Biochimie 131 (2016) 115–127

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Geminin a multi task protein involved in cancer pathophysiology and developmental process: A review

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ARTICLE INFO

Article history:
Received 27 June 2016
Accepted 29 September 2016
Available online 1 October 2016

Keywords:
DNA replication
Cell cycle
Inhibitors
Development
Cancer
Geminin

ABSTRACT

DNA replicates in a timely manner with each cell division. Multiple proteins and factors are involved in the initiation of DNA replication including a dynamic interaction between Cdc10-dependent transcript (Cdt1) and Geminin (GMNN). A conformational change between GMNN-Cdt1 heterotrimer and hetero-hexamer complex is responsible for licensing or inhibition of the DNA replication. This molecular switch ensures a faithful DNA replication during each S phase of cell cycle. GMNN inhibits Cdt1-mediated minichromosome maintenance helicases (MCM) loading onto the chromatin-bound origin recognition complex (ORC) which results in the inhibition of pre-replication complex assembly. GMNN modulates DNA replication by direct binding to Cdt1, and thereby alters its stability and activity. GMNN is involved in various stages of development such as pre-implantation, germ layer formation, cell commitment and specification, maintenance of genome integrity at mid blastula transition, epithelial to mesenchymal transition during gastrulation, neural development, organogenesis and axis patterning. GMNN interacts with different proteins resulting in enhanced hematopoietic stem cell activity thereby activating the development-associated genes' transcription. GMNN expression is also associated with cancer pathophysiology and development. In this review we discussed the structure and function of GMNN in detail. Inhibitors of GMNN and their role in DNA replication, repair, cell cycle and apoptosis are reviewed. Further, we also discussed the role of GMNN in virus infected host cells.

Contents

1. Introduction

Defective DNA replication is associated with abnormal

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http://dx.doi.org/10.1016/j.biochi.2016.09.022
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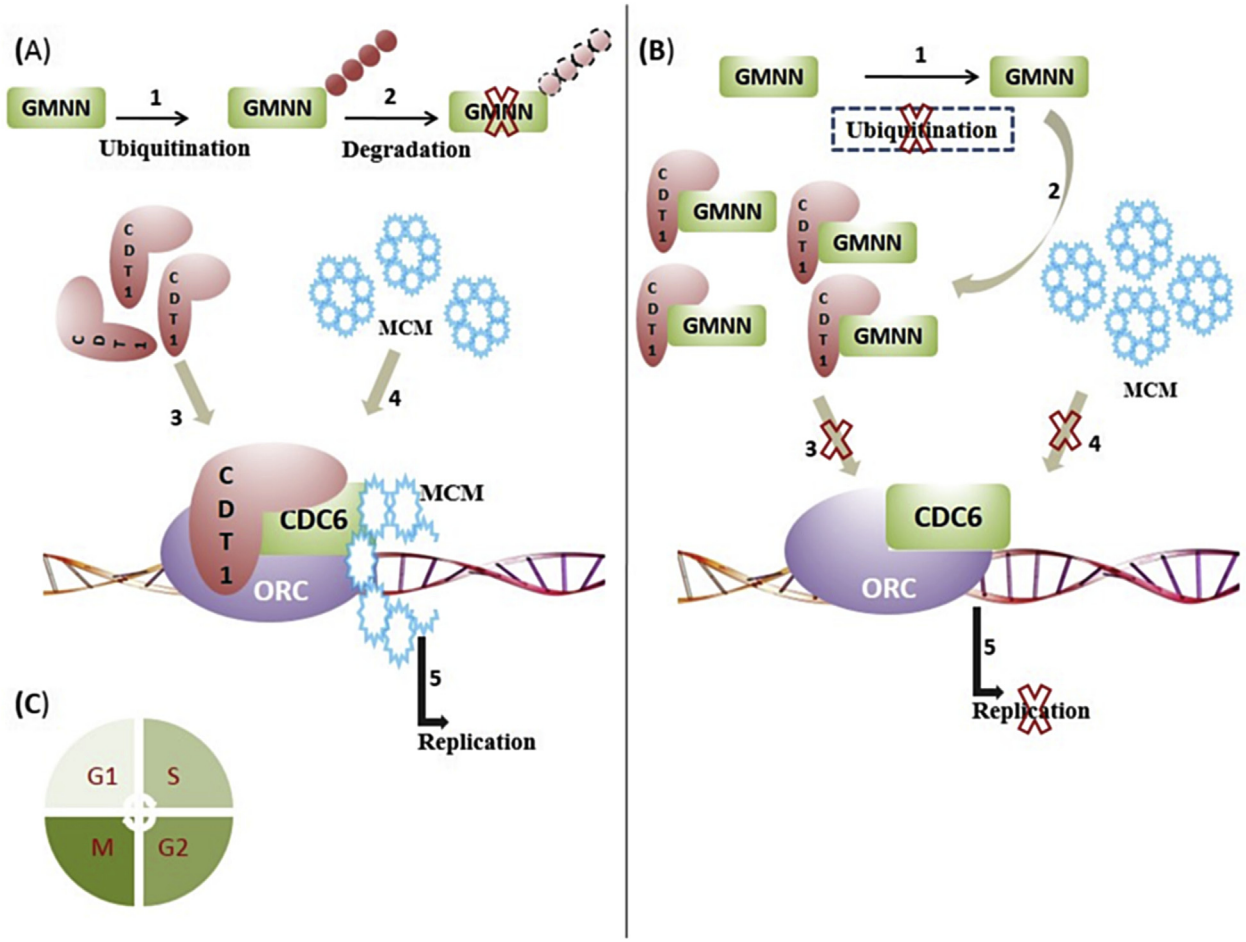

Fig. 1. A) Licensing mechanism of replication initiation in absence and B) Presence of GMNN protein C) Differential presence of GMNN across the cell cycle stages (G1, S, G2 and M blocks does not represent the time dependent stage of cell cycle it only shows the presence of GMNN across various stages. GMNN levels drop at the metaphase/anaphase transition of mitosis due to its degradation by the Anaphase Promoting Complex and completely degraded at the end of mitosis stage). Step A1: Ubiquitination of GMNN; Step A2: Degradation of ubiquitinated GMNN; Step A3: Loading of Cdt1 proteins onto the ORC; Step A4: Loading of MCM proteins onto the ORC (heterotrimer Cdt1 residues exposed and free to engage in replication licensing by promoting MCM chromatin association); StepA5: Pre-RC formation results replication progression. StepB1: No GMNN ubiquitination; Step B2: GMNN bind to Cdt1 proteins and formation of GMNN-Cdt1 complex (formation of heterohexamer); Step B3: GMNN-Cdt1 complex formation inhibits loading of Cdt1 onto the ORC (In heterohexamer, residues in the tertiary interface of Cdt1 buried and unable to engage with MCM and obstruct replication licensing); Step B4: Due to absence of Cdt1 on ORC, no further recruitment of MCM onto the ORC; Step B5: Pre-RC formation inhibition results no further replication.

development and disease such as cancer [1] [2]. Initiation of **e**ukaryotic DNA replication involves interaction of a protein complex with the origin of replication (OR). This complex includes ORC, cell division cycle 6 (Cdc6), CMG helicase (Cdc45–MCM–GINS complex), DNA polymerase, alpha-primase, leading strand DNA polymerase epsilon, lagging strand DNA polymerase delta, proliferating cell nuclear antigen (PCNA) clamp, replication factor C (RFC) clamp loader, replication protein A (RPA), single stranded binding protein (SSB) protein and Cdt1 [3]. This process known as 'licensing' is tightly regulated to achieve a single whole genome duplication event per cell cycle [4]. ORC- mediated independent binding of Cdc6 and Cdt1 to OR follows MCM recruitment which leads to the formation of pre-recognition complex. This initiates the DNA replication licensing [5]. GMNN binds with Cdt1 and prevents the loading of MCM complex to OR resulting in licensing inhibition. GMNN activity depends on equilibrium between a heterotrimer (two GMNN proteins and one molecule of Cdt1) and a heterohexamer (four GMNN proteins and two molecules Cdt1). The relative abundance of this hetrotrimer/hexamer is regulated during the cell cycle. It has been reported that heterohexamer inhibits DNA licensing while heterotrimer exposes the Cdt1 residues and hence promotes MCM chromatin association and allow licensing even in the presence of GMNN [6]. GMNN is indeed a component of the pre-replication complex [7,8,9]. Inhibition of licensing by GMNN in early S-phase occurs on chromatin. Tetramerization followed by accumulation of GMNN on chromatin is the key event that inhibits further licensing [6]. The function of GMNN in licensing inhibition outside chromatin occurs mainly in mitosis, at a time when Cdt1 is stabilized and is not chromatin bound. Uncontrolled accumulation of Cdt1 has been reported for the multiple DNA replication events during G1 phase of cell cycle. Alteration of Cdt1 by ubiquitination and proteolysis affect the licensing of DNA replication. DNA damage mediated proteolytic degradation of Cdt1 in S-phase might serve as checkpoint control is not yet clear [10,11]. Controlled expression of GMNN regulates the Cdt1 level during cell cycle. Thus, GMNN safeguards DNA replication in eukaryotes (Fig. 1) [12]. Alterations in GMNN expression are associated with cell proliferation, differentiation, development and transcriptional regulation. GMNN

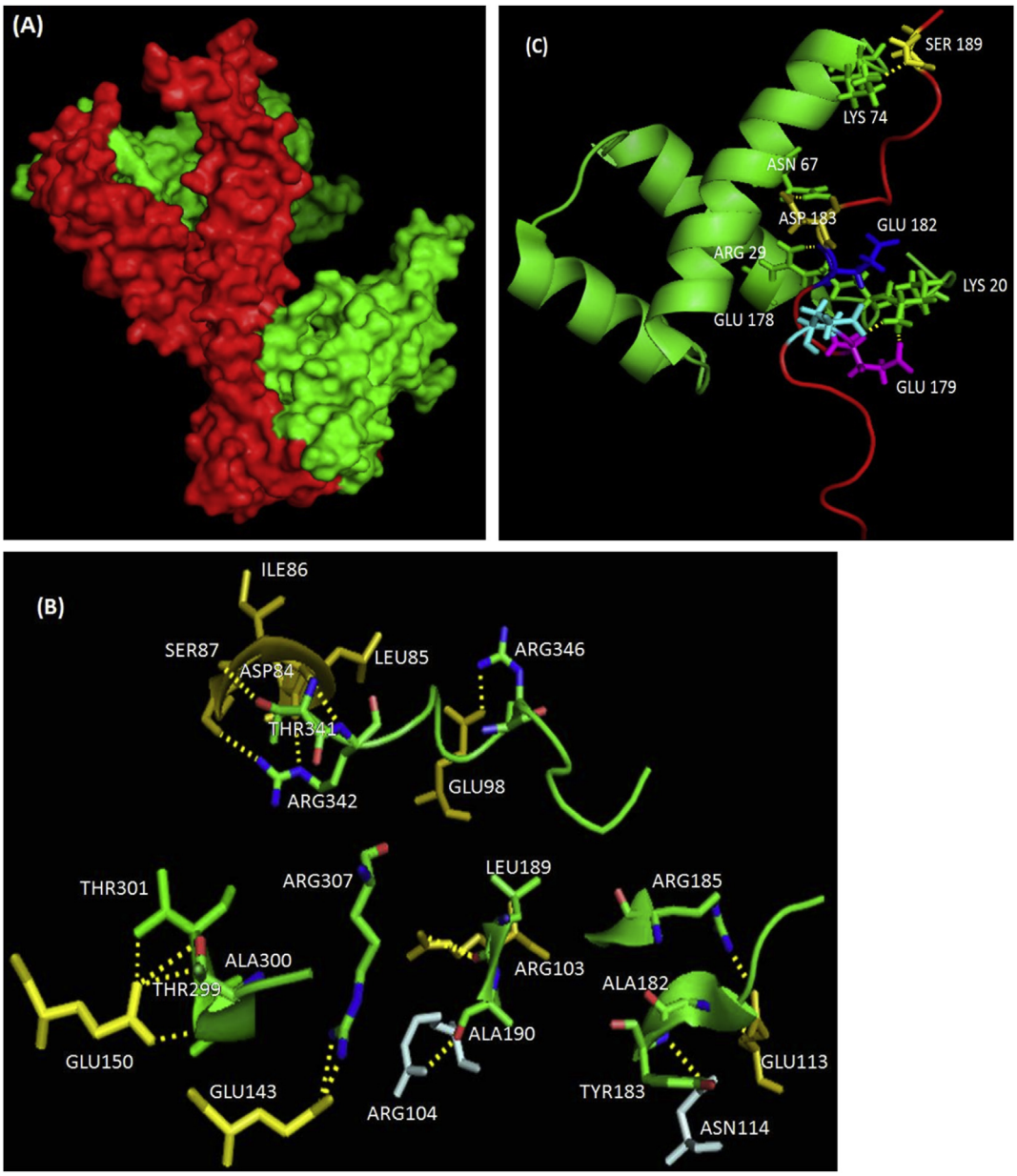

Fig. 2. A) Molecular surface structure of GMNN-Cdt1 (red-green color respectively) complex (PDB-2ZXX) **B)** Residues involved in GMNN-Cdt1 interaction (Green color shows Cdt1 while other color codes for GMNN) **C)** Residues involved in homeobox protein HOX C9 (Green color) and GMNN (red) complex (PDB-2LP0).

regulates cellular decision of self-renewal versus commitment of neuronal progenitor cells [13]. It is also involved in inhibition of DNA replication of virus infected host cells [14].

2. Geminin structure, function and its role in disease

Initially, GMNN was identified as a general inhibitor of DNA replication in *Xenopus laevis* egg extracts. However, its specific function was not known [15]. Later, it was reported that GMNN is an inhibitor of Cdt1 [16,17]. GMNN protein (molecular weight, 23565 Da) has about 209 amino acids and its gene is located on the 6th chromosome. It is a tetramer protein. The monomers of each dimer are known to interact with each other by coiled-coil domain interaction [18,19]. The peptide harbors leucine zipper domain consisting of internal polar residues and a negatively charged surface that interacts with the basic domain of interacting partners [19]. For example R43 and M54 in helix III and the basic amino acid cluster in the N terminus of Hox homeodomain are known to be involved in the formation of Hox homeodomain- GMNN complex (Fig. 2C). This interaction inhibits the transcriptional activity of Hox and also recruits it for the control of cell proliferation [20]. The upstream and downstream residues of the leucine zipper domain prevent DNA synthesis. It is also reported that the coiled-coil dimerization of the functional domain of GMNN is required for its activity [21]. Cdt1-binding domain lies adjacent to the dimerization domain which inhibits DNA replication and restricts the entry of cell into mitosis phase. Ubiquitin-mediated proteolysis of GMNN allows cell to enter into mitosis phase and thereby allow a new

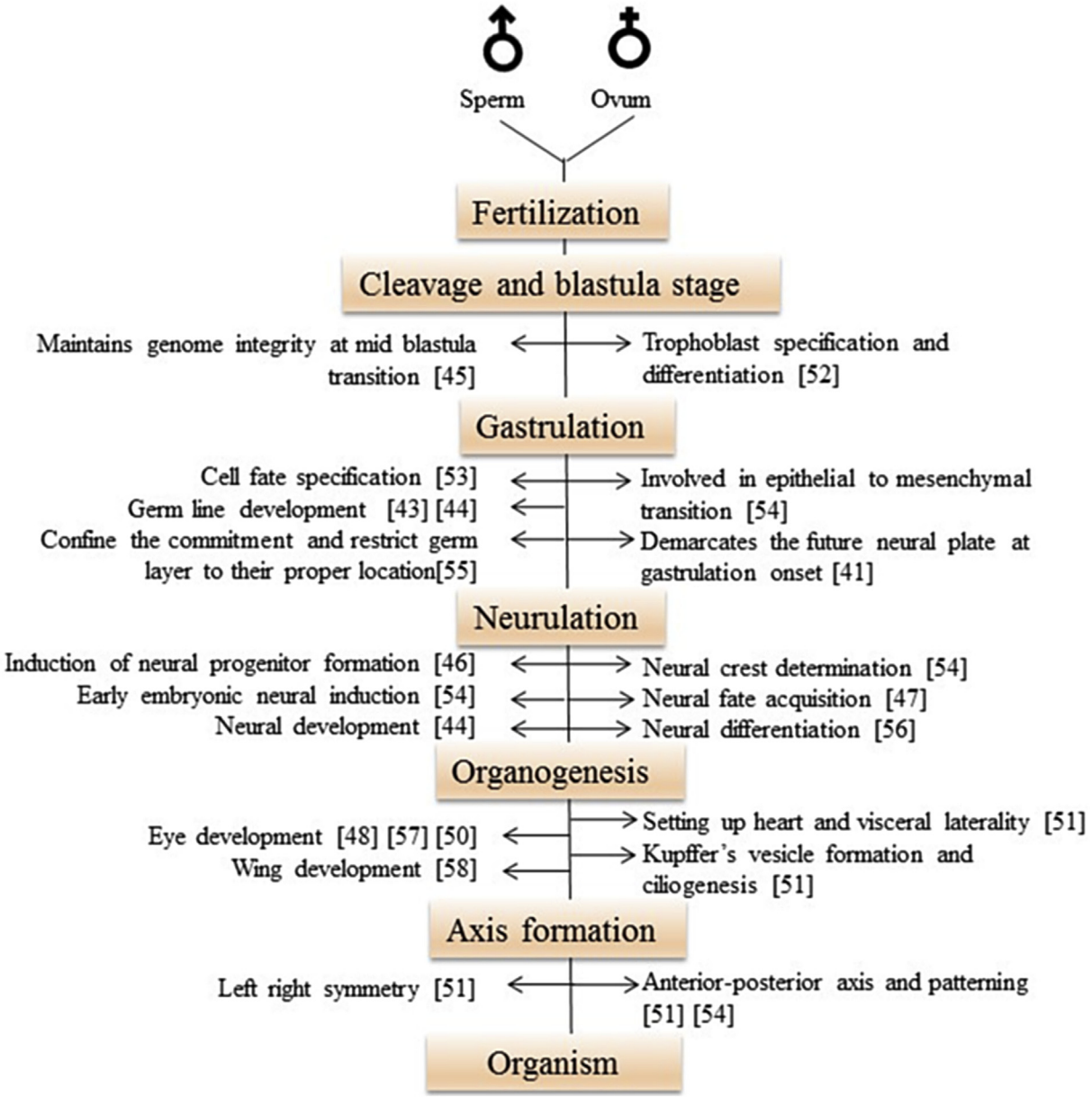

Fig. 3. Role of Geminin at different developmental stages [52–58].

round of replication in the subsequent cell cycle [15]. Bipartite nuclear localization signal of GMNN is required for its degradation during mitosis. GMNN modulates the stability and activity of Cdt1 at various stages in cell cycle such as initiation and loading of MCM on the DNA. Binding of GMNN with Cdt1 protects its proteasomal degradation and ensures sustainenace during S phase and mitosis. It is now known that GMNN acts both as positive and negative regulator for the formation of pre-replication complex [22]. Loss of GMNN resulted in multiple defects (multi-polar spindles) during mitosis [23]. Increase of GMNN levels from G1 to G2 inhibit re-licensing in G2 phase thereby controls the licensing process spatiotemporally [9]. Replication licensing control has been subjected to chromatin accessibility to MCM proteins (by histone acetylation). The process is regulated by Cdt1-HBO1 and GMNN -HDAC11 interactions in G1 and S-phase of the cell cycle respectively [24].

Dihydrofolate reductase (DHFR) reduces dihydrofolic acid to tetrahydrofolic acid using NADPH as electron donor which in turn generates different tetrahydrofolate cofactors used for one carbon transfer in biological reactions including DNA synthesis. DHFR gene amplification is actively inhibited by GMNN and p53 thus maintaining the integrity of genome. Depletion of GMNN may cause excess replication resulting in giant nuclei formation consisting of either wild type or mutant p53 [25]. In blood vessels, vascular smooth muscle (VSM) lies between endothelial and fibroblast cell layers. Contraction and relaxation of VSM alters the blood vessel volume and local blood pressure, which upholds the redistribution of blood in the body, Excessive vasoconstriction/vasodilation may lead to high/low blood pressure condition. In VSM cell, GMNN expression is increased as the cell cycle progresses and further decreased with S/G2/M phase of cell cycle exit [26]. Angiotensin II and norepinephrine upregulates the GMNN expression in VSM cells. It is also established that inhibition of GMNN expression could increase Cdk1 expression, which in turn stimulates VSM cell

Table 1
Association of Geminin with other proteins and their functions.

Geminin associated protein	General function of Geminin associated protein	Geminin associated function	References
Hox DNA binding protein			
Involved in pattern formation in developmental process via regulating cell aggregation and proliferation			
HOXD13, HOXD11, HOXA13	Binds to replication origin, interacts with Cdc6 and promote pre-replication complex formation	Geminin interact with HOXD13, blocks Pre-replication leading to inhibition of replication	[60]
HOXb4	Located on 3′ HOX gene enhance hematopoietic stem cell proliferation	Degradation of Geminin by activating E_3 ubiquitin ligase mediated ubiquitination	[61]
HOXa9	Located on 3′ HOX gene enhances hematopoiesis and leukemogenesis	Induces ubiquitination of Geminin and enhance hematopoietic progenitors activity	[61]
Polycomb-gp (PcG) complex 1			
Silence transcription by E_3 ubiquitin ligase mediated ubiquitination of H2A			
Scmh1	Forms complex with Polycomb group (PcG) multiprotein complexes required to maintain the transcriptionally repressive state of some genes	Acts as sub-stoichiometric component of PcG complex 1 to provide an interaction domain for Geminin	[63]
HBO1	H4 specific histone acetylase required for licensing process	Geminin inhibit the formation of Cdt1-HBO1 complex formation by inhibiting HBO1 acetylase activity	[64]
Brm	It is a SWI/SNF related chromatin remodeling complex required for maintenance of gene expression steps	Geminin antagonize the Brahma chromatin remodeling protein Brahma related gene 1 (Brg1)	[65]
Idas	Involved in cell cycle progression and play role during developmental process	Coiled-coil mediated interaction with Idas, changes Geminin subcellular localization	[66]
Aurora A	A kinase involved in cell cycle proteins phosphorylation	Phosphorylates Geminin on Thr25 during M phase and induces Geminin stabilization	[67]
TIPT	Links transcription to chromatin remodeling	Interacts with Geminin and activates TATA Box containing promoter	[68]
Tcf	Downstream DNA-binding transcription factors known to regulate Wnt signal mediated target gene expression	Binds with 5′ sequence domain of Geminin and involved in Wnt signaling mediated neural specific gene expression during gastrulation	[69]

HOX=Homeotic genes, HBO1=Histone acetyltransferase binding to origin recognition complex 1, Brm = Brahma, TIPT = TATA box-binding protein related factor 2 interacting protein in testis, Tcf = T cell factor proteins.

proliferation [27]. Thus, GMNN plays a crucial role in vascular diseases. Similarly GMNN also plays a prominent role in proliferation of fetal hematopoietic stem cells, thymocytes and mature T cells, erythrocytes and megakaryocytes [13] [28,29]. A study revealed that GMNN destruction leads to disorganization of hematopoietic lineages and cause anemia and thrombocytosis [30]. By virtue of inhibition of Cdt1- GMNN complex formation (due to chromatin-bound GMNN), inhibition of centrosome duplication, facilitation of Topo IIα activity (required for the termination of DNA replication) GMNN is known to be actively involved in the maintenance of proper cytokinesis [31,32].

3. Geminin translocation and phosphorylation

Nuclear localization sequence of GMNN has been initially discovered in *Xenopus* sp. N-terminal sequences of GMNN constitutes destruction box while sequences of the central domain are accountable for nuclear expunction and accumulation. Destruction box sequences play a role in the nuclear expunction of GMNN. Nuclear accretion of GMNN helps information of licensing system and suppression of Cdt1-induced re-replication [33]. Cdt1 also has a role in subcellular localization of GMNN as upregulation of the protein directs GMNN towards the nucleus while diminished expression maintains GMNN in the cytoplasm [34]. GMNN shuttling from nucleus to cytoplasm and vice-versa regulates its functions during the cell cycle. It is imported into the nuclei during S phase and later exported (by Crm1 exportin protein) from nuclei at the end of mitosis. Unavailability of Crm1 in the nucleus during the subsequent G1 phase of cell cycle is responsible for proper MCM loading onto chromatin leading to transcription of target gene. GMNN acts as a substrate for various protein kinases such as protein kinase II and Casein kinase II [35]. Phosphorylation of GMNN by protein kinase II is essential in the proceedings during S phase. Post S phase, re-replication of the DNA is inhibited by cyclin-dependent kinase-mediated phosphorylation of CDC6 and ORC. Tetrabromobenzotriazole (TBB), an inhibitor of CK2 is known to interact with the C-terminal region of GMNN thereby blocking its phosphorylation. In spite of this, TBB does not affect the binding ability of GMNN to Cdt1 [35].

4. Inhibitors of Geminin-Cdt1 interaction

Hyperfunctioning of Cdt1 is a result of Cdt1- GMNN imbalance. For eg., GMNN silencing with siRNA induces DNA re-replication and eventual cell death in few cancer-derived cell lines. It is found that CoQ, polyunsaturated fatty acids (linoleic and oleic acid) and sulfoquinovosyl-diacylglycerol (SQDG) could inhibit the Cdt1-GMNN interactions [36–38]. Yoshida et al. identified a small peptide that binds to the 31–111 amino acid stretch of GMNN and inhibit the Cdt1- GMNN interaction [39]. Thus, inhibitors that can disrupt Cdt1- GMNN interaction has potential to be developed as anticancer agents. Mechanistically, Cdt1 is either destined to load MCM proteins on DNA or bind to GMNN. Studies demonstrated that Cdt1 can bind to both GMNN and MCM proteins at the same time [38]. Mizushina and coworkers identified that Arg243 and Arg342 residues of Cdt1 is involved in the hydrogen bond formation with CoQ and polyunsaturated fatty acid respectively [36,37]. Salabat et al. investigated the effect of apigenin (flavonoid) on pancreatic cancer cell proliferation *in vitro* [40]. The microarray analysis data of this study depicted the down regulation of GMNN in apigenin-treated pancreatic cancer cells. Apigenin inhibited GMNN promoter activity and down regulated the gene at both transcriptional and translational levels. The effect of this flavonoid (Apigenin) on the expression of Cdc6, Cdt1, and MCM7 was monitored in cell lines. These data indicates that GMNN is regulated by natural products.

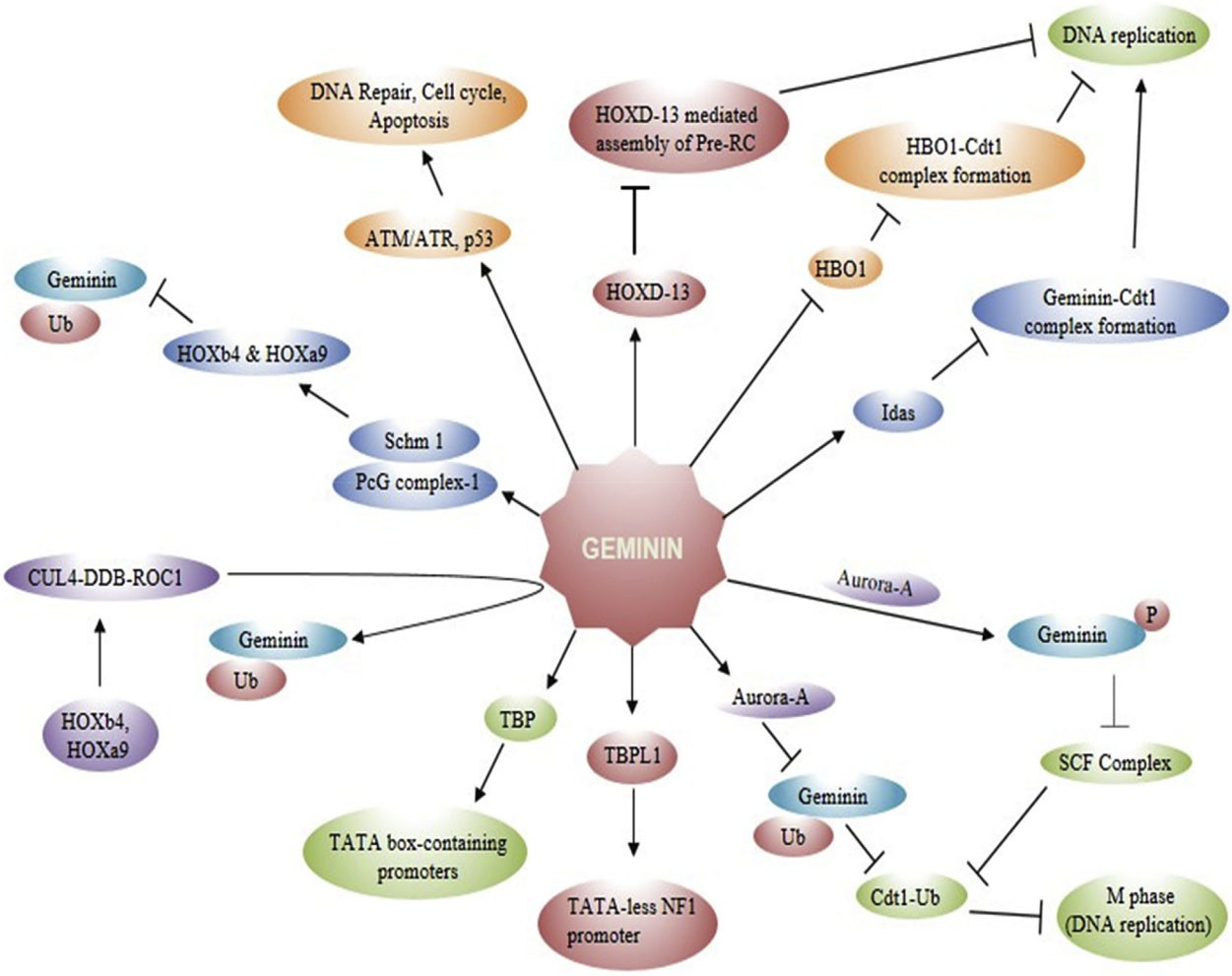

Fig. 4. Outcome of interaction of Geminin with other proteins.

5. Fate of Geminin during development

Developmental begins with the fertilization of egg followed by cleavage, blastulation, gastrulation, organogenesis, and axis formation. Kroll et al. first showed that GMNN is an important regulator of neural development [41]. Several studies followed which demonstrated the role GMNN in the development (Fig. 3). GMNN supports cell cycle progression (S and M phase) during preimplantation stage *in vivo* [42]. It also has a role in blastula to gastrula transition (formation of three germ layers). Studies on various animal models including *Danio rerio*, *C. elegans* and *Xenopus* embryos demonstrated the upregulation of GMNN during germ line development. The mechanism involves the inhibition of Cdt1 and MCM6 proteins; provides licensing activity for DNA replication; cell commitment confirmation; cell fate specification and germ layer restriction to specific location. Geminin is also required to maintain genome integrity during mid blastula transition [43–45]. At the onset of gastrulation, GMNN demarcates the future neural plate [41]. GMNN is convoluted in the induction of neural progenitor formation at the expense of non-neural ectodermal derivatives [46]. Yellajoshyula et al. suggested that GMNN is actively involved in epithelial to mesenchymal transition (EMT), which is mandatory prerequisite during gastrulation, neural crest formation, anterior-posterior axis formation and patterning sequences. It also maintains hyperacetylation of chromatin at neural genes that leads to neural fate acquisition of embryonic stem cells [47]. Stringent control of cell proliferation and differentiation is required during organogenesis in vertebrates. Role of GMNN along with Six 3 transcription factor is reported in cell proliferation Geminin and Six 3 proteins function in tandem. Increase or decrease of either of these proteins can lead to developmental abnormalities such as expanded optic vesicles via abnormal retinal precursor-cell proliferation, forebrain and eye defects [48–50]. Besides cell proliferation, GMNN's involvement in ciliogenesis, setting up heart and visceral laterality and proper Kupffer's vesicle formation is reported in model organisms [51].

6. Association of Geminin with other proteins

Interaction of GMNN with various proteins is listed in Table 1. DNA double strand breaks, activates and recruits ATM and ATR (Ataxia telangiectasia mutated/ataxia telangiectasia and Rad3-related protein) serine/threonine protein kinases at the point of damage. These kinases phosphorylate several key proteins involved in the activation of DNA damage checkpoints leading to the activation of DNA repair, cell cycle arrest and apoptosis. Saxena et al. demonstrated that ATM/ATR kinase and tumor suppressor protein, p53 are activated by GMNN or cdt1 imbalance (Fig. 4) [59]. The interaction of GMNN with Hox protein is elucidated in detail. Hox proteins are involved in head-tail axis formation and segmentation.

Table 2
Association of labeling and proliferation index of Geminin with aggressiveness of different cancer.

Cancer type	Aggressiveness strategies	Geminin (PIs or LIs)	Interpretation	References
NB	Proliferation Index (PI) among low and sever neuroblastomas patients with unfavorable clinical, biological, and pathological factors was measured.	Median PI was 16.8% high in sever neuroblastomas sample	Expression increases with severity of cancer and may involve in aggressiveness of the disease.	[77]
SCC				
Oral squamous cells	NOE < LD < OSCC	6.8% < 9.2%<32.2%	Expression increased with aggressiveness of cancer	[78]
Head & neck	Precise local (T)<Regional nodal (N)<Distant (M) stage	–	Expression was not associated with aggressiveness of cancer	[79]
Oral mucosa, OED and their corresponding	NOM < OED < OSCC	Increased from normal to cancer stage	Expression increased with aggressiveness of cancer	[80]
Cell carcinoma of penis	Less to high aggressive stage	Geminin LIs increased with other proteins such asKi-67 and MCM2	Expression was not independently associated with aggressiveness of cancer	[81]
SGT	LIs in different types of salivary gland tumors such asACC, CEPA, MEC, PLGA, PA, AcCC and SDC was studies	Low LI_s –AcCC(mean 1.55%) & MEC (mean 2.43%) Intermediate LI_s -ACC (mean 4.09%) High LI_s in SDC (mean 15.22%).	Expression may differentiate the prognosis of different salivary gland tumors	[82,83]
BC	LIs studied in breast cancer-specific survival (BCSS) and disease-free survival (DFS)	Geminin LI was high in BCSS in comparison to DFS	Geminin expression may be used as predictor of adverse outcome in breast cancer patients.	[84]
	LIs studied in Ki-67 low and high subset of ER positive &HER2negative breast cancers	LI was low in low Ki-67 (about 93%) and about 60% high in Ki-67 high subset	Geminin may be useful tool to identify patients of Ki-67-high subset that can be avoiding unnecessary chemotherapy.	[85]
	LIs were studied in NBC and MBC	LI was significantly different in NBC and MBC samples	Geminin may be useful tool to identify breast cancer aggressiveness.	[86,87]
CC	Stage I, II and III	LI was high in stage II and III	Geminin assessment may give predictive prognosis in colorectal cancer patients	[88]
MM	IMM &LGMFS	Not significant difference in expression pattern	Geminin cannot be used to differentiate IMM and LGMFS	[75]
RMC & MMC	LIs compared in RMC and MMC	LI_s RMC < LI_s MMC	Geminin assessment may be used to differentiate RMC and MMC	[89]
GHPPA & IC	LIs assessed from Stage I to IV	LI_s increased from Stage I to IV	Geminin may be associated with overall survival in gastric cancer.	[90]

NB=Neuroblastoma, PI=Proliferation index, LI = Labeling index, SCC = squamous cell carcinoma, NOE=Normal oral epithelia, LD = lesions with dysplasia, OSCC = oral squamous cell carcinomas, NOM=Normal oral mucosa, OED=Oral epithelial dysplasia, GMNN = Geminin, MCM2 = Minichromosome maintenance protein, SGT=Salivary gland tumors, ACC = Adenoid cystic carcinomas, CEPA=Carcinoma expleomorphic adenomas, MEC = Mucoepidermoid carcinomas, PLGA=Polymorphous low-grade adenocarcinomas, PA=Pleomorphic adenomas, AcCC=Acinic cell carcinomas, SDC = salivary duct carcinoma, BC=Breast cancer, ER = Estrogen receptor, HER2 = Human epidermal growth factor receptor 2, NBC=Normal breast cancer, MBC = Malignant breast cancer,CC=Colorectal cancer, MM: Myxofibrosarcoma and myxoma, IMM=Intramuscular myxoma, LGMFS = Low-grade myxofibrosarcoma, RMC & MMC = Reactive mesothelial cells & malignant mesothelioma cells, GHPPA & IC=Gastric hyperplastic polyps, adenomas& intestinal type carcinomas.
Proliferation index: Measurement of number of cells in any tumors that are dividing.
Labeling index: Mitotic activity measurement of a cell population is defined as the number of cells in the S phase of the cell cycle divided by the total cells in the population. The index measures the rate of the reproduction of the cells as in fetal tissue development or the growth of tumors.

HOXD13, HOXD11 and HOXA13 are known as HOX DNA-binding proteins. HOXD13 is implicated in the formation of pre-replicative complex at OR. GMNN interacts with HOXD13 and inhibits the HOXD13-mediated assembly of pre-replicative complex there by preventing the HOXD13-induced DNA replication [60]. Hox genes such as Hoxb4 and Hoxa9 are known to enhance hematopoietic stem cell (HSC) activity. CUL4A binds with DNA damage binding protein-1 (DDB1), which in turn allows the binding of ubiquitin ligase complex and ROC1 at its N and C-terminus respectively. Further, CUL4-DDB-ROC1 complex weakens the histone-DNA interaction by histone ubiquitination and facilitates the transcription of developmental genes, Studies revealed that Hoxb4 and Hoxa9 forms a complex with the CUL4A-DDB1-ROC1 and induces the ubiquitination of GMNN [61–62]. GMNN inhibits the licensing of HOX-mediated replication origin [60]. Polycomp-group (PcG) complex 1 silences histone H2A mediated transcription and regulates GMNN stability by its E3 ubiquitin ligase activity. GMNN interacts with PcG complex 1 via its Scmh1 interactive domain. Yasunaga et al. observed that deficit of Schm1 restores the GMNN dysregulation by derepressing Hoxb4 and Hoxa9 (Fig. 4) [63].

In general, acetylation of histones (H1/H5, H2A, H2B, H3 and H4) by histone acetyltransferases unwraps the DNA and thereby increase gene expression. HBO1 (histone acetyltransferase binding to ORC 1) is a H4-specific histone acetylase which acts as co-activator of the Cdt1. Thus, it is essential for DNA replication licensing and is inhibited by GMNN [24]. Idas, a coiled-coil protein is localized into the nucleus (by C-terminal nuclear localization signal) wherein it interacts with GMNN. This interaction inhibits GMNN binding to Cdt1 and thereby block the DNA replication [66,70]. GMNN destruction box/nuclear localization signal tagged to Azami Green (AG, a fusion protein) acts as a fluorescent probe which is used to visualize G2 arrest in ionizing radiation induced living cells [71]. TBP (TATA-box binding proteins) and TBPL1 (TATA box-binding protein-like protein1) that specifically binds to TATA box are known to interact with GMNN leading to the activation of TATA box-containing promoters and TATA-less NF1 promoter respectively (Fig. 4). GMNN also interacts with TIPT2, an isoform of TATA-binding protein-like factor-interacting protein (TIPT) [68]. Human genome contains Aurora A, B and C kinases, localized in the centrosome during mitosis. Aurora-A phosphorylates GMNN

Table 3
Expression profile of Geminin and other related proteins in different types of cancer.

Cancer type	Gene involved	↑	↓	Interpretation	References
NB	GMNN	↑	–	A higher-than-median AURKB and Geminin Proliferative Index (PI) was	[77]
	AURKB	↑	–	associated with unfavorable clinical (high-risk group, advance stage and abdominal sites), biological (MYCN amplification, 1p deletion and 17q gain) and pathological factors (undifferentiated status, high mitosis karyorrhexis index, unfavorable histology) in patients. AURKB and Geminin PIs were also correlated with shorter overall survival of patients.	
SCC					
Oral	GMNN	↑	–	Geminin overcomes; MCM7 mediated low survival of patients at stage	[78]
	MCM 7	↑	–	III-IV.	
Head & neck	GMNN	↑	–	Connexin 43 (one of the six connexin proteins composing connexon-hemichannels of gap junction) did not show any correlation with Geminin (cell cycle regulation related biomarker) expression.	[79]
	Cx 43	↑	–		
Oral mucosa, OED and their corresponding	GMNN	↑	–	MCM2, GMNN and Ki-67 expression increased progressively from NOM,	[80]
	MCM2	↑	–	OED to OSCC. Higher expression of GMNN in OED indicated a constant	
	Ki-67	↑	–	cell cycle re-entry and predicted as novel biomarker of growth and prognostic tool for OED.	
SCCP	GMNN	↑	–	Geminin, MCM2 and Ki-67 shown to be mutual dependent prognostic	[81]
	MCM 2	↑	–	biomarkers in surgically treated SCCP. They displayed positive	
	Ki-67	↑	–	correlation with histological tumor grade, lympho-vascular invasion and nodal status in SCCP.	
SGT	GMNN	↑	–	Geminin significantly correlated with Ki-67 labelling index and	[83]
	Ki-67	↑	–	histopathological factors (pathological T factors, lymphatic and blood vessel infiltration and lymph node metastasis). Study revealed that GMNN is a significant and independent prognostic marker for patient survival and tumor relapse.	
BC	GMNN	↑	–	Regarding breast cancer, most of the Geminin associated studies were	[84–87,91,92,100]
	MCM 2	↑	–	focused on its prognostic ability.	
	Ki-67	↑	–	Beside that study revealed that Geminin overexpression promotes the	
	AURKA	↑	–	imatinib sensitization in triple negative breast cancer tumor.	
	CD133	↑	–	Geminin expression has been positively correlated with Ki-67, ER-negativity, nuclear grade, distant metastases development, breast cancer specific survival and disease free survival. Geminin with Ki-67 expression has been reported to increase in metastatic breast carcinomas. Some of the proteins such as CD133 expression have been found significantly associated with high Geminin level in triple negative breast cancer.	
	Cyclin A	↑	–		
	c-Abl	↑	–		
CC	GMNN	↑	–	Study showed that these proteins including Geminin expression may be	[88]
	MCM 7	↑	–	used as prognostic marker in colorectal cancer patients.	
	Ki-67	↑	–		
RMC & MMC	GMNN	↑	–	Labeling Index of GMNN including other proteins may serve as	[89]
	MCM 7	↑	–	differential diagnostic markers of reactive mesothelial cells and	
	Ki-67	↑	–	malignant mesothelioma.	
	Topo II α	↑	–		
SLA	GMNN	↑	–	Geminin has been reported overexpressed in small lung	[93]
	MCM 7	↑	–	adenocarcinomas. Like Ki-67 and MCM7, GMNN may also be used as	
	Ki-67	↑	–	independent prognostic biomarker in small lung adenocarcinomas patients. Geminin Labeling index was found to be associated with gender, histological grade, subtypes, N-status, p-factor and tumor stage in lung cancer adenocarcinomas.	
STS	GMNN	↑	–	Study revealed the correlation of Geminin expression with histological	[103]
	MCM 7	↑	–	grade of soft tissue sarcoma. Geminin and MCM7 may be used as prognosis markers for patients with STS.	
LMT & MTLA	GMNN	↑	–	In this study several gene expression including Geminin, were studied	[104]
	S100A4	↑	–	to differentiate between micro and macro-metastatic tumors of lung	
	ALDH 1	↑	–	adenocarcinoma.	
	E-cadherin	↑	–	Geminin expression was not found to be significantly different among	
	SMA	↑	–	micro and macro-metastatic lung adenocarcinoma tumor.	
	CD34	↑	–		
	CD204 stromal cell	↑	–		
MT	GMNN	↑	–	Study showed that Geminin overexpression promotes cytokinesis failure, production of aneuploidy leading to aggressiveness of breast tumors.	[98]
RCC	GMNN	↑	–	Study revealed that high expression of these proteins including Geminin	[95]
	MCM 2	↑	–	is associated with reduced disease-free survival time.	
	Ki-67	↑	–		
PC	GMNN	–	↓	Study showed the expression profile of several genes including Geminin	[96]
	MCM 2	↑	–	involved in the oncogenesis and progression of prostate cancer.	
	Ki-67	↑	–	Geminin was not found to be significantly expressed in androgen-sensitive and androgen-refractory prostate cancer samples.	
	β-catenin	–	–		
	P^{27}	–	–		

Table 3 (*continued*)

Cancer type	Gene involved	↑	↓	Interpretation	References
	p^{21}	–	–		
	p^{16}	–	–		
	MGDMT	–	–		
	AR	–	–		
	HIF1α	–	–		
ALC	GMNN mRNA	↑	–	Study explored the Geminin and Cdt1 expression levels in peripheral blood and bone marrow with newly diagnosed AL. Geminin level was found to significantly high in bone marrow of AL patients suggesting its role in pathogenesis of AL.	[97]
	Cdt1 mRNA	↑	–		
ABT	GMNN	↑	–	Increased expression of Geminin was found in high grade astrocytomas. Geminin overexpression was significantly correlated with survival in patients with high grade astrocytoma especially in early stage.	[94]
PPNET	GMNN	–	↓	Apigenin (a bioflavonoid) treatment decreased the expression of Geminin and Cdc6 in pancreatic cell lines. Study revealed anticancer property of apigenin by modulating Geminin and other study gene expression in pancreatic cancer cell lines.	[40,101]
	MCM7	–	↓		
	Cdt1	–	–		
	Cdc 6	–	–		
GHPPA & IC	GMNN	↑	–	Study revealed the Geminin could be a possible prognostic biomarker in advanced intestinal type gastric carcinomas.	[90]
	MCM 2	↑	–		
	Ki-67	↑	–		
ONM	GMNN	↑	–	Study indicates the involvement of Geminin in pathogenesis of oral melanomas. Geminin may also use as additional diagnostic tool to differentiate oral benign and malignant melanocytic lesions.	[76]
	MCM 2	↑	–		
	Ki-67	↑	–		

↑ = Upregulation, ↓ = Downregulation, NB=Neuroblastoma, AURKB = Aurora kinase B, SCC = squamous cell carcinoma, MCM7 = Minichromosome maintenance protein 7, Cx43 = Connexin 43, MCM2 = Minichromosome maintenance protein 2, OED=Oral epithelial dysplasia, OSCC=Oral squamous cell carcinomas, SCCP= Squamous cell carcinoma of penis, SGT=Salivary gland tumors, BC=Breast cancer, AURKA = Aurora kinase A, CD133 = Cluster of differentiation 133, c-Abl = Mammalian Abelson murine leukemia, CC=Colorectal cancer, RMC & MMC = Reactive mesothelial cells & malignant mesothelioma cells, Topo II α = Topoisomerase II alpha, SLA=Small lung adenocarcinomas, STS=Soft tissue sarcoma, LMT & MTLA = Lymph node micrometastatic tumors &micrometastatic tumors of lung adenocarcinoma, SMA=Smooth muscle actin, CD34 = Cluster of differentiation34, CD204 = Cluster of differentiation204, MT = Mammary tumors, RCC = Renal cell carcinoma, PC=Prostate cancer, MGDMT = Methyl guanine DNA methyltransferase, AR = Androgen receptor, HIF1α = Hypoxia inducible factor 1α, ALC = Acute leukemia cancer, Cdt1 = Chromatin licensing and replication factor 1, AL = Acute leukemia, ABT = Astrocytic brain tumors, PPNET=Pancreatic & Pancreatic neuroendocrine tumors, Cdc6 = Cell division cycle 6, GHPPA & IC=Gastric hyperplastic polyps, adenomas & intestinal type carcinomas, ONM=Oral nevi and melanoma.

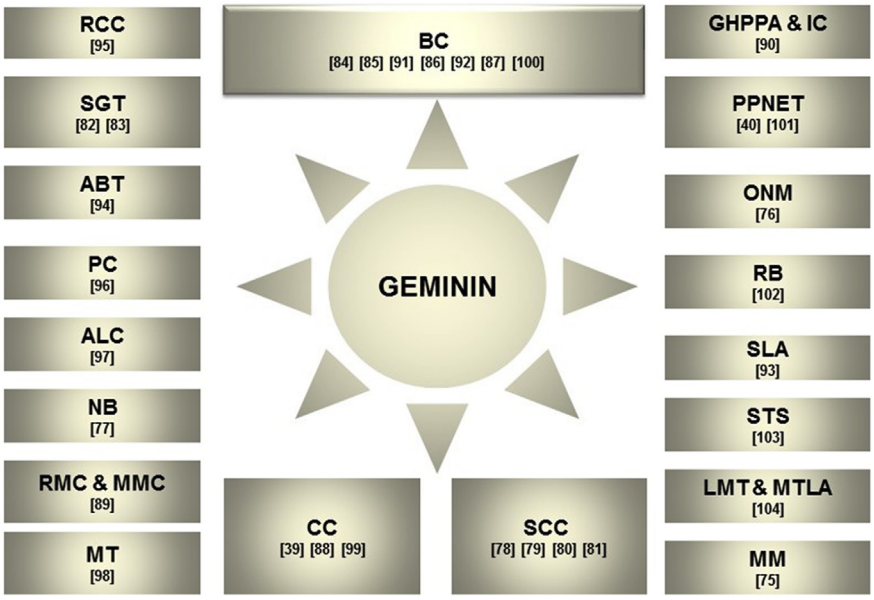

Fig. 5. Association of Geminin with different cancer. RCC = Renal cell carcinoma, SGT=Salivary gland tumors, ABT = Astrocytic brain tumors, PC=Prostate cancer, ALC = Acute leukemia cancer, NB=Neuroblastoma, RMC & MMC = Reactive mesothelial cells & malignant mesothelioma cells, MT = Mammary tumors, CC=Colorectal cancer, SCC = squamous cell carcinoma, BC=Breast cancer, GHPPA & IC=Gastric hyperplastic polyps, adenomas& intestinal type carcinomas, PPNET=Pancreatic & Pancreatic neuroendocrine tumors, ONM=Oral nevi and melanoma, RB = Retinoblastoma, SLA=Small lung adenocarcinomas, STS=Soft tissue sarcoma, LMT & MTLA = Lymph node micrometastatic tumors &micrometastatic tumors of lung adenocarcinoma, MM = Myxofibrosarcoma and myxoma [99].

(thr25) during mitosis which inhibits the APC/C mediated ubiquitination and stabilizes the GMNN. The stabilized GMNN interacts with Cdt1 and participates in the regulation of DNA replication. The GMNN also inhibits SCF complex (S-phase kinase-associated protein, Cullin and F-box)-mediated Cdt1 degradation that ensures the pre-replicative complex formation in the subsequent S phase [67].

7. Significance of Geminin in cancer

In normal cells, one time origin firing per cell cycle is regulated by Cdt1 and GMNN levels [72]. Any imbalance in Cdt1 and GMNN levels could cause replication defects and genomic instability which might lead to cancer. Significant GMNN levels were observed

in proliferating lymphocytes, hematopoietic stem cells, epithelial cells and leukemic stem cells [73]. siRNA suppression of GMNN can arrest cancer cell proliferation by the induction of DNA re-replication and DNA damage-mediated apoptosis without affecting the normal cells. Thus, inhibiting GMNN activity could selectively control the cancerous cell without affecting the normal cell [74]. Review of available literature suggested GMNN's involvement in diseases such as cancer, neuronal and renal dysfunction. The association of GMNN with apoptosis regulation (Bcl2, activated caspase-3, phospho- H2A.X, and cleaved PARP), cell cycle stage specific regulatory proteins (Rb1, Cyclin-A, CDKN1B, and Cdt1), cell proliferation markers (Ki-67, MCM2, phospho-histone H3, and GMNN), cell signaling molecules (c-Myc, EGF, EGFR, PLA2G4A, and HSP90), a dendritic cell marker (CD209), CD 34, CD133 and the extracellular matrix proteoglycan decorin was demonstrated [75]. The GMNN labeling index is associated with clinic-pathological profiles including gender, histological grade, subtypes, N-status, p-factor, and tumor stage (Table 2) [76].

Differential GMNN expression is associated with different types of cancer (Table 3). GMNN expression levels significantly associated with nuclear grade and poor prognosis in breast cancer patients [85]. Joshi et al. demonstrated that GMNN is a proliferation marker that is associated with high grade and ER-negativity in breast cancer [91]. Gonzalez et al. reported that GMNN is an independent indicator of adverse prognosis, poor overall survival and the development of distant metastases in invasive breast cancer [86]. Bonito et al. showed positive correlation of GMNN expression with CD133, Ki-67 & tumor grade and negative correlation with lymph node metastases. Statistical significance is attributed to the GMNN expression and survival of cancer patients [92]. In a different study, it is predicted that GMNN could be a valuable marker for estimation of tumor aggressiveness and clinical outcome in salivary gland carcinomas. GMNN is indicated be a possible prognostic marker in advanced intestinal-type gastric carcinomas, soft tissue sarcomas and small lung adenocarcinoma [90,93]. Kimura et al. suggested that GMNN with of MCM 7 and topo IIα labeling index could be a reliable tool for the differential diagnosis of reactive mesothelial cells and malignant meso-thelioma cells [89]. In another study, high GMNN LI is shown as predictive factor of outcome in patients with high-grade astrocytomas [94]. The role of GMNN in breast, colorectal and squamous cell carcinomas is fastly emerging (Fig. 5).

As GMNN's role is implicated in various cancers, obviously studies were carried out to study the effect of drugs/phytoconstituents on its expression. In this regard, the effect of apigenin on pancreatic cancer cell lines reported downregulation of the GMNN expression [40]. In another study, treatment with Imatinib/nilotonib revealed upregulation of GMNN in triple negative breast cancer patients [100]. Yoshida et al. explored the possibility of GMNN as a molecular target in the development of novel anticancer drugs [105]. It is shown that GMNN/Ki-67 ratio can determine the relative length of G1 phase. A high ratio indicates a short G1 phase and a high rate of cell proliferation. Markey et al. revealed the link between GMNN expression and RB/E2F pathway and represented the first promoter analysis of GMNN [102]. Blanchard et al. showed that upregulated GMNN acts as an oncogene that promotes cytokinesis failure and production of aneuploids and aggressive breast tumors and thus a worthful therapeutic target (oncotarget) for aggressive breast cancer [98]. Taken together, GMNN can act as a novel biomarker of growth and be a valuable prognostic tool for cancer [80].

8. Geminin and viruses

Replication of virus in host cell involves multiplication of the viral genome. The virus utilizes the host cell machinery and metabolic processes according to their need and either suppress or enhance the various host cell mechanisms which may eventually lead to formation of tumors. Viruses that possess the ability to cause cancer are known as oncoviruses such as human herpes virus 4 (HHV4)/Epstein Barr virus (EBV). HHV4 is often associated with gastric, nasopharyngeal cancer, Hodgkin's and Burkett's lymphoma. Studies revealed that GMNN accumulation in virus infected host cell inhibits the process of DNA replication and thereby dysregulate the host cell cycle. This might be due to defective pre-replication complex formation by virtue of decreased Cdt1, increased Cdc6 and MCM family protein levels [14]. GMNN is also inhibits the viral plasmid replication by inhibiting their origin of replication (oriP) [106]. Hepatitis B virus is another oncovirus which is, implicated in hepatocellular carcinoma by Hepatitis B virus X protein (pX). Rakotomalala et al. observed that the pX is involved in GMNN suppression and increased expression of Cdc6 and Cdt1, which in turn promotes DNA re-replication in hepatic cells [107].

9. Conclusion

From zygote to fully development of an organism cell division have its own importance. Further studies on GMNN in developmental model organisms may unprevail new aspects of the developmental process. Literature revealed that GMNN is involved in ATM/ATR and p53 mediated DNA repair, Cell cycle and apoptosis processes. Beside these it has been also involved in the transcription of TATA box containing promoters. Targeting GMNN, there may be chance to regulate oncogenes, tumor suppressor genes having TATA box containing promoters. Studies are needed to explore GMNN-protein interaction mediated regulation of DNA replication, repair and cell cycle progression. GMNN differential expression has been found to associate with variety of cancer and other diseases. It is suggested to execute the study based on role of GMNN mutation in different cancer. Over all the review indicates that there is an urgent need to study this protein in much more depth that may reveal the clear cut diagnostic and prognostic potential of GMNN.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

PPK acknowledges financial support from University Grants Commission, India in the form of CSIR-UGC Junior Research fellowship. SK acknowledges Central University of Punjab, Bathinda for providing necessary infrastructure facility and financial support in the form of Research Seed Money Grant [GP: 25].

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