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REVIEW – CANCER RESEARCH

Oncogenic potential of nucleoporins in non-hematological cancers: recent update beyond chromosome translocation and gene fusion

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Abstract

Introduction The nuclear pore complex is comprised of approximately 30 proteins named nucleoporins (Nups) and tightly regulates nucleocytoplasmic transport of macromolecules across the nuclear membrane. Genetic alterations in many *NUP* genes are associated with many human maladies, such as neurological disease, autoimmune disorders and cancer.

Methods We reviewed the status quo of recent advancement of the knowledge of oncogenic role of nucleoporins in human carcinogenesis, focusing on major non-hematological malignancies in the recent literature. Both clinical study-derived and experiment-based reports were critically reviewed. We have also discussed the potential of nucleoporins as novel cancer biomarkers and promising therapeutic target against human malignancies.

Results Several Nups such as Nup53, Nup88, Nup98, Nup160 and Nup214 modulated a plethora of cellular and physiological pathways involved in tumorigenesis such as GSK3β-Snail, Wnt/β-Catenin and RanGap1/RanBP2 signaling axes, DNA damage response, resistance to apoptosis and chemotherapy.

Conclusion Although classically, majority of studies have shown oncogenic roles of nucleoporins as genetic fusion partners in several types of leukemia, emerging evidence suggests that nucleoporins also modulate many cellular signaling pathways that are associated with several major non-hematological malignancies, such as carcinomas of skin, breast, lung, prostate and colon. Hence, nucleoporins are emerging as novel therapeutic targets in human tumors.

Keywords Nuclear pore complex · Nucleoporins · Signaling pathway · Biomarker · Cancer

Abbreviations

NE	Nuclear membrane
NPC	Nuclear pore complex
NUP	Nucleoporin
AFM	Atomic force microscopy
AML	Acute myeloid leukemia
CML	Chronic myeloid leukemia
ABL	Acute biphenotypic leukemia
TNBC	Triple negative breast cancer
PC	Prostate cancer
CRPC	Castration-resistant prostate cancer
SCC	Squamous cell carcinoma
CIN	Cervical intraepithelial neoplasia
IHC	Immunohistochemistry
PDA	Pancreatic ductal adenocarcinoma

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Introduction

Nucleocytoplasmic trafficking of biological macromolecules such as transcription factors and RNAs across inner and outer nuclear membranes of the nuclear envelop (NE) is a highly regulated process. This trafficking is achieved by a large multiprotein structure called nuclear pore complex (NPC) that spans the NE and acts as a gatekeeper of molecular transit (Fradkin and Budnik 2016). The structural and functional units of NPC, termed nucleoporins, (Nups) show high degree of evolutionary conservation across various species, such as yeast, drosophila, xenopus and mammals (Aitchison and Rout 2012; Pante and Fahrenkrog 2014). Mammalian NPC, about 120 nm in diameter, is approximately 125 MDa and consists of 30–32 Nups that are arranged in an annular conformation with a distinct barrel-like shape (Kabachinski and Schwartz 2015). The Nups are assembled in the NPC according to their distinct

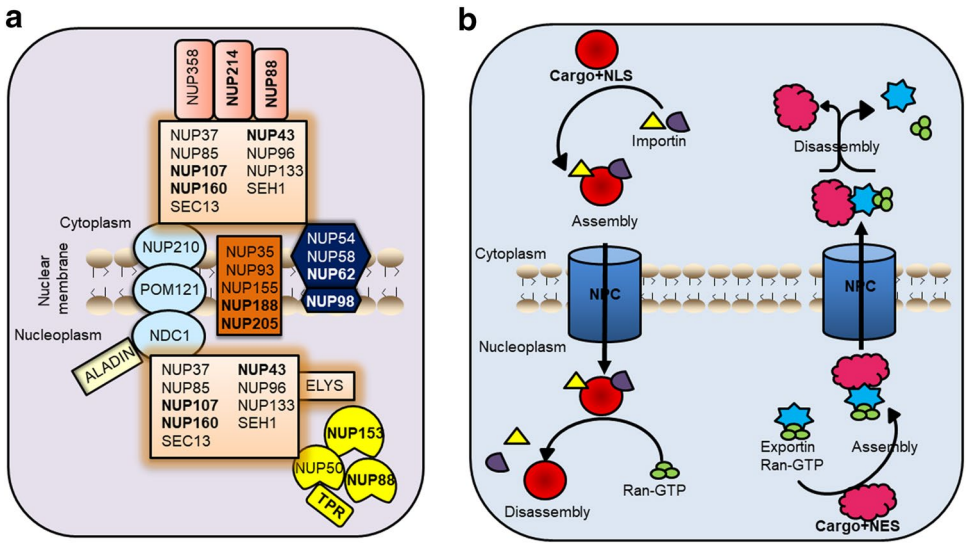

Fig. 1 Structural and functional properties of nucleoporins. **a** Schematic illustration of the nuclear pore complex (NPC). Nucleoporins (Nups) are grouped according to their structural and functional properties: transmembrane Nups (light blue), scaffolding Nups (light orange), central channel Nups (dark orange), nuclear basket Nups (yellow) and cytoplasmic filament Nups (light pink). Nups with oncogenic roles are highlighted by bold characters. **b** Simplified cartoon showing nucleocytoplasmic cargo transport by te NPC. A cargo containing nuclear localization signal (NLS) is recognized by importins and transported through the NPC. Ran-GTP is required for the disassembly of the cargo and importins. Exportin-Ran-GTP complex recognizes nuclear export signal (NES) in a cargo and delivers the cargo in the cytoplasm

structural and functional motifs (Fig. 1a). The dynamic NPC is ~ 50 nm thick with outer and inner diameters of ~ 90–120 nm and ~ 40 nm, respectively, and contains cytoplasmic and nucleoplasmic units, nuclear basket and cytoplasmic filaments (Bui et al. 2013). The nucleocytoplasmic transport of cargos is a highly regulated and complex process (Fig. 1b). The extraordinary barrier created by the NPC to regulate cargo transport is achieved by FG-Nups, the Nups that contain an FG (Phe-Gly) sequence separated by 20–70 residues hydrophilic linker region (Wente and Rout 2010). The roles of FG-Nups in selective transport of cargo are active area of research. It is to be noted that many of these FG-Nups are oncogenic, such as Nup68, Nup98 and Nup214, a discussion of which is the focus of this review. The cargo must contain nuclear localization signal (NLS) and nuclear export signal (NES) for import into and export from the nucleus, respectively. These cargos are recognized by nuclear transport receptors (NTRs) such as importin, exportin, transportins and karyophorins (Kabachinski and Schwartz 2015) and the gradient of nuclear Ran-GTP concentration determines the direction of cargo transport. A detailed review on the nucleocytoplasmic transport is out of the scope of this review and can be found elsewhere (Wente and Rout 2010; Bonnet and Palancade 2014).

Besides regulating nucleocytoplasmic transport, the NPC is also involved in many cellular functions such as differentiation, cell division, chromatin organization and epigenetic modification (Nofrini et al. 2016). Genetic alterations including chromosomal translocation, fusion and aberrant expression of the Nups are linked to many human diseases such as neurological disorder, autoimmune disease and cancer. Since the discovery of the oncogenic role of Nup214 in leukemogenesis by Blobel et al. emerging evidence suggests that other Nups are involved in development and progression of hematological malignancies. To date, there is no agreed-upon theory which explains how the dynamic NPC and its components positively drive leukemogenesis; but, a plethora of work has established several candidates, such as Nup98, Nup214 and Tpr as translocation partners in several types of hematological malignancies including acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and acute biphenotypic leukemia (ABL) (Takeda and Yaseen 2014). For example, translocation of *NUP98* with homeobox genes (*HOX)* such as *HOXA9*, *NUP214* with tyrosine kinase encoding gene *ABL1* and *TPR* with cell surface tyrosine kinase encoding gene *MET1* result in alteration of chromatin structure, unregulated transcriptional activation of target genes, enhanced cell proliferation and constitutive tyrosine kinase activity, leading to leukemogenesis. Detailed role of Nups in hematological malignancies, which is out of the scope of this review can be found elsewhere (Takeda and Yaseen 2014).

Emerging evidence suggests that beside hematological cancers, Nups act as tumor drivers of major non-hematological malignancies such as carcinomas of skin, breast, lung, pancreas, prostate and colon. In the following sections, we discuss recent advancement in understanding the importance of Nups in development and progression of these deadly cancers and review the

possibility of establishing Nups as promising biomarker and novel therapeutic target against some lethal solid tumors.

Nucleoporins as driver of major non-hematological cancer

Excitingly, recent research indicates that apart from being fusion partners in hematological malignancies, Nups contribute to development and progression of many solid tumors by modulating a series of physiological processes and cellular signaling pathways. For example, aberrant expression of Nups in tumor samples correlating with tumor grade (Martinez et al. 1999), interaction of Nups with proteins involved in epithelial-to-mesenchymal transition (EMT) (Makise et al. 2018); modulation of cell cycle machinery by Nups leading to disruption of centrosome separation and aneuploidy (Naylor et al. 2016) and delayed NPC disassembly/mitotic entry lead to tumorigenesis (Laurell et al. 2011). In the next sections, we present recent advancements in the field by dissecting the molecular role of Nups in several major non-leukemic malignancies.

Lung cancer

Lung cancer remains at the top of the list of global cancer deaths with approximately 2.1 million (11.6%) new cases and 1.7 million deaths in 2018 (Bray et al. 2018). Emerging evidence suggests that Nups are involved in development and progression of lung adenocarcinoma. In a recent study, Kikukate et al. analyzed multi-omic data including 26 lung adenocarcinoma cell lines and a control normal lung epithelial cell line to identify novel epigenetic biomarker of lung adenocarcinoma (Kikutake and Yahara 2016). It was revealed that Nup210 was aberrantly expressed in all lung adenocarcinoma cell lines and the *NUP210* promoter element displayed H3K27ac and H3K4me3, two histone modifications that were higher in colon, breast and prostate cancer cell lines as compared to normal cells (Takeshima et al. 2015). Hence, the authors argued that *NUP210* is a promising epigenetic biomarker for lung adenocarcinoma. After analyzing a poorly differentiated lung adenocarcinoma tissue of a 60-year-old Korean patient using anchored multiplex PCR and sequencing, Choi et al. identified a novel translocated promoter region (TPR)-anaplastic lymphoma kinase (ALK) fusion as a tumor-driver (Choi et al. 2014). Using A549 non-small lung cancer cell line, Akkafa et al. demonstrated oncogenic potential of Transmembrane protein 48 (TMEM48), a protein that is localized on the NPC and plays a critical role in nuclear trafficking (Akkafa et al. 2018). They have shown that microRNA miR-421 significantly suppressed TMEM48 expression, increased apoptosis, tumor-suppressor proteins Caspase-3, PTEN and p53 in A549 cells. Very recently, a study by Shi et al. showed that Nup58 promotes EMT and metastasis of lung adenocarcinoma via the GSK-3β-Snail signaling axis (Shi et al. 2019). Mechanistically, Nup58 positively regulated Snail, Twist, GSK-3β and phospho-GSK-3β^{Ser9} and it might serve as a novel biomarker for lung cancer. Altogether, these studies have established Nups as emerging drivers of lung cancer and as a new therapeutic choice.

Breast cancer

Breast cancer is second most deadly cancer with around 2 million (11.6%) new cases and 0.6 million (6.6%) cancer-related deaths in 2018 (Bray et al. 2018). Although earlier studies indicated that Nup88 and Nup153 are overexpressed and associated with high aggressiveness of breast cancer (Agudo et al. 2004; Tan et al. 2010), no significant research focused on the oncogenic role of Nups on this lethal cancer. Until recently, two studies have shown involvement of Nup43 and Nup98 in development and progression of breast cancer. In the first study, using both bioinformatics and clinicopathological analysis, Tian et al. for the first time, have shown that Nup43 was significantly upregulated in breast cancer tissues and Nup43 expression correlated with poor survival with Luminal A + and HER2 + breast cancer (Tian et al. 2018). Moreover, Nup43 overexpression was related to DNA amplification and independently predicted poor overall survival in breast tumors. Mullan et al. have demonstrated that overexpression of Nup98 correlated with lethal triple negative breast cancer (TNBC) and it could be a novel biomarker that can predict response to anthracycline-based chemotherapy against TNBC (Mullan et al. 2019). In summary, with the evidence of Nup43, Nup88 and Nup98 to be drivers of breast cancer, more research is required to establish the molecular role of nucleoporins in this fatal malignancy.

Prostate cancer

Prostate cancer (PC) is the second most leading cause of death in males with approximately 1.3 million (7.1%) new cases and 0.3 million (3.8%) death globally in 2018 (Bray et al. 2018). Although early diagnosis and screen methods are available, treatment of late-stage metastatic prostate cancer is scarce. Recent research on the role of Nups in carcinogenesis of the prostate has shown promise for improved therapeutic intervention. Using androgen-responsive and castration-resistant prostate cancer (CRPC) cell lines, Karacosta et al. showed that Nup62, but not Nup88 or Nup98, positively regulates cell growth and viability of castration-resistant C4-2 cells (Karacosta et al. 2016). Moreover, it was demonstrated that Nup62 mediates interaction between Ca^{++}/Calmodulin-dependent kinase kinase 2β (CaMKK2)

and androgen receptor (AR), resulting in the regulation of AR transcriptional activity. Recently, Re et al. demonstrated the oncogenic role of Nup153-endothelial nitric oxide synthase (eNOS)-Estrogen receptor β (ERβ) signaling axis in PC (Re et al. 2018). Mechanistically, Nup153 regulates nuclear translocation of eNOS/ERβ and positively contributes to cell proliferation, migration of PC cell lines in an estrogen-dependent manner. In a recent issue of Cell, Rodriguez-Bravo et al. demonstrated that the nucleoporin POM121 drives PC aggressiveness by promoting importin-β-dependent nuclear transport of oncogenic and PC-specific transcription factors (Myc, E2F1 and AR-GATA2) (Lim and Wong 2018; Lokareddy 2018). It was also shown that treatment with Importazole, an importin-β inhibitor, inhibited tumor aggressiveness and thus, this study presented POM121-Importin-β signaling axis as a novel therapeutic target. In conclusion, therapeutic targeting of nucleoporins raised great promise to manage advanced PC and more research is highly warranted to decipher the precise role of Nups in PC.

Colorectal cancer

With over 1.8 million deaths and 0.9 million deaths in 2018, colorectal cancer ranks third in terms of incidence, but second in terms of death (Bray et al. 2018). Although earlier publications showed that the expression of Nup88 positively correlated with aggressiveness and metastatic potential of colorectal cancer (CRC) (Emterling et al. 2003; Zhang et al. 2007; Zhao et al. 2010, 2012), not much research was conducted in the involvement of Nups in CRC in last decade. Surprisingly, recent works by several groups have indicated both oncogenic and tumor-suppressor functions of Nups in CRC.

After analyzing several bioinformatics tools such as miRBase and Oncomine, Bhattacharjya et al. identified that Nup214 is a novel downstream target of miR-133b in several transformed cell lines including human colon cancer cell line HCT116 (Bhattacharjya et al. 2015). Downregulation of Nup214 by miR-133b caused mitotic delay followed by chromosomal segregation defects and cell death by apoptosis, hence, implying its oncogenic role in CRC. Using high-speed atomic force (HS-AFM) and electron microscopy, Mohamed et al. demonstrated that treatment of CRC cells with Aurora A kinase inhibitor alisertib caused loss of several FG-Nups such as Nup98, Nup153 and Nup214, followed by nuclear blebbing and deformation (Mohamed et al. 2017). This study not only identified loss of Nups as a hallmark of the dying code in tumors, but also demonstrated that HS-AFM could be used as a powerful diagnostic tool to visualize intracellular architecture in cancel cells. With an aim to identify genes responsible for colorectal cancer risk, Closa et al. analyzed colon tumor and paired adjacent normal mucosa tissue samples by genome-wide association study (GWAS) and identified POM121, a transmembrane nucleoporin as a potential candidate gene among others (Closa et al. 2014).

Contrary to the tumor-promoting role of Nups, a recent publication by Labade et al. showed a novel tumor-suppressor role of Nup93 in colorectal adenocarcinoma cell line DLD1 (Labade et al. 2016). Mechanistically, Nup93 and its interacting partners Nup188 and Nup205 associated with *HOXA* promoter and transcriptionally repressed the gene, whose aberrant expression is linked to many malignancies including breast cancer (Makiyama et al. 2005). In line with this notion, Wu et al. identified Nup153 as a tumor suppressor in CRC (Wu et al. 2019). Nup153 was highly expressed in adjacent normal tissue than the cancerous counterpart and overexpression of Nup153 inhibited CRC cell proliferation and tumor growth in a xenograft model. Mechanistically, overexpression of Nup153 inhibited Wnt/β-catenin signaling pathway and negatively regulated Axin-2, Cyclin D1, c-Myc and Lef-1, downstream targets of Wnt. Taken together, it is evident that Nups, both as tumor suppressors and oncogenes, play a bi-functional role in CRC. An in-depth investigation is highly warranted to establish the role of Nups to discover novel therapeutic interventions against CRC.

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is lethal malignancy arising from the epithelium of multiple organs such as skin, head and neck, and esophagus. High incidence and mortality rate due to esophageal and head and neck SCC is attributed to high degree of alcohol abuse, smoking and tobacco product usage (Bray et al. 2018). In 2018, approximately 1 million new cases of SCC of the skin were reported (Bray et al. 2018). Recently, Hazawa et al. demonstrated that Nup62 is aberrantly expressed in human SCC and its expression is required to maintain undifferentiated status of SCC (Hazawa et al. 2018). Nup62 does so by regulating ΔNp63α, predominant isoform of p63 (a p53 homolog and master transcriptional regulator of epithelial development and maintenance) in SCC. Using human oral SCC cell UPCI: SCC084, Bhattacharjya et al. identified oncogenic role of Nup214 and its mechanistic aspect is described before in Sect. 2.4. Brustmann et al. analyzed formalin-fixed, paraffin-embedded tissues of invasive squamous cell carcinoma (ISCC) of the cervix and found that Nup88 was significantly overexpressed in ISCC tissues as compared to normal ectocervical squamous epithelium (Brustmann and Hager 2009). Altogether, Nups might play a critical role in development and progression of SCC and more investigation should be carried out to establish their precise role of in this lethal disease.

Skin cancer

Skin cancer including melanoma, basal cell carcinoma and squamous cell carcinoma is one of the deadly diseases. More than a decade ago, Zhang et al. analyzed several cutaneous melanoma cell lines such as 451Lu and 1205Lu using biochemical and immunological approaches and showed that Nup88 overexpressed in most of the cell lines (Zhang et al. 2002). The authors concluded that Nup88 might be a tumor driver of melanoma. Further extending the oncogenic potential of Nup88 in this deadly disease, Takahashi et al. demonstrated a novel tumorigenic role of Nup88 in metastatic melanoma cells (Takahashi et al. 2008). The authors showed that Nup88 was overexpressed in metastatic melanoma cell lines such as BLM and non-metastatic melanoma cell line 530 and overexpression of Nup88 was associated with constitutively active NF-κB found in both cytoplasm and nucleus. Furthermore, depletion of Nup88 reduced TNF-induced NF-κB accumulation in the nucleus. Taken together, it is evident that Nups play vital role in development and progression of skin cancer and further investigation needs to be carried out to precisely establish their role in this disease.

Gynecological cancer

Gynecological cancer is referred to carcinoma of woman's reproductive organs: cervix, ovary, uterus, vagina and vulva. Globally, cervical cancer and refractory ovarian cancer remain major threat and novel chemotherapeutic interventions are highly warranted. Almost a decade ago, Brustmann et al. analyzed formalin-fixed, paraffin-embedded tissue samples of cervical intraepithelial neoplasia (CIN) by immunohistochemistry (Brustmann and Hager 2009) and found that Nup88 was overexpressed in high grade CIN lesions as compared to normal cervical tissue. Since then, unfortunately, no major progress has been made on the role of Nups in gynecological malignancies. Recently, Alanee et al. analyzed genomic DNA isolated from the saliva of a cohort of platinum (Pt)-sensitive and Pt-resistant ovarian cancer patients and found single nucleotide variants (SNV) in 3 Nups that were associated with Pt-response (Alanee et al. 2017). Among them, SNV rs79419059 (10T > C) in Nup107 was significantly associated with Pt-resistance (odds ratio 4.519, 95% confidence interval 1.317–15.501, $p = 0.0457$). With validation of this SNV, the authors proposed Nup107 to be a novel predictive marker of refractory ovarian cancer. Using human ovarian cancer cell line TOV112D, Kinoshita et al. demonstrated a functional role of Nup62 in the disease progression (Kinoshita et al. 2012). Knockdown of Nup62 by siRNA altered the NPC structure, arrested the cells at G1 phase of the cell cycle and partial knockdown of Nup62 conferred resistance to cisplatin. Taken together, it is conceivable that further research on the oncogenic role of Nups in these deadly cancers should be carried out to discover new therapeutic interventions.

Pancreatic cancer

Due to its poor prognosis, pancreatic ductal adenocarcinoma (PDA), the most common form of pancreatic cancers is seventh leading cause of death with highest rate of incidence in North America and Europe (Bray et al. 2018). Lack of in-depth research made the oncogenic role of Nup in PDA elusive, until, in 2010, Tan et al. analyzed cDNA microarray from two hamster pancreatic cancer cell lines and identified Nup170 to be upregulated in this disease (Tan et al. 2010). In line with this observation, Shen et al. in a bioinformatics approach, analyzed array data of GSE74629 that includes 34 PDA and 16 healthy samples (Shen et al. 2018). Their observation concluded that Nup107 and Nup160 were enriched and could be used as possible biomarkers for early detection of PDA. Further investigation on the role of Nups in PDA will help us to identify new prognostic marker and better therapeutic choice for this deadly disease.

Nucleoporins in other non-hematological cancers

Although, some older reports link Nups to certain other types of malignancies, no major progress has been made to elucidate the underlying mechanisms of Nups involved in tumorigenesis. By analyzing the expression pattern of Nup88 in different tumor tissues using immunological techniques, Gould et al. found that Nup88 was highly expressed in several cancers including gastric adenocarcinoma, hepatocellular carcinoma, clear cell carcinoma and large cell lymphoma (Gould et al. 2002). In line with this finding, Knoess et al. investigated the expression of Nup88 in hepatitis-B (HBV) and hepatitis-C virus (HCV)-related liver diseases (Knoess et al. 2006). After analyzing the expression of Nup88 in 294 paraffin-embedded hepatocellular carcinoma samples along with HBV-positive hepatoma cell line (HepG2.2.15 and HB611) and HBV-negative cell line (HepG2) by immunological techniques, the authors found that the intensity of Nup88 overexpression significantly correlated with the disease. In other independent studies, chromosomal translocation and fusion of Tpr with a variety of partners such as Met, NTrk1 and FGFR1 were reported to be associated with gastric carcinoma (Soman et al. 1991), papillary thyroid carcinoma (Greco et al. 1997) and myeloproliferative syndrome (Li et al. 2012).

Several reports from last decade indicated that Nups, such as Nup62, Nup107 and Nup205 are associated with many diseases of the central nervous system (CNS) including infantile

bilateral striatal necrosis (Basel-Vanagaite et al. 2006), sporadic amyotrophic lateral sclerosis (Kinoshita et al. 2009) and Alzheimer's disease (Sheffield et al. 2006). Recent studies extended our notion of the association of Nups with CNS disorders and identified several candidates such as Nup93, Nup62 and Nup160 are associated with different diseases including Huntington's disease (Gasset-Rosa et al. 2017; Grima et al. 2017), depression (Kinoshita et al. 2014) and Parkinson's disease (Ryan et al. 2017). Mounting evidence suggests that Nups also play major role in development and progression of many cancers of the CNS. In an early study, Emig et al. investigated about the role of glycosylation in subunits of the NPC and found that nucleoporin p62 was highly sialated in mouse neuroblastoma Neuro-2a cells (Emig et al. 1995). Moreover, sialic acid-specific agglutinin from *Sambucus nigra* inhibited nuclear protein transport and hence the authors suggested that sialic acidification of p62 might have clinical significance. Recently, Lu et al. demonstrated that karyopherin β1, a cytosolic protein involved in selective nucleocytoplasmic transport, docked at the NPC, positively regulates human glioma by modulating Wnt/β-Catenin pathway (Lu et al. 2016). Karakoula et al. analyzed a cohort of 47 pediatric intracranial ependymoma samples by quantitative RT-PCR and identified that copy number amplification of *TPR* gene was significantly associated with poor survival of the patients (Karakoula et al. 2008).

Taken together, it is evident that Nups play a major role in development and progression of a wide range of malignancies and future research should be directed towards identifying their precise molecular role in tumorigenesis to discover novel therapeutic interventions.

Discussion and concluding remarks

In addition to its primary function of nucleocytoplasmic transport of biomolecules, nuclear pore complex (NPC) plays critical role in other cellular processes such as gene expression, epigenetic regulation and cell cycle (Sakuma and D'Angelo 2017). Emerging evidence suggests that nucleoporins (Nup), the structural and functional units of the NPC are expressed in a tissue- and cell type-specific manner and play critical role in orchestration of many human maladies, such as neurological disorders (Triple A syndrome, Huntington's disease, etc.), autoimmune disease, cardiomyopathy and cancer (Nofrini et al. 2016; Juhlen and Fahrenkrog 2018).

In context of cancer, the oncogenic role of Nups is classically associated with hematological malignancies. In 1994, the discovery of the involvement of the CAN protein, now known as Nup214 in leukemogenesis by Blobel et al. (von Lindern et al. 1992; Kraemer et al. 1994) ushered new research direction towards understanding the role of Nup fusion proteins in hematological malignancies. Since then, several oncogenic Nup fusion proteins such as *NUP98-HOXA9, NUP98-MLL, NUP214-DEK* and *NUP214-SET* and their molecular role have been established in leukemogenesis (Takeda and Yaseen 2014; Zhou and Yang 2014; Gough et al. 2011). More than a decade ago, several research groups have identified that the components of the NPC was associated with non-hematological malignancies such as carcinomas of breast (Agudo et al. 2004), cervical (Brustmann and Hager 2009) and melanoma (Zhang et al. 2002); but as compared to leukemogenesis, not much efforts had been put in deciphering the detailed molecular role of Nups in development and progression of major solid tumors. Recent report suggests that there were 18.1 million new cases of cancer and 9.6 million deaths from cancer in 2018 with carcinomas of lung, breast, prostate, skin, pancreas and colorectum staying at the top of the chart (Bray et al. 2018). Hence, in hope to discover novel therapeutic interventions against these maladies, the connection between nucleoporin malfunction and carcinogenesis was revisited. Emerging evidence strongly suggests that Nups, especially Nup88, Nup98, Nup153 and Nup214 modulate many cellular and physiological functions contributing to tumorigenesis and might be promising therapeutic targets.

In this review, we have examined the status quo of nucleoporins in terms of their oncogenic potential and presented a summary of their oncogenic roles (Fig. 2) in major non-hematological cancers. Furthermore, we categorized the above-mentioned findings according to clinical study-derived and experiment-derived reports and summarized the evidences presented in this review (Table 1). Growing evidence suggests that Nups modulate a plethora of cellular signaling pathways such as regulation of gene transcription, epigenetic modification cell proliferation and EMT and act as tumor-promoter in majority of the non-leukemic malignancies. Using biochemical, bioinformatics and genomic approaches, several research groups showed Nups such as Nup98, Nup107 and Nup160 to be novel prognostic biomarker in cancer, a knowledge that holds promise in early detection and optimal management of several deadly malignancies such as breast cancer and PDA. Recently, several research groups have undertaken measures to validate Nups as promising targets in anti-cancer therapy. Using zebrafish angiogenesis and mouse oxygen-induced retinopathy models, Kim et al. have demonstrated that *R*-(-)-β-*O*-methylsynephrine (OMe-Syn), a naturally occurring small molecule inhibitor isolated from plants from the Rutaceae family can inhibit Nup153 and angiogenesis (Kim et al. 2015). In an independent study, Liashkovich et al. have shown that clathrin inhibitor Pitstop-2 disrupts the NPC ultrastructure and its permeability barrier and could be potentially developed into a novel anti-cancer drug (Liashkovich et al. 2015).

Table 1 Components of nuclear pore complex linked to major non-hematological human cancers

Name of the disease	Method of the study presented and mode of action		References
	Clinical study-derived	Experiment-derived	
Lung cancer	*NUP210*: aberrant expression, H3K27Ac/H3K4Me3 histone modification *TPR-ALK* fusion *NUP58*: positive regulator of EMT, metastasis via modulation of GSK3β-Snail signaling axis	*TMEM48*: anti-apoptotic, inhibitor of Caspase-3, PTEN and p53. *NUP58*: positive regulator of EMT, metastasis via modulation of GSK3β-Snail signaling axis	Kikutake and Yahara (2016) Choi et al. (2014) Akkafa et al. (2018) Shi et al. (2019)
Breast cancer	*NUP88*: overexpression, associated with aggressiveness, poor survival *NUP43*: copy number amplification *NUP98*: overexpression, associated with aggressiveness, poor survival	*NUP153*: positive regulator of cytoskeletal rearrangement, cell motility and migration	Agudo et al. (2004) Tan et al. (2010) Tian et al. (2018) Mullan et al. (2019)
Prostate cancer		*NUP62, NUP98*: positive regulator of Ca^{++}/Calmodulin-dependent kinase kinase 2β (CaMKK2) and androgen receptor (AR) *NUP153*: positive regulator of endothelial nitric oxide synthase (eNOS)-Estrogen receptor β (ERβ) signaling axis *POM121*: promotes importin-β-dependent nuclear transport of oncogenic and Prostate Cancer-specific transcription factors (Myc, E2F1 and AR-GATA2)	Karacosta et al. (2016) Re et al. (2018) Lim and Wong (2018); Lokareddy et al. (2018)
Colorectal cancer	*NUP88*: overexpression, associated with aggressiveness, poor survival *POM121*: associated with increased risk of colorectal cancer	*NUP214*: inhibitor of apoptosis, positive driver of mitosis and cell proliferation *NUP98, NUP153, NUP214*: maintenance of nuclear envelop structure, inhibitor of tumor cell death	Emterling et al. (2003), Zhang et al. (2007); Zhao et al. (2010, 2012) Bhattacharjya et al. (2015) Mohamed et al. (2017) Closa et al. (2014)
Squamous cell carcinoma (SCC)	*NUP88*: overexpression and association with increased risk of invasive SCC of the cervix	*NUP62*: maintains undifferentiated status of SCC by regulating p63 isoform ΔNp63α *NUP214:* inhibitor of apoptosis, positive driver of mitosis and cell proliferation in oral SCC	Hazawa et al. (2018) Bhattacharjya et al. (2015) Brustmann and Hager (2009)
Skin cancer		*NUP88*: enhanced expression associated with risk of development of melanoma *NUP88*: overexpression and constitutive activation of NF-κB in melanoma	Zhang et al. (2002) Takahashi et al. (2008)
Gynecological cancers	*NUP88*: overexpression and association with increased risk of cervical intraepithelial neoplasia (CIN) *NUP107*: SNV rs79419059 (10T > C) in Nup107 was significantly associated with Pt-resistance	*NUP62*: maintenance of NPC architecture, positive regulator of G1-S transition of cell cycle, tumor cell dormancy and chemo-resistance	Brustmann and Hager (2009) Alanee et al. (2017) Kinoshita et al. (2012)

Table 1 (continued)

Name of the disease	Method of the study presented and mode of action		References
	Clinical study-derived	Experiment-derived	
Pancreatic cancer	*NUP107, NUP160*: enrichment and possible biomarker for pancreatic ductal adenocarcinoma	*NUP170*: gene upregulation and overexpression	Tan et al. (2010) Shen et al. (2018)
Malignancies of the central nervous system	*TPR*: gene amplification and associated with poor patient survival	*NUP62*: modification by sialic acid and associated with progression of neuroblastoma *Karyopherin β*: overexpression, positively regulates Wnt/β-Catenin signaling axis to drive glioma	Emig et al. (1995) Lu et al. (2016) Karakoula et al. (2008)

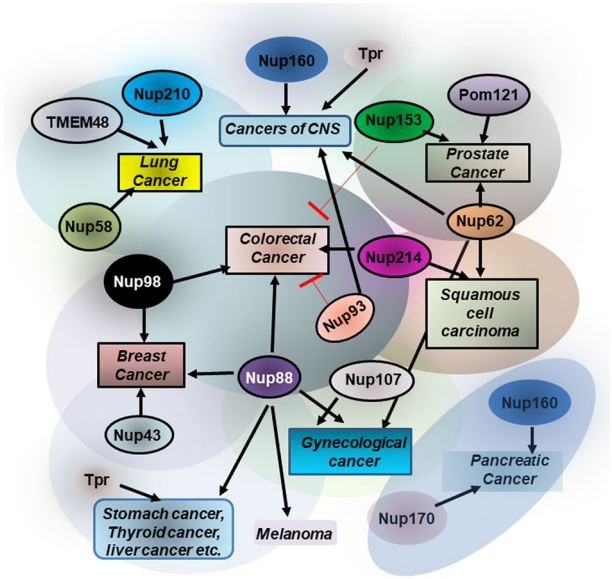

Fig. 2 Tumor-specific roles of Nups in major non-hematological malignancies. Several Nups such as Nup88, Nup98 and Nup214 promotes carcinogenesis (black arrow), whereas Nup93 and Nup153 also act as tumor suppressor in colorectal cancer (red line)

Considering evidences presented in this review, Nups are emerging as promising target for therapeutic intervention against cancer, especially non-hematological malignancies, although there remain many unanswered questions: what are the molecular cues that dictate Nups to drive oncogenic signaling in a tissue-specific manner? At molecular level, how Nups, such as Nup153, share both oncogenic and tumor-suppressor role in cancer? What would be the best strategy to develop novel small molecule inhibitor or humanized monoclonal antibody against Nups that will selectively eradicate its oncogenic potential while preserving its biological function? Further research aimed to decipher the role of Nups in functional genomic approach will help us to identify novel downstream targets and therapeutic interventions against cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest to disclose.

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