Mmi1-like activity to degrade 238meiotic transcripts as cells can tolerate these mRNAs due to them 239 being functionally inert, possibly even remaining untranslated. 240241This said, the meiosis-specific cohesion gene RAD21L1 has expression tightly restricted to the testis in humans (31); interestingly, 242production of an ectopic GFP-fused Rad21L1 in mitotically 243dividing murine primary fibroblasts increases adjacency of 244homologous chromosomes, a clear pseudomeiotic activity with 245oncogenic and tumor evolutionary potential (67). 246

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 250tumors, have long been thought of as being embryo-like, con-251252tributing to a long established embryologic theory of cancer, 253which espouses the view that tumors have extensive embryo-like characteristics (e.g., cellular self-renewal and differentiation 254capacity with some cancer cells capable of differentiating to give 255256rise to the major germline cell layers; see ref. 8 and citations 257therein). CT genes contribute to a wide range of these embryonal 258cell-like processes, including an ability to migrate, extensive proliferative potential, and change cellular morphology (13). 259However, embryonic cells in normal embryo development exe-260cute these characteristics and developmental changes in a highly 261262orchestrated and temporally controlled fashion, with cascades of gene expression regulation at the heart of this process. Impor-263264tantly, during embryogenesis, all cells, from the zygote on, maintain ploidy and avoid mutational genetic change. Indeed, early 265embryo stem cells have evolved distinct genome maintenance 266 pathways to ensure this, and to avoid excessive germline muta-267tions (68, 69). Cancer cells differ considerably in these core 268features. For example, gene expression regulation does change, 269but it is not done in a programmed and preordained temporal 270271fashion, as would be the case during embryogenesis. Rather, tumor cells have the capacity to undergo a relatively rapid geno-272mic and epigenetic evolution over time in response to the imme-273diate requirements and pressures of the tumor/tumor cells (36, 27437, 70). Indeed, tumor cells deviate considerably from the normal 275276cellular constraints that control embryogenesis, such as apoptosis 277and telomeric regulation. Therefore, the ability for tumor genomes to evolve is a fundamental distinguishing feature that 278279differentiates these cells from all embryonic cells. The new findings that indicate key features of oncogenic genomic evolution, 280namely altered DNA repair, centromeric polarity control, and 281chromosomal end protection (Fig. 1), are all potentially modu-282283lated by pseudomeiotic functions, strongly suggesting that meiotic factors play a fundamental role in distinguishing oncogenesis 284 from embryogenesis. This would mean that the embryologic 285theory of cancer, in which cancers mimic cellular behavior in 286287 embryogenesis, appears too restrictive. We postulate that a more

290 appropriate viewpoint is simply to state that cancers undergo a 291degree of soma-to-germline transition, which can encompass 292 embryo development-like and gametogenic-like features, but 293does not mimic embryogenesis per se. The functions that become 294activated might be inter-related, but they are simply activated on 295the basis of the evolutionary drivers/requirements within a 296 tumor/tumor cells located within distinct environmental con-297texts, and are not part of a rigid, defined embryo-like program for 298tumor development.

299 Concluding Remarks

300 We speculate that the importance of pseudomeiotic functions 301 does not lie simply in conferring/enhancing the evolutionary 302 capacity of a tumor/tumor cell, but that they can also potentially 303 provide single event initiator capability, as illustrated by the 304 finding that activation of SYCP3 can alter BRCA2-mediated DNA 305 repair (38) and rec8 activation (ref. 63; in fission yeast, at least) can 306 drive abnormal reductional segregations. Thus, activation of 307pseudomeiotic functions/meiCT genes can not only serve in 308 tumor evolution and maintenance, but might also be an impor-309 tant single first step oncogenic initiator that does not require a

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genetic change [i.e., can arise due to epigenetic/misregulated gene311activation in the absence of genome sequence alteration (70)].312

Importantly, the finding that these meiotic factors can contrib-313 ute to tumor maintenance, and potentially to tumor cell thera-314peutic resistance by driving rapid tumor evolution, marks them as 315potential cancer-specific drug targets. This makes the study of 316 meiosis and meiotic processes in a wide range of model organisms 317of importance not only for elevating our basic understanding of 318 life on earth, but also because it could reveal new features of 319 exceptional importance in clinical oncology. 320

 Disclosure of Potential Conflicts of Interest
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 No potential conflicts of interest were disclosed.
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