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Research Article

DMC1 Protein-Protein Interactions are Directly Linked to Meiosis Homeostasis and Fertility

Silva KSF*

Biological Sciences Institute, Federal University of Goiás, Brazil

***Corresponding author:** Kleber Santiago Freitas e Silva, Biological Sciences Institute, Federal University of Goiás, Brazil

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Abstract

Infertility is a disorder of the reproductive system. Couples are infertile when they are unable to conceive children by a functional pregnancy after one year of regular and unprotected sexual intercourse. About 15% of couples in the reproductive age around the world cannot conceive children and around 30% of all cases of infertility are idiopathic, with unknown underlying causes. Protein-protein interactions have not yet been extensively explored regarding those underlying causes of infertility and one can assume that PPIs could be directly related to some of the idiopathic cases of infertility. Meiosis is a cell division process governed by a multitude of proteins and multiprotein complexes that regulate DNA double strand breaks, homologous recombination, synapsis [1], mismatch repair, chromosome maintenance and synaptonemal complex. PPI studies have been used in a variety of ways in other to shed some light on unknown molecular biologic processes that take place in the microenvironment of cells and may lead to diseases. PPI approaches have been used to identify the dynamic of biological systems and diseases onset, progression, diagnosis and treatment. Here, we present bioinformatics and in silico analysis of DMC1 and interacting protein partners that play important roles in meiosis homeostasis and consequently in human fertility. The in silico approaches performed, show that the interaction of DMC1, an essential protein to cell division, with partners with similar function that could be related to meiosis disruption and infertility in males and females.

Keywords: Infertility; Meiosis; DMC1; Protein-Protein Interactions

Introduction

Infertility is a disorder of the reproductive system characterized by the inability to conceive children successfully by a functional pregnancy after at least one year of regular and unprotected sexual intercourse. Infertility assessment should be performed for patients with risk factors for infertility or for female patients older than 35 years [2]. About 15% of couples in the reproductive age around the world cannot conceive children [3,4]. The underlying causes of infertility can be assigned to male, female or both and around 30% of all cases of infertility are idiopathic [5]. Protein-protein interactions (PPIs) have not yet been extensively explored regarding those underlying causes of infertility and one can assume that PPIs could be directly related to some of the idiopathic cases of infertility.

Cell division may also be intimately related to infertility. Meiosis is the cell division process that results in four daughter cells, each with half the number of chromosomes present in the parent cell. This process is governed by a multitude of proteins and multiprotein complexes that regulate DNA double strand breaks [6], homologous recombination [7], synapsis [1], mismatch repair [8], chromosome maintenance and synaptonemal complex [9]. Centrosomes and the microtubule cytoskeleton, for example, exert essential roles during meiotic spindle formation and any dysfunction in those structures may lead to aneuploidy [10], other genetic disorders [11], cancer [12] and infertility [13].

Currently, PPI studies have been used in a variety of ways in other to shed some light on unknown molecular biologic processes that take place in the microenvironment of cells and may lead to diseases. PPI approaches have been used to identify the dynamic of biological systems and diseases onset, progression, diagnosis and treatment. Research studies on cancer [14–16], diabetes [17,18], coronary artery disease [19,20], epilepsy [21,22], glaucoma [23,24] and infertility [25], among others, have shown that PPIs dysfunction could play important roles in disease onset.

Meiosis is a complex process and several proteins act together in other to ensure that chromosomes segregate properly to form daughter cells that differentiate into gametes. DMC1 (disrupted meiotic cDNA1) is a meiotic recombination protein important for homologous recombination. Its function is related to protein assembling at programmed DNA double strand breaks sites and finding allelic DNA sequences on homologous chromatids during meiosis. Thus, along with other proteins, DMC1 is pivotal for DNA break repair. The DMC1 protein is highly conserved among species [26,27] (Figure 1). Here, we present bioinformatics and in silico analysis of DMC1 and interacting protein partners that play important roles in meiosis homeostasis and consequently in human fertility.

Material and Methods

DMC1 interactome and PPIs: The profile of PPI interaction for the human protein DMC1 was retrieved from the BioGrid database [28] and from STRING database [29]. The protein interacting to

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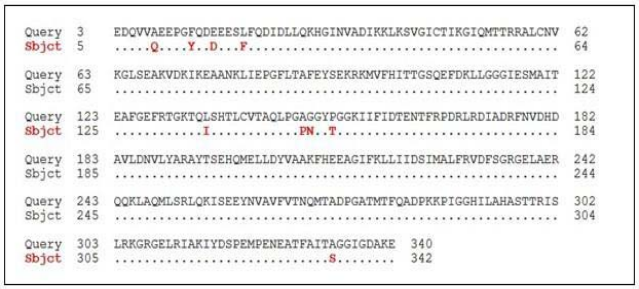

Figure 1: The DMC1 protein is highly conserved among species. The alignment between amino acid sequence of DMC1 from Homo sapiens and from Merops nubicus show that few residues are changed. The query line refers to human DMC1 and the subject line refers to the M. nubicus.

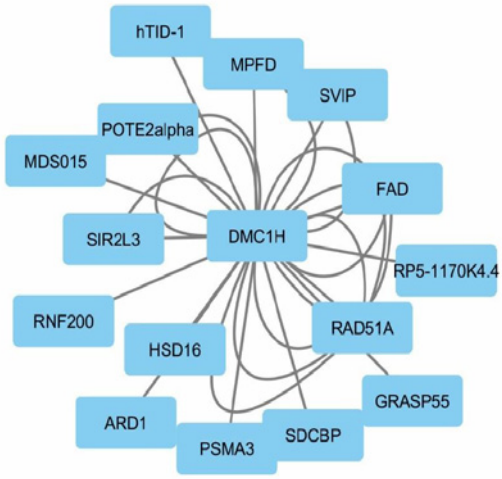

Figure 2: DMC1 interacts with a variety of partner proteins. The DMC1 interacting network shows DMC1 partners retrieved from BioGrid database. The netword was constructed through the Cytoscape platform.

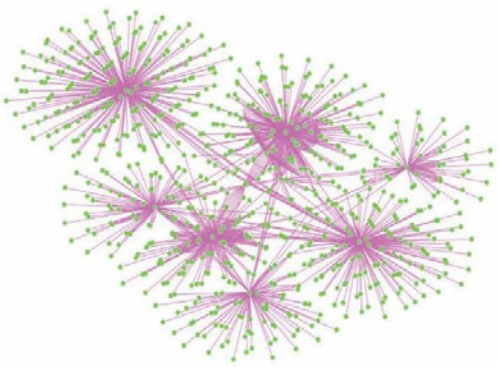

Figure 3: The complete PPIs for DMC1, including neighboring interactors. Each green node represent a protein and each green edge represents interaction between two or more proteins. The DMC1 interactome is has a complex trait, a reflex of the function DMC1 and its partners exert.

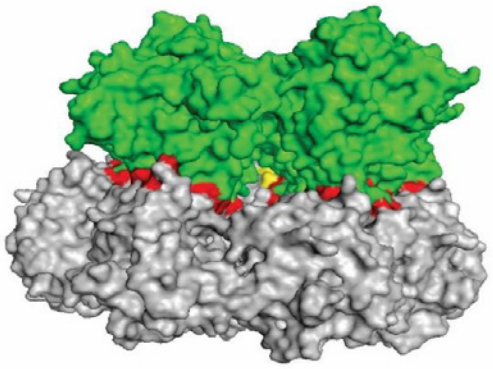

Figure 4: *In silico* model of DMC1 and RAD51A interaction. The green protein is DMC1 and the grey protein is RAD51A. The red region represents the interaction interface while the yellow spot represents the most visible hot spot in this configuration of the complex.

DMC1 network was generated by Cytoscape [30].

3-D structure of DMC1 and partners: All 3-D structures are available and were retrieved from the PDB databank [31].

Domain analysis: The domains of each protein were retrieved by searching the FASTA file of the proteins in the KBDOCK databank [32].

Hotspots analysis: The hotspots in each binary interaction was evaluated by the algorithm available in the KFC2 server [33].

Interaction interface: The interaction between DMC1 and partner and the interaction interface figures were built in the PyMol visualization program.

Results and Discussion

DMC1 protein-protein interactions network

Genetic recombination occurs during meiotic cell division. This process is responsible for the genetic diversity observed in nature and promotes the important reductional segregation of homologous chromosomes for formation of reproductive male and female cells and the maintenance of the correct number of chromosomes in animal cells [34]. DMC1 catalyzes homologous DNA strand intrusion, loop and double strand breaks formation and processing in order to guarantee correct meiotic recombination and chromosome synapsis [34–36]. DMC1 interacts with a variety of other proteins (Figure 2) with different functions to enhance its activity.

DMC1 protein interactors have been validated by experimental PPI assays such as RAD51A [37], SIRT3 (NAD-dependent deacetylase sirtuin-3) [38], KCTD17 (potassium channel tetramerization domain containing 17) [39], DNAJA3 (DnaJ heat shock protein family member A3) [40], TRIM23 (tripartite motif containing 23) [39], SDCBP (syntenin-1) [39] and RFWD2 (E3 ubiquitin-protein ligase) [38]. The complete PPIs for DMC1, including neighboring interactors, are shown in schematic Figure 3.

DMC1 and RAD51A interaction interface

DMC1 and RAD51A interact with single-stranded DNA during meiosis in order to stabilize and promote the recombination processes between homologous chromosomes [37,41]. It has been shown that DMC1 and RAD51A physically interact to promote chromosome synapsis formation and consequently recombination [37,42]. Figure 4 shows an in silico model of interaction for DMC1 and RAD51A based on hotspots calculations. There are five main contact regions in DMC1-RAD51 interaction interface (Table 1). The red region

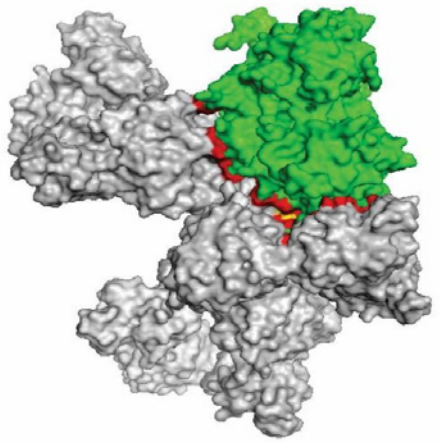

Figure 5: *In silico* model of DMC1 and SIRT3 interaction. The green protein is DMC1 and the grey protein is SIRT3. The red region represents the interaction interface while the yellow spot represents the most visible hot spot in this configuration of the complex.

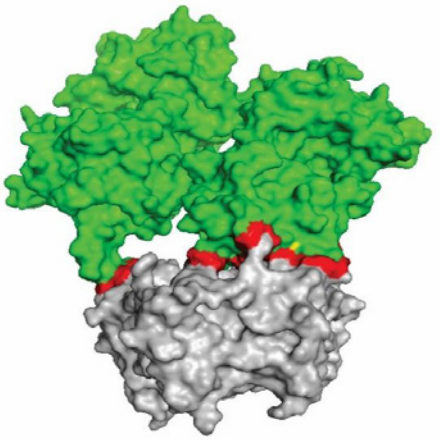

Figure 6: *In silico* model of DMC1 and KCTD17 interaction. The green protein is DMC1 and the grey protein is KCTD17. The red region represents the interaction interface while the yellow spot represents the most visible hot spot in this configuration of the complex.

marked on figure 4 represents the interaction interface between DMC1-RAD51 and a hotspot is shown in yellow and corresponds to a tyrosine residue at position 314 and an arginine residue at position 316 within the J chain of RAD51A.

Interestingly, both proteins contain a RAD51 conserved domain, which is pivotal to DNA binding and interaction with proteins with similar function. Both proteins participate in processes related to DNA damage response [43,44] and meiosis homeostasis [42], thus, they are also linked to the success of gametes formation and fertility. DMC1 and RAD51A interaction disruption may be one of the causes for male and female infertility.

DMC1 and SIRT3 interaction interface

We identified 12 hotspot residues in the DMC1 and SIRT3 interaction interface, one of those hotspots is visible in Figure 5, which is a phenylalanine residue at the position 294 on chain 'b'. The hotspots residues play important roles regarding free energy to maintain those proteins together so they can perform their functions properly and maintain cellular homeostasis.

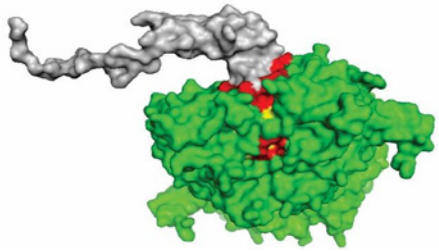

Figure 7: *In silico* model of interaction of DMC1 and zinc finger domain from DNAJA3. The green protein is DMC1 and the grey protein is the zinc finger motif. The red region represents the interaction interface while the yellow spot represents the most visible hot spot in this configuration of the complex.

The sirtuin class of protein shows a wide range of biomolecular roles [45]. Their functions are related to aging [46], stress response [47] and metabolic regulation [48]. Sirtuins take part epigenetically in gene silencing in a way that its activity is able to suppress DNA recombination. In addition, sirtuin proteins may be related to infertility through a variety of ways such as failing to prevent oxidative during gamete formation [49], ageing [50] and disrupted interaction with proteins related to DNA damage response and DNA recombination such as DMC1, which could reduce the activity and functions of the latter.

DMC1 and KCTD17 interaction interface

We found 10 main points of interaction between DMC1 and KCTD17. The visible hotspot is shown in yellow in Figure 6. The 3-D structure of KCTD17 is a star shape. The best score of energy (the lowest free energy) for this model of interaction forms a bridge in the final confirmation of the complex (Figure 6), and this specific shape is what guarantees the activity of the complex. It is possible that this conformational state varies slightly if these proteins take part in a multimeric protein complex in order to exert different functions.

KCTD17 regulates positively ciliogenesis, a bio molecular activity related to motility and spermatogenesis [51,52]. The protein catalyzes the proteasomal degradation of trichoplein (TCHP), which is a negative regulator of ciliogenesis [53]. KCTD17 is indirectly related to cell division processes, controlling TCHP's activity. The latter is also related to centrioles, an organelle responsible for forming the spindle fibers. DMC1 exerts activities toward normal spindle formation. It has been shown that mutants lacking DMC1 have altered spindle format and activity, which may bring genetic defects to daughter cells after meiosis recombination [54,55].

DMC1 and DNAJA3 interaction interface

We found 10 hotspots in the interaction interface between the proteins DMC1 and DNAJA3. The part of the DNAJA3 structure that interacts with DMC1 is mediated by a zinc finger domain (Figure 7). DNAJA3 belongs to the heat shock protein (HSP) family and its function is related to maintenance of the 3-D structure of proteins and stabilization of protein complexes [56]. In addition, HSPs promotes correct protein folding and degradation at the right time [57,58]. The PPI between these proteins may influence the stabilization of multiproteic complexes with DMC1 in a way that the latter can

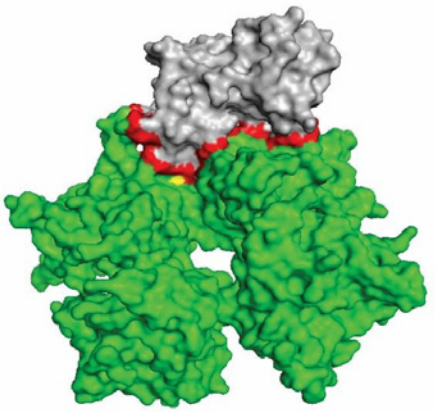

Figure 8: *In silico* model of interaction of DMC1 and B-box zinc finger domain from DNAJA3. The green protein is DMC1 and the grey protein is the zinc finger motif. The red region represents the interaction interface while the yellow spot represents the most visible hot spot in this configuration of the complex.

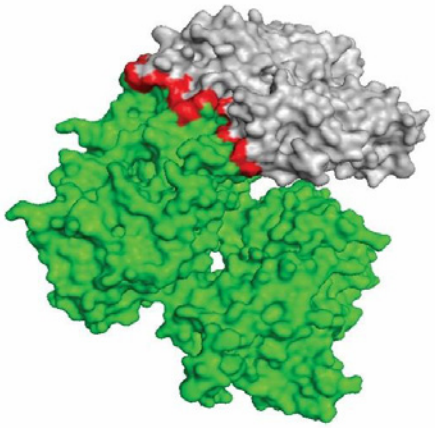

Figure 9: *In silico* model of interaction of DMC1 and PDZ domain from SDCBP. The green protein is DMC1 and the grey protein is the PDZ domain. The red region represents the interaction interface. Here, the hotspots are buried in the interaction interface and are not visible.

perform its functions and guarantees proper DNA recombination during meiosis.

DNAJA3 is linked to a large variety of diseases, including metabolic [59], degenerative [60], inflammatory [61] diseases and tumors [62]. It has been shown that proteins belonging to the HSP family is related to some cases of infertility [63,64]. HSPs have found to be linked to homologous recombination as well as spindle stabilization [65] and regulation of centrosomes [66] during cell division.

DMC1 and TRIM23 interaction interface

The analyses of the interaction between DMC1 and TRIM23 resulted in eight hotspots within the interaction interface. Most of the hotspots are deep in the interface and it cannot be seen on the surface of the complex. However, there is at least one visible hotspot on the surface of the complex (Figure 8). The part of the TRIM23 that interacts with DMC1 is a B-box zinc finger domain. Generally, TRIM proteins contain an N-terminal RING finger (so-called A-box), a 1 and/or 2 B-box domains and lastly, a coiled-coil domain. The most common activity of this type of protein is ubiquitinylation [67].

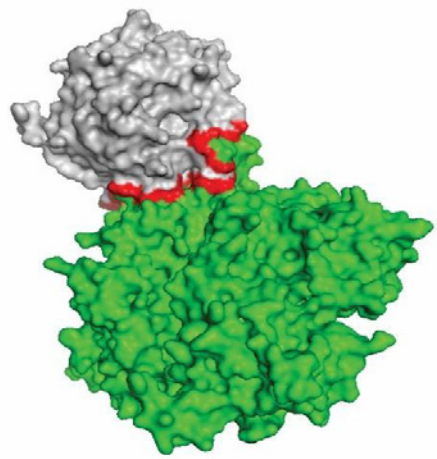

Figure 10: *In silico* model of interaction of DMC1 and WD40 domain from RFWD2. The green protein is DMC1 and the grey protein is the WD40 domain. The red region represents the interaction interface. Here, the hotspots are buried in the interaction interface and are not visible.

TRIM23 was found to be up-regulated as a germline gene involved in uniquitinylation and immunity [68]. This may be reflex of its interaction with DMC1 and other proteins related to meiosis and DNA recombination, linking this gene and its interactors to idiopathic infertility. TRIM23 has also been linked to cancer-related proteins, the down-regulation of TRIM23 affects other proteins and this may lead to diseases onset [69].

DMC1 and SDCBP interaction interface

The interaction analyses of DMC1 and SDCBP identified five hotspots within the interaction interface. The PDZ domain structure is responsible for the binding to a protein partner and this domain is conserved across the proteins that contain them, and conserved among species as well. In addition, PDZ domains is also conserved regarding its folding, due to the presence of specific amounts of beta and alfa strands [70]. PDZ domains are monomers, however in some proteins the PDZ domains fold into dimers, as in SDCBP (Figure 9). Moreover, the PDZ domain in SDCBP is highly hydrophobic, which facilitates its interaction with the target protein DMC1.

SDCBP protein contain a PDZ domain, which is present in signaling proteins [71]. The activity of PDZ domains are related to its docking to a receptor protein localized in the membrane and to the transmission of signals into cytoskeletal components [70]. PDZ domain containing proteins are versatile in their interactions, normally binding to several different protein partners. SDCBP is related to apoptosis [72] and tumor onset and progression [73], thus it is linked to cell cycle and cell division processes. Moreover, SDCBP has been found to be a possible cause of infertility since it has been detected patients with immunological infertility by anti-sperm antisera [74].

DMC1 and RFWD2 interaction interface

In our model, the protein RFWD2 binds to DMC1 through its WD40 domain (Figure 10). We found three hotspots in the interaction interface (Table 2). The name of the domain comes from

Table 1: Hotspot analyses by KFC2 for the interactions between DMC1 and the partners RAD51A, SIRT3 and KCTD17.

Chain	Hotspots	Num	KFC2-A Conf	KFC2-B Conf
DMC1 + RAD51A				
J	PHE	137	0.65	0.15
J	GLN	258	0.65	0.08
J	TYR	314	1.16	0.18
J	ARG	316	0.71	0.09
K	ARG	245	0.64	0.01
DMC1 + SIRT3				
B	GLU	90	1.36	0.05
B	LYS	96	1.75	0.3
B	MET	97	1.41	0.26
B	VAL	98	1.22	0.01
B	ARG	252	0.06	0.21
B	LYS	255	1.31	0.11
b	PHE	180	1.45	0.39
b	GLU	181	1.05	0.11
b	PHE	294	0.92	0.01
c	HIS	248	1.5	0.24
c	PHE	293	0.03	0.38
c	PHE	294	1.87	0.36
DMC1 + KCTD17				
A	GLU	127	1.88	0.23
A	PHE	128	1.62	0.33
A	ARG	129	0.9	0.29
A	ARG	169	0.69	0.18
A	GLN	269	0.85	0.08
A	LYS	305	0.95	0.01
A	ARG	311	1.16	0.36
A	ILE	330	1.17	0.04
E	TRP	32	1.39	0.32
E	ARG	70	0.91	0.17

Table 2: Hotspot analyses by KFC2 for the interactions between DMC1 and the partners DNAJA3, TRIM23, SDCBP and RFWD2.

Chain	Residues	Num	KFC2-A Conf	KFC2-B Conf
DMC1 + DNAJA3				
C	ARG	129	1.09	0.18
D	LEU	111	1.09	0.25
D	LEU	112	0.1	0.15
D	ARG	300	0.14	0.15
D	ILE	315	1.57	0.29
D	ASN	324	0.8	0.04
a	TYR	50	0.99	0.13
a	PHE	64	0.8	0.25
a	Met	66	1.84	0.18
a	ARG	67	1.33	0.3
DMC1 + TRIM23				
B	HIS	211	1.07	0.03
D	HIS	137	0.76	0.14
D	ARG	166	0.7	0.01
D	ARG	169	0.6	0.15
D	TYR	190	0.5	0
b	LEU	102	1.48	0.04
c	LEU	60	0.14	0.18
c	ILE	70	0.77	0.09
DMC1 + SDCBP				
C	ARG	300	0.24	0.27
C	ASN	324	0.51	0.01
E	LEU	149	1.76	0.17
E	ARG	191	0.03	0.11
F	ARG	197	0.41	0.2
DMC1 + RFWD2				
B	TYR	91	1.5	0.33
E	LEU	417	1.49	0.21
E	LYS	444	0.89	0.21

its last two residues, which generally are tryptophan (W) and aspartic acid (D) [75]. The WD40 domain comprises a circular shape folded in this format through a series of sequential WD repeats [76,77]. The functions of proteins that contain the WD40 repeat are related to signal transduction, transcription and translation regulation, cell cycle, cell division and growth control, autophagy and apoptosis [78].

WD40 repeat proteins have been implicated in cases of infertility in several studies [79,80]. The interaction of RFWD2 and DMC1 could affect fertility of individuals as these proteins are linked to important processes that take place during meiosis. Conserved proteins among species with WD repeat in their structure have been shown to play a role in meiotic division [81]. WD 40 repeat proteins have been found to regulate microtubule organization during cell division [82]. Protein with functions that fall under similar categories are prone to interact, RFWD2 and DMC1 complementary functions are guaranteed by one binding to the other, thus, maintaining meiosis homeostasis and a proper gamete formation.

Concluding Remarks

Infertility is a worldwide health-care problem. It affects more than 15% of couples at reproductive age. Recent advances have helped couples to achieve successful pregnancy. However, new approaches need to be developed in order to increase our understanding of the molecular basis that falls under the classification of idiopathic infertility. Bioinformatics, system biology, high-throughput techniques can help researches achieve that goal. Little is known how PPIs could affect the homeostasis of the reproductive system leading to infertility. Several genes and proteins are implicated in disrupted PPI that could lead to meiosis and homologous recombination anomalies. Here, we showed through in silico approaches the interaction of DMC1, an essential protein to cell division, with partners with similar function that could be related to meiosis disruption and infertility in

males and females.

Declaration

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