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Review Article

Nuclear envelope defects in epithelial ovarian cancer

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Abstract: Nuclear morphology is a universal indicator of neoplastic cells, and is often used to diagnose cancer and assess the degree of malignancy. Although an association between a misshapen nucleus and cancer has been well established, the causes and consequences of a defective nuclear envelope in cancer are just starting to be revealed. Focusing on ovarian epithelial cancer, this article reviews the recent progress and discusses the critical roles and postulated mechanisms for nuclear envelope defects in ovarian cancer initiation and progression. Recent findings indicate that nuclear envelope proteins including lamin A/C, emerin, nesprins, and nuclear pore complex (NPC) proteins, are frequently altered in their expression or cellular localization in ovarian cancer. Loss of expression of the nuclear envelope structural proteins accounts for the nuclear morphological deformation of the ovarian cancer cells. Alterations of the nuclear envelope proteins impact regulation of gene expression, modulate signaling pathways, and induce chromosomal numerical instability. The ongoing discoveries have begun to reveal underlying mechanisms linking nuclear envelope defects to nuclear morphological deformation and aneuploidy, two prominent hallmarks of ovarian cancer.

Keywords: Nuclear envelope, lamina, nuclear pore complex, lamin A/C, aneuploidy, polyploidy, chromosomal instability, ovarian cancer, carcinomas

Ovarian cancer and nuclear envelope

Although nuclear deformation is a hallmark of malignancy and is often used as a diagnostic marker, the molecular basis of the nuclear changes is unclear, and the consequences of nuclear deformation have not been established. In this article we review recent studies of cancer cells related to components of the nuclear envelope, and make the link between nuclear deformation and aneuploidy. In particular, we focus our discussion on epithelial ovarian cancer.

Hallmarks of ovarian cancer: nuclear shape deformation and aneuploidy

Epithelial ovarian cancer has long been thought to originate from inclusions cysts or deep invaginations derived from ovarian surface epithelium [1-5], though another idea has been proposed that ovarian cancer is derived from the remains of the mullerian ducts (such as the rete ovarii) [6, 7]. However, recent strong evidence indicates a large portion of the cancer is derived from fallopian tube fimbria [8, 9]. Likely ovarian cancer has duel origins, both the surface and fallopian tube fimbria [10]. Germline mutation of BRCA1 and BRCA2 increases ovarian cancer risk [11-13]. Recently, the Cancer Atlas project [14] determined that p53 is the only common genetic mutation found in high-grade serous epithelial ovarian cancer (96%), the most common histological subtype [15-17]. However, inactivation of p53 in ovarian epithelial cells in mouse models has not demonstrated a clear path for epithelial tumorigenesis [11, 18], even in aged mice following transplantation of p53 mutant ovaries [19]. Thus, the etiology and mechanism of epithelial ovarian cancer is not yet understood.

The “roundness” of the nucleus is a good indicator to distinguish between benign and malignant cells [20-22]. An enlarged nuclear size also represents a very useful and reasonably faithful predictor of the degree of malignancy and prognosis of ovarian cancer [23]. In gener-

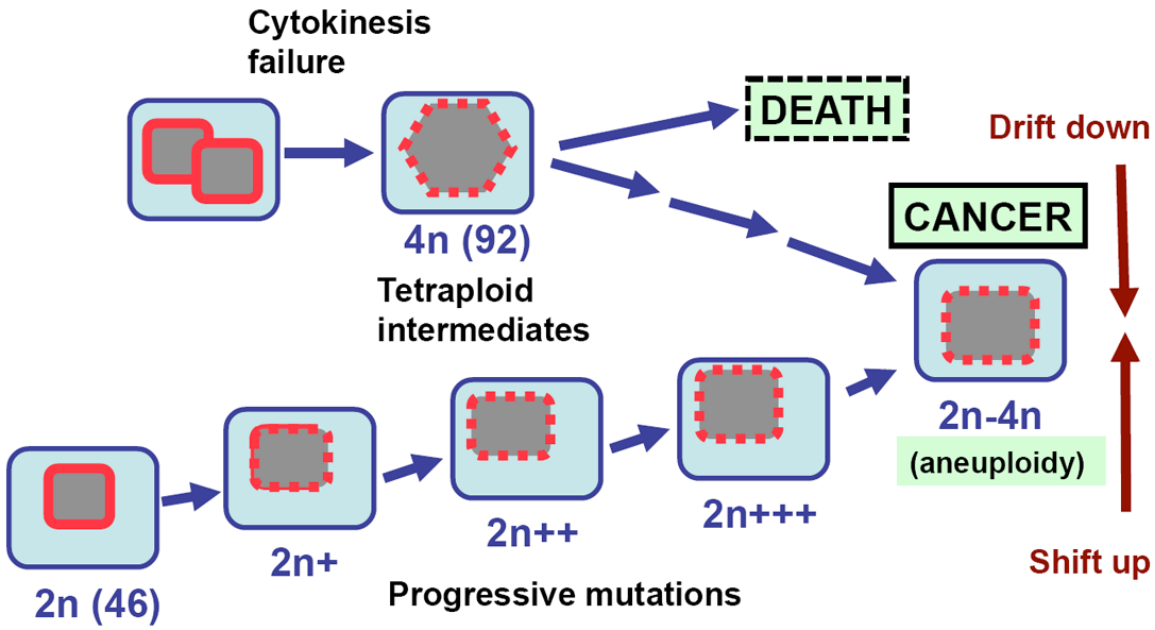

Figure 1. Illustration of the development of aneuploidy in cancer development. Human cancer cells often contain a hyperdiploid to hypotetraploid chromosome number. Two possible routes, a progressive "shift up" pathway and a tetraploid intermediate and "drift down" pathway, may convert a diploid normal cell to an aneuploid cancer cell. Cells with the optimal chromosome composition may be selected and become neoplastic. Thus, aneuploidy, or chromosomal numerical instability, is thought to contribute to rapid genomic selection and cancer development.

al, enlarged and deformed nuclei are characteristics of cancer cells, and the aberrant nuclear morphology correlates with malignancy and is a diagnostic and prognostic indicator, referred to as "nuclear grade" [24]. Oncologists and cancer biologists have an intense interest to understand the molecular basis for such a remarkable predictor of cancer, and in the last five decades, many have sought to decipher the secret behind the deformed and enlarged nucleus of cancer cells. Changes in nuclear matrix and/or nuclear envelope have been postulated, and deformation of nuclear morphology was shown to associate with oncogenic signaling [25-28], but no definite conclusions have been established regarding the molecular basis of nuclear deformation in malignant cells [24, 29].

In the clinical setting, the morphology of the nucleus is used universally for diagnostic and prognostic prediction of malignancies of tumor cells [24]. The best-known diagnostic test based on nuclear morphology is the PAP Smear/PAP test. Few persons in the history of cancer prediction and diagnosis have achieved as much as George Papanicolaou, the inventor of the cervical PAP smear [30]. Based on the nuclear morphology of cells sampled, the PAP test (or PAP smear) is able to make diagnosis and prognostic prediction of the degree of malignancy of uterine and cervical cancers [30]. Invented by Dr. Papanicolaou in the 1930s, widely implemented by the 1960s, and still universally practiced worldwide today, the simple procedure is credited for saving millions of lives. The PAP test can also be used to predict and diagnose other cancers when potential tumor cells can be obtained. In general, no or few markers can be used to distinguish a benign from a malignant cell.

Another hallmark of cancer cells, first recognized over one hundred years ago by Boveri [31, 32], is aneuploidy, or an abnormal and unbalanced number of chromosomes compared to normal cells. The majority of human ovarian cancer cells are aneuploid and possess a hyperdiploid (>46) to subtetraploid (<96) chromosome number [28, 33]. The increasing number of chromosomes over normal cells accounts for the larger nuclear size in cancer. Additionally, within one tumor or cell line, the cancer cells vary in chromosomal number, indicating the presence of a chromosomal numerical instability phenotype. Although a correlation has been recognized between aneuploidy

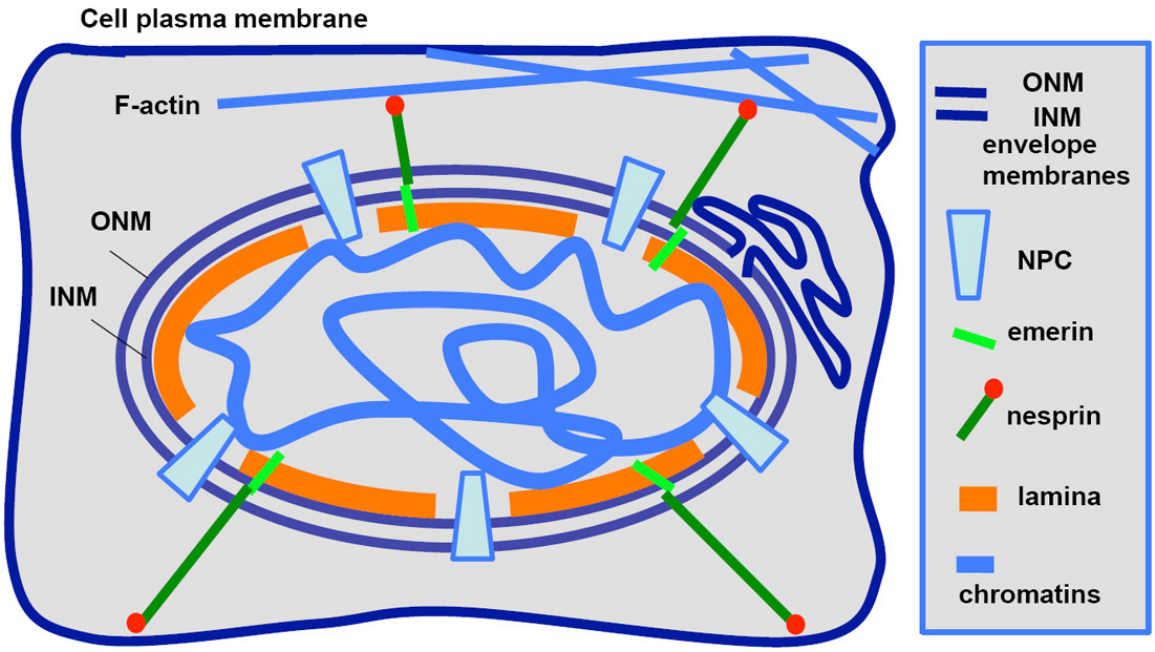

Figure 2. Nuclear envelope structure and key components. In mammalian cells, the genetic materials are housed in nuclei that are enveloped by a double membrane, an inner (INM) and outer (ONM) shell. The nuclear envelope structure is supported by a layer of nuclear lamina, which is composed of structural protein lamins (lamin A/C, lamin B1 and B2). Nuclear lamina associate with chromatins and control gene expression. Nuclear pore complexes (NPC) are channels distributed on the surface of the nuclear envelope and regulate the import and export of RNAs, proteins, and other small (signaling) molecules. The transmembrane protein emerin functions in attaching the nuclear lamina to the inner lipid membrane. Nesprins and SUN proteins form bridges crossing the inner and outer nuclear membrane. One end of nesprin also binds actin and microtubular fibers and tethers the nucleus to the cytoskeletal networks.

and malignancy, the causes and significance of aneuploidy in cancer are debated and remain unsettled [32, 34-39]. Several mechanisms have been noted for the origination of aneuploidy [40-44]. Among these, consequence of mitotic failure accounts for the majority of cases [35, 45]. Tetraploid cells are believed to form following mitotic failure, and aneuploid cells are produced in subsequent mitotic events [35, 45] (**Figure 1**). In vitro, cultured cells can be transformed to tumorigenic cells by mutations and deletion of individual oncogenes and tumor suppressor genes without the need for chromosomal instability [46], and animal tumor models based on engineered oncogenic mutations often develop tumors of normal ploidy [47]. The commonly accepted doctrine, the progressive mutation model, does not account for the prevalence of aneuploidy in human cancer [48-50]. Nevertheless, the common occurrence in human cancer cells suggests an important role of aneuploidy in the development of human cancer. It was reported that drug-induced cytokinesis failure generates tetraploids that promote tumorigenesis in p53-null mammary epithelial cells [51]. However, direct evidence for a role of aneuploidy in cancer is still not abundant. One unique view is that chromosome instability and aneuploidy may provide an unbalanced global expression profile of increases and decreases in gene dosages that create the cancer cell properties [36]. In non-cancerous cells, aneuploidy is detrimental to development and causes growth impairment [52-54]. A generally accepted idea is that chromosome numerical instability and thus aneuploidy promotes the accelerated loss and gain of specific tumor suppressor genes and oncogenes, respectively, leading to selection of mutant cells with a growth advantage and subsequent malignant transformation [38, 54, 55]. In either case, aneuploidy likely plays important roles in cancer initiation and progression.

General nuclear envelope biology

Eukaryotic cells store their genome in the nucleus, an oval to round organelle surrounded by a double lipid membrane shell, located prominently within or near the center of the

cytoplasm [56]. The structural components of the nuclear envelope have been progressively identified and studied in the last several decades [57, 58], and about 80 unique nuclear envelope-associated proteins have been identified in mammalian cells [59]. The knowledge about nuclear envelope structural proteins has been expanded rapidly in the last decade because of the finding of gene mutations associated with human diseases, such as muscular dystrophy and progeria [60-62]. So far, only several key components have been linked to cancer [63].

The many aspects of the biological functions of the nuclear envelope have been revealed from the investigations of mechanisms in causing muscular dystrophy and progeria. Studies of model organisms also have provided abundant mechanistic insights. The lamina of the nuclear envelope has a role in modulation of gene expression by its association with chromatin and sequestering transcription factors and signal transduction proteins. The nuclear pore complex (NPC) can also control the traffic of signaling proteins in and out of the nucleus and export of mRNA into the cytoplasm. These roles may account for a range of biological functions and associated pathology. Roles in mitosis and a defective nuclear envelope also contribute to chromosomal and genetic instability, and related diseases.

Major nuclear envelope components and nuclear morphology: The structural features of the nuclear envelope are conserved throughout diverse organisms (**Figure 2**). The most prominent nuclear envelope proteins make up the nuclear lamina that lines the inner nuclear membrane, and which consists of intermediate filament proteins, lamin A/C, lamin B1 and B2 [57]. The inner side of nuclear lamina contacts chromatin. Most of the inner membrane proteins bind lamina [57]. Emerin is one of the several lamina-binding transmembrane proteins that tether the nuclear lamina to the inner membrane. Nesprins and SUN transmembrane proteins form bridges across the nuclear membranes, and the complex, known as LINC, anchors the nucleus to the cytoskeleton [64-67]. The nucleus communicates with the cytoplasm by the exchange of proteins, nucleic acids, and small molecules through pores distributed on the surface of the envelope. The pores are assembled from proteins of the nuclear pore complex (NPC), and the central channel within the NPC allows the import and export of components in a regulated fashion [68, 69].

The most obvious function of the nuclear envelope in eukaryotic cells is to provide an enclosed physical compartment to house the genome so that the expression of the genetic information can be regulated at additional levels than found in prokaryotes. In normal mammalian cells, the nuclear envelope is oval to round in shape, and gene knockout studies show that emerin and lamin A, but not lamin B, are critical for the maintenance of the smooth and oval shaped nucleus [70-72]. Another class of nuclear envelope proteins required for maintaining the smooth oval shaped nuclear morphology is the nesprins [73]. Likely, additional nuclear envelope structural proteins affect nuclear morphology.

Thus, the loss and reduced presence of certain nuclear envelope structural proteins are the cause of deformation of cancer nucleus. The increased chromosomal number typically found in aneuploid cancer cells likely accounts for the enlarged nuclear size.

Nuclear envelope and lamina in chromatin organization: The nuclear envelope and lamina play important roles in the organization of chromatin and regulation of gene expression [74]. Heterochromatin, which is highly condensed and transcriptionally inactive, appears to have a higher affinity for the lamina of the nuclear envelope and usually localizes at the nuclear periphery adjacent to the nuclear lamina [75].

Hence, a defective nuclear lamina can lead to reorganization of chromatins, which is associated with global changes in gene expression. This functional aspect of nuclear lamina and its roles in chromatin organization, cell cycle, and signaling have been relatively well studied and considered [76].

Conserved roles of nuclear envelope proteins in mitosis: The biological roles of nuclear envelope proteins have been best studied in *C. elegans* [77]. Mutations or loss of function in several nuclear envelope structure proteins, including emerin and Man1, Baf, and lamin, exhibit similar nuclear and mitotic phenotypes such as an enlarged and deformed nucleus, deficient chromosome segregation, and the formation of chromatin bridges between divided nuclei, sug-

gesting a critical role for the nuclear envelope in cytokinesis and mitosis [76, 78, 79].

The roles of nuclear envelope proteins in cytokinesis and mitosis are also beginning to be revealed in mammalian cells: Baf is required for chromatin condensation and segregation [80, 81]; and mutations in lamin A/C interfere with mitosis and cell cycle progression [82, 83]. Emerin participates in chromatin condensation and the formation of a new nuclear envelope during cytokinesis, but if its loss impacts cytokinesis or not has not yet been well defined [28, 84]. These findings are consistent with roles for these nuclear envelope proteins in both maintaining the nuclear structure and mediating cytokinesis/mitosis across species. Because of the roles of these nuclear envelope proteins in chromatin organization and mitosis, defective nuclear envelope proteins will generate genomic instability due to both aberrant gene expression and chromosomal numerical instability [85], and are known to lead to several human diseases such as muscular dystrophy and progeria [60, 61].

Nuclear envelope in regulation of signaling pathways: Abundant examples demonstrate that the nuclear envelope and lamina affect signal transduction. Transcription factors such as c-Fos and Rb are known to be sequestered to the nuclear lamina [86-89]. In binding to Rb, nuclear lamina participates in cell cycle regulation by stabilizing the Rb protein [87-89]. The association of c-Fos with lamina is proposed to provide a fine regulation of AP-1 activation [86, 90]. Both lamin A/C and emerin can affect MAPK signaling pathways [91, 92], as does nesprin-2 that binds and sequester to retain the activated MAPK in the cytoplasm [93]. Additionally, nesprin-2 regulates Wnt signaling [94]. Emerin binds beta-catenin and also affects the Wnt pathway [89, 95]; lamin A/C affects Wnt [96, 97], and TGF-beta [98] signaling pathways; and Man1 modulates the TGF-beta pathway [99].

Thus, interaction with specific transcription regulation appears to be a common mechanism for the nuclear envelope to modulate multiple signaling pathways [65, 92, 100]. Additionally, NPC is a key regulatory site in controlling the flux of signaling information, specifically as trafficking of proteins and transcriptional factors through the nuclear envelope, which is a process in nearly all signaling pathways that regulates gene expression [101-103].

Defective nuclear envelope components in ovarian cancer

Many of the nuclear envelope defects may be applicable to many types of cancer in general; however, in this review we will focus on the studies in epithelial ovarian cancer. Particularly, we will discuss lamin A/C, emerin, nesprin-1, and NPC, which have been linked to ovarian cancer in several recent publications.

Lamin A/C

Lamin A/C expression is absent or very low in embryonic stem cells and early embryos, and is progressively expressed in nearly all tissues in later developmental stages [104], though its expression is not known to be cell cycle dependent [100]. The initiation of lamin A/C expression is associated with cell differentiation, suggesting that lamin A/C expression may serve as a limit on the plasticity of cells for further developmental events [105]. Additionally, the cell types that seem to lack lamin A/C, such as embryonic carcinoma cells and some cells of the spleen, thymus, bone marrow and intestine in the adult mouse may fall into the 'stem cell' category, but the correlation will need to be carefully tested [100, 105].

Mutations in lamin A/C gene associate with muscular dystrophy and severe premature aging (progeria) in humans [61]. Although no mutations have been linked to cancer, loss of lamin A/C expression is often found in cancer cells [106], including breast cancer [107], leukemia and lymphoma [108, 109], colon cancer [110, 111], prostatic cancer [27], lung cancer [112], and gastric cancer [111, 113, 114]. For ovarian cancer, several studies report changes in lamin expression in the neoplastic cells [115, 116]. One study reported high lamin A/C expression in a fraction of ovarian cancer cases using high-density protein microarrays [116]. However, normal ovarian surface epithelial cells were also stained strongly positive for lamin A/C [116]. The observation may be explained by the low fraction of epithelial cells relative to the total ovarian tissue mass used for protein array analysis. In contrast, perhaps the correct interpretation for the study is that lamin A/C was lost in most but retained in a fraction of ovarian cancer.

A recent systematic study using immunohistochemistry found that lamin A/C is absent in a significant fraction of ovarian (47%) cancers [117]. Intriguingly, most ovarian carcinoma tissues and cancer cell lines exhibit a heterogeneous pattern of lamin A/C expression in the population of cancer cells, which may account for the variation of nuclear shapes within an ovarian tumor. Thus the heterogeneous lamin A/C expression in cancer cells may link to heterogeneity of tumor cells. Furthermore in the study, siRNA down regulation of lamin A/C in non-cancer primary ovarian surface epithelial cells led to misshapen nuclei and promoted polyploidy and aneuploidy [117]. The study concluded that that the loss of nuclear envelope structural proteins, such as lamin A/C, may underlie the two hallmarks of cancer - aberrations in nuclear morphology and aneuploidy.

Emerin

Emerin, encoded by the EMD gene, is ubiquitously expressed [118]. Emerin mutations in human are the causes of the X-linked Emery-Dreifuss muscular dystrophy, and the gene was mapped by linkage studies [118]. Similar to that of lamin A/C gene, an emerin mutation has not been linked to cancer. However in a study of GATA6 in ovarian cancer, emerin was determined to be an affected down stream effector accounting for nuclear deformation and aneuploidy in a large fraction of the ovarian cancer cases [28]. Emerin expression was found absent in 38% of epithelial ovarian cancer [28]. Most of the emerin-positive ovarian cancer cells had abnormal emerin distribution, such as heterogeneous staining in the tumor cell population or not being localized to the nuclear envelope but instead being distributed in the cytoplasm. Based on experiments of emerin suppression in ovarian surface epithelial cells, the mechanism was thought that the loss of emerin caused an increased frequency of mitotic failure and furrow regression to form tetraploid, and subsequently tripolar division generated aneuploid cells [28].

Nesprin-1

Several newly identified nuclear envelope proteins, including SUN and Nesprin family members, anchor in the nuclear envelope membrane and also bind microtubules and actin, forming the LINC (links the nuclear envelope to the cytoskeleton) complex [64, 119]. LINC complex plays a role for positioning the nucleus in the center of a cell [73]. Suppression of these LINC complex proteins leads to a skewed positioning of the nuclei within a cell, results in nuclear envelope deformation, and increases cell mobility (as a result of reduced cytoskeletal rigidity) [119, 120]. The LINC complex is absent in the major blood granulocytes, which facilitates cellular malleability for rapid recruitment of the cells to sites of bacterial and fungal infections [121].

Nesprin-1 (or referred to as syne-1) has numerous alternative spliced products and various spliced isoforms are widely expressed depending on specific cell types [66]. Mutations in Syne/Nesprin- 1 and -2 frequently accumulate in colorectal and breast cancer tumors, respectively [122]. Additionally, an mRNA of nesprin-1 gene was found to be downregulated 20- to 180-fold in the majority of ovarian and mammary carcinomas [123]. The link between nesprin-1 and ovarian cancer was also supported by in a single nucleotide polymorphism (SNPs) association study [123], in which a nonsynonymous coding SNP in the nesprin-1 gene was found to associate with an increased risk of invasive ovarian cancer.

The loss or mutation of nesprin-1 in ovarian cancer cells leads to defect in the LINC complex [62], which may account for the malignant features, the deformed nuclear morphology and invasiveness/high motility. As in the LINC negative blood granulocytes, the absence or defective nesprin-1 likely makes ovarian cancer cells more malleable, and allows the cancer cells to penetrate blood vessels and migrate through tight tissue spaces [121].

Thus, the loss of nesprin-1 is another possible molecular basis for nuclear morphological deformation and increased malignant properties of ovarian cancer cells.

Nuclear pore complex (NPC)

The flux of proteins and nucleic acids through the nuclear pores is an important regulatory site in the production of proteins and also a key check point of many signaling pathways [101-103]. Pre-mRNAs are spliced and exported from the nucleus, through the pores, into the cytoplasm for translation and production of polypeptides. For many signal transduction

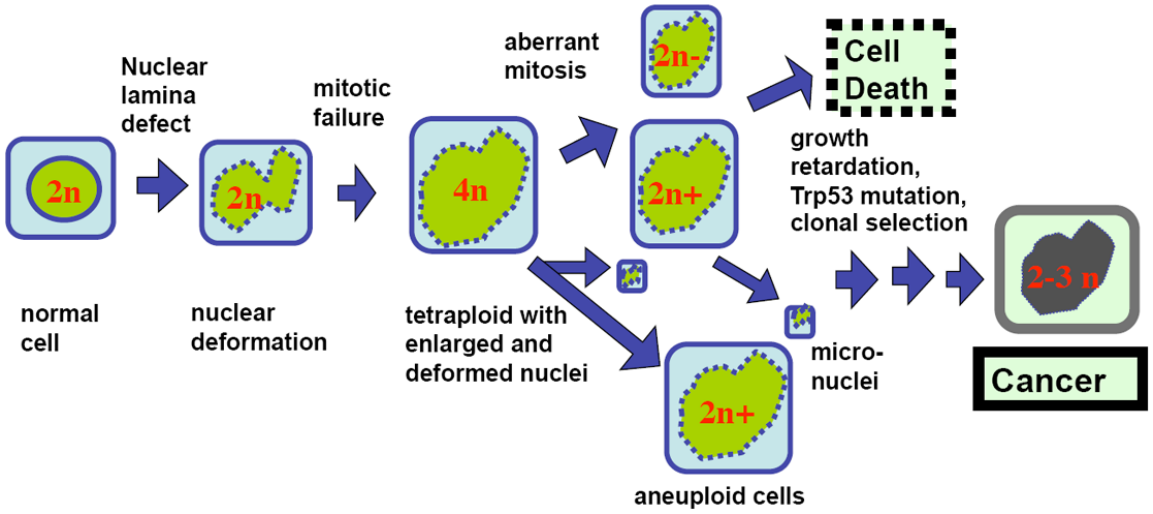

Figure 3. Hypothesis: Consequences of nuclear envelope structural defects. A cartoon illustrates our hypothesis for the consequences of a nuclear envelope defect. We reason that loss of a nuclear envelope structural component such as lamin A/C results in a misshapen nucleus. Additionally, the lamin A/C-deficient cells frequently fail to complete cytokinesis. Thus, tetraploid cells and subsequently aneuploid cells are generated. Formation of micronuclei is another mechanism for the loss of individual chromosomes. Aneuploid cells may be growth retarded and undergo cell growth arrest or death. Trp53 (or p53, Tp53) mutation may allow the cells to survive and undergo clonal selection. Most aneuploid cells will die, but ultimately, a population of cells with a unique chromosomal composition is selected and expanded to form cancer. The deformed nuclear envelope also is the cause of chromosomal instability of the cancer cells.

pathways, import of transcription factors or regulators into the nucleus to initiate gene expression is the final step. Such signaling pathways include Ras/MAPK, in which phosphorylated/activated MAPK is imported into the nucleus; the TGF-beta/Smads, in which activated Smad2/3 is imported into the nucleus to modulate transcription; and the Wnt and Notch pathways. Thus, the number (or density) of nuclear pores as well as the composition of the NPC will impact metabolism and signaling activities. The number of nuclear pores is known to vary depending upon the growth state of the cell, and is higher in proliferating and lower in quiescent cells [125]. A connection between changes in the nuclear pore with cancer has been recognized [126].

For ovarian cancer, NPCs are much increased over non-cancer primary cells [127]. In the study, it was found that phosphorylated/activated MAPK had limited ability to enter the nucleus, and the restriction of MAPK nuclear entry was abolished in cancer cells as a result of increased expression of nuclear pores and/or nuclear transport factors [127].

Additionally, alteration of nuclear pore component was shown to induce ovarian carcinoma into a state of dormancy that is resistant to cisplatin [128], and thus nuclear pore complex architecture can impact ovarian cancer cell survival and drug resistance.

Defective nuclear lamina in chromosomal numerical instability of ovarian cancer

Loss or mutation of nuclear envelope proteins such as lamin A/C or emerin causes muscular dystrophy, progeria, and several additional diseases catalogued as laminopathies [61, 85], but a link between gene mutations and human cancer has not been established. However, several nuclear envelope proteins including lamin A/C, emerin, and nesprin-1 have found to be aberrantly expressed or mutated (in the case of nesprin-1) in ovarian cancer. A defective nuclear envelope protein may explain the deformed nuclear morphology of cancer cells, which is nearly a universal feature of malignancy. From several of the recent studies, a link between nuclear envelope defect and chromosomal numerical instability/aneuploidy is speculated [28, 107, 117].

Nuclear envelope proteins such as emerin and lamin A/C are not essential for mitosis in mammalian cells, although lamin is essential for mitosis in lower organism such as *C. elegans*

[78]; however, defects in nuclear envelope proteins likely increase the frequency of mitotic failure and furrow regression, as the formation of the new nuclear envelope may not occur as efficiently in the absent of a lamina component. Thus, tetraploid intermediates are formed, and aneuploid cells are produced from subsequent aberrant divisions of the polyploid cells.

Furthermore, absence of lamin A/C or emerin in cancer cells may contribute to loss of individual chromosomes in interphase. Lamin A/C or emerin deficient cells often produce long nuclear protrusions, also known as herniations [71, 72, 129]. These protrusions may break off to form micronuclei, leading to loss of one or a few chromosomes. Such transient nuclear envelope rupturing to produce micronuclei has been observed in cancer cells [130, 131].

The accumulated evidence supports a hypothesis that nuclear envelope defects (loss of lamin A/C, emerin, or nesprin proteins) may the common cause of chromosomal numerical instability and aneuploidy in ovarian cancer, and the combination of nuclear envelope defect and p53 mutation is sufficient for the development of ovarian cancer (**Figure 3**). Past studies of the mechanism of aneuploidy mainly focused on chromosomal nondisjunction [32, 40, 42, 132]. The idea that a nuclear envelope structural defect causes chromosomal instability and aneuploidy in cancer underlies these two hallmarks of cancer: nuclear envelope defects and chromosomal instability (**Figure 3**). We reason that loss of a nuclear envelope structural component such as lamin A/C results in a misshapen nucleus. Additionally, the lamin A/C-deficient cells frequently fail to complete cytokinesis. Thus, tetraploid cells and subsequently aneuploid cells are generated. Formation of micronuclei is another mechanism for the loss of individual chromosomes [41]. Aneuploid cells may be growth retarded and undergo cell growth arrest or death [52, 53, 107, 117]. Trp53 (or p53, Tp53) mutation may allow the cells to survive and undergo clonal selection [54]. Most aneuploid cells will die, but ultimately a population of cells with a unique chromosomal composition is selected and expanded to form cancer. The deformed nuclear envelope also is the cause of chromosomal instability of the cancer cells. Thus, a nuclear envelope structural defect, such as the loss or reduction of lamin A/C, emerin, or nesprin-1, may lead to aneuploidy by both mitotic failure to form tetraploid intermediates and the formation of micronuclei by nuclear budding. Nuclear structural defects as a consequence of the loss of lamin A/C (and also loss of emerin) may be a principal mechanism for the chromosomal numerical instability, and the underlying cause of aneuploidy in ovarian cancer.

Concluding remarks/perspectives

The recent integrated genomic analyses of ovarian carcinoma by the Cancer Genome Atlas Project have provided a profile of the molecular aberrations in the diseases [14]. Tp53 mutations were found in essentially all high-grade serous ovarian cancer, though no other common mutations were identified. Since Tp53 mutation alone is insufficient for ovarian cancer development in mouse models, additional mechanisms for ovarian tumor development warrants further consideration. The Cancer Genome Atlas data also indicated widespread gene copy number changes and an indication of aneuploidy in ovarian carcinomas. Aneuploidy is not tolerated in development. It has severe consequences on cell proliferation, and can be detrimental to individual normal cells. However, with additional oncogenic changes (such as Tp53 mutation) to bypass cell growth regulation and cellular stress, chromosomal instability brought on by the loss of nuclear structural integrity may enable the cells to undergo oncogenic evolution and development of malignant tumors. Thus, the collaboration between chromosomal instability and Tp53 mutation may fit the data as a possible mechanism of ovarian cancer initiation and development (**Figure 3**).

Despite its being such a prominent feature of malignancy, what role a deformed nucleus may play in the development of cancer is unclear. The identification of the loss of nuclear envelope structural proteins nesprin-1, emerin, or lamin A/C as the molecular basis of nuclear deformation in cancer cells may provide some explanation. Loss of expression of emerin or lamin A/C leads to mitotic failure and the formation of polypoid and subsequent aneuploid cells, and this may be the main mechanism of aneuploidy in ovarian cancer.

Preliminary studies summarized in the current review provide an explanation for the link between nuclear envelope morphological defect and aneuploidy, and also a model for chromo-

somal instability in ovarian cancer initiation and development (**Figure 3**). These ideas will be tested in the coming years to define how prevalent and significant the nuclear envelope defect as a cause of aneuploidy and ovarian cancer.

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Disclosure of conflict of interest

The authors declare no competing interests.

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