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The Structure and Physiology of the Nuclear Pore Complex and its Role in Gene Expression and Human Disease

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The Nuclear Pore Complex (NPC) is a protein channel that communicates and transports molecules between the cytoplasm and the nucleoplasm. It has a complex structure composed of many structural proteins, mainly nucleoporins and transporter proteins, and its biosynthesis is an extremely regulated and cell cycle phase dependent process. Moreover, in the present review, it will be shown that this structure could play a decisive role in gene expression and in the pathogenesis of several diseases. On the one hand, NPC affects gene expression by regulating epigenetic enzymes and affecting the nucleocytoplasmic balance of transcription factors and small nuclear RNAs. On the other hand, diverse studies show that NPC is involved in some diseases and pathological processes like aging, neurodegenerative diseases and extrapyramidal syndromes, cancer, cardiovascular diseases, infectious diseases and genetic syndromes. In conclusion, NPC might be an important element in the control of gene transcription and cell phenotype, and perhaps, it will become a future pharmacologic target for several diseases in which it is involved in.

INTRODUCTION

The Nuclear Pore Complex (NPC) is a cellular component that is located within the nuclear envelope. It is a protein channel that allows macromolecules to cross from the cytoplasm to the nucleoplasm and vice versa. This establishes an important physiological process known as nucleocytoplasmic transport (Jamali et al. 2011). NPCs are not only involved in transport but also have an important relationship with epigenetic enzymes and transcription factors, which are both proteins that participate in gene expression (Van de Vosse et al. 2011). Moreover, it has been demonstrated that the NPC is linked to many diseases such as aging, neurodegenerative diseases and extrapyramidal syndromes, cancer, cardiovascular diseases (arrhythmias and sudden death), infectious diseases and genetic syndromes. For example, in cancer or genetic syndromes, mutations exist in the proteins that form the NPC (Capelson and Hetzer 2009). The objectives of this review are to revise the structure and physiology of the NPC and investigate its role in gene expression and diseases in order to clearly understand the possible role of the NPC as a gene expression regulator and a future therapeutic target.

Structure of the nuclear pore complex

The NPC is an octagonal protein channel (Fabergé 1973) that is between 40 and 90 nm in diameter (Webster et al. 2009) and 200 nm in depth (Gall 1967). There are approximately 2000 NPCs in a cell. Nevertheless, this number can vary depending on the cell type studied, the phase of the cell cycle and external aggressions (Maeshima et al. 2011; Maul et al. 1980).

There are three structures within a NPC: nuclear basket, cytoplasmic filaments, and nuclear ring. They are all made by approximately 30 different proteins called nucleoporins (D'Angelo and Hetzer 2008).

Nuclear basket is composed of a ring of nucleoporins (Nup153 and Nup50) which bind filaments of Tpr protein, making up a structure with a basket shape (Brohawn et al. 2009; Hoelz et al. 2011). Cytoplasmic filaments are made up by the nucleoporins Nup88, Nup214 and Nup358 (Brohawn et al. 2009; Hoelz et al. 2011). Finally, the nuclear ring has four parts, namely, the membrane ring, the spoke ring, the inner ring or nuclear ring, and the outer ring or cytoplasmic ring. The membrane ring anchors the NPC to the nuclear envelope and comprises nucleoporins gp210, Ndc1 and Pom121. The spoke ring is located centrally in respect to the membrane ring and is built by nucleoporins Nup53, Nup54, Nup58, Nup62 Nup93, Nup98, Nup155, Nup188 and Nup205 (Brohawn et al. 2009; Hoelz et al. 2011). Finally, the outer and the inner rings are composed of nucleoporins Nup37, Nup43, Nup85, Nup96, Nup107, Nup133, Nup160, Sec13 and Seh1 (Alber et al. 2007; Beck et al. 2007; Brohawn et al. 2009; Cronshaw et al. 2002; Hoelz et al. 2011; Lim et al. 2008; Stoffler et al. 2003). Another protein called Aladin or Adracalin (Cronshaw and Matunis 2003) is located at the NPC as well and binds to a nucleoporin named Ndc1 (Kind et al. 2009; Yamazumi et al. 2009) (Figure 1).

The nucleoporins that form the NPC can be classified into three groups: transmembrane nucleoporins (approximately 10%); structural nucleoporins (50%); and FG-nucleoporins (40% of the total population) (Rout and Wente 1994).

The deepest nucleoporins in the NPC project some of their peptide fragments into the pore hole. These peptide sequences are natively unfolded and hence are polypeptides without a secondary structure folding. They make up a peptide web within the pore complex hole. In this web there are nucleoporins containing GLFG (glycine-leucine-phenylalanine-glycine repeats), FXFG (phenylalanine-x-phenylalanine-glycine repeats) and FG (the most common type) (phenylalanine-glycine

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repeats). These FGs are extremely important for the NPC's involvement in the nucleocytoplasmic transport of macromolecules, as FGs function as the anchoring points for the cargo, indicate the direction of transport and adapt to appropriate pore size (Denning et al. 2003; Terry and Wente 2009; Yang 2011).

The NPC is tightly bound to the nuclear membrane and the nuclear lamina by protein Pom121 and another NPC proteins, respectively (Hawryluk – Gara et al. 2005; Mitchell et al. 2010). The protein Pom121 comprises membrane ring in the NPC (Mitchell et al. 2010) and anchors NPC to nuclear membrane, while other NPC proteins are involved in the anchorage with

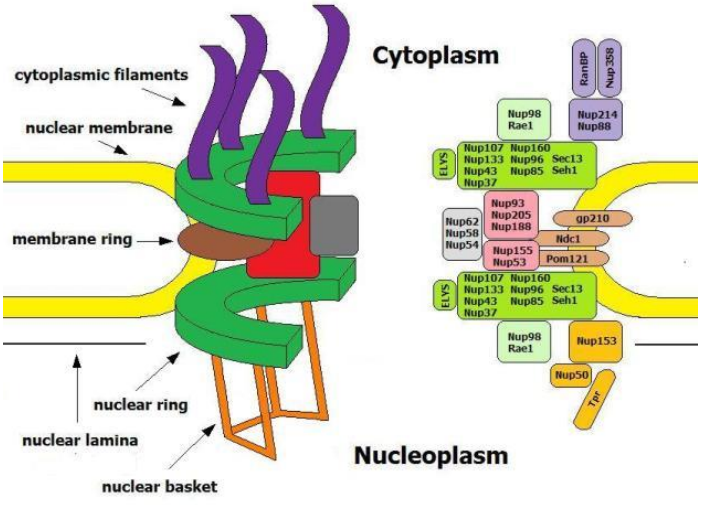

Figure 1. The nuclear pore complex (NPC). This image shows the main parts in which the NPC is divided and the specific proteins that compound them. Nuclear basket (in orange) is composed of Nup153 and Nup50 which bind filaments of Tpr protein. Cytoplasmic filaments (in purple) are made up by the nucleoporins Nup88, Nup214 and Nup358. The nuclear ring has four parts, namely, the membrane ring (in brown), the spoke ring (in red and grey), the inner ring or nuclear ring and the outer ring or cytoplasmic ring (both in green). The membrane ring anchors the ring complex to the nuclear envelope and comprises nucleoporins gp210, Ndc1 and Pom121. The spoke ring comprises the nucleoporins Nup53, Nup54, Nup58, Nup62 Nup93, Nup155, Nup188 and Nup205. The outer and the inner rings are composed of nucleoporins Nup37, Nup43, Nup85, Nup96, Nup107, Nup133, Nup160, Sec13 and Seh1. Other important proteins are also show in the picture.

nuclear lamina (A-lamina and B-lamina proteins) Lamina determines the location of NPC, because NPCs are more frequent in places of the nuclear envelope with B – lamina and less common in the regions with A – lamina. Nup53, Nup153 and Pom121 bind to B – lamina, while Nup 88 binds to A – lamina (Hawryluk – Gara et al. 2005; Hawryluk – Gara et al. 2008; Lussi et al. 2011; Mitchell et al. 2010; Schwarz – Herion et al. 2007; Smythe et al. 2000).

Function of the nuclear pore complex

NPC is responsible for the exchange of macromolecules and other substances between the nucleus and the cytoplasm (nucleocytoplasmic transport). There are two forms of transport. 1) simple diffusion, which occurs in molecules smaller than 40 kDa (e.g. water, ions and metabolites) (Keminer and Peters 1999) and 2) nuclear translocation, for macromolecules like mRNA, snRNA, tRNA, microRNA, transcription factors, histones, enzymes and even viral proteins and nucleic acids (Ribbeck and Görlich 2001).

Nuclear translocation can happen in two directions: nuclear import, in which molecules go into the nucleus, and nuclear export, a phenomenon where molecules go out to the cytoplasm. Both of them are extremely regulated processes and require transporter proteins (Jamali et al. 2011).

Transport proteins involved in nucleocytoplasmic transport

Transporter proteins can be classified into two groups: energetic molecules and anchoring molecules. Both of them are located in the NPC and are fundamental for nucleocytoplasmic transport (Marelli et al. 2001).

Ran is a protein, from the family of Ras, which supplies the energy needed for the nucleocytoplasmic transport. It binds GTP or GDP, so it carries phosphate groups between the nucleoplasm and the cytoplasm (Sekiguchi et al. 2000).

Anchoring transport proteins are called kariopherins. There are two kinds of kariopherins, namely exportins and importins (Gorlich and Laskey 1995; Marelli et al. 2001). Exportins, a protein group with seven elements, transport cargo from nucleus to cytoplasm (nuclear export) after recognizing them by a peptide sequence called nuclear export signal (NES) which is rich in leucine (Kutay and Güttinger 2005). On the other hand, importins transport molecules from the cytoplasm to the nucleus (nuclear import) when a sequence known as nuclear localization signal (NLS) is located in the cargo (Kalderon et al. 1984).

Importins are more complex than exportins because they are composed of two subunits called importin A and importin B that work together, but in some cases they can also work separately. There are many forms of importin A and B, and consequently, lots of different combinations exist as well (Gorlich et al. 1995)

Nuclear Import

Nuclear import starts with a cytoplasmic protein that contains a NLS that is recognized by importin A, which then subsequently binds to Importin B. Although, this is the paradigm, many NLS are recognized by importins that are not made up by two subunits. The Cargo NLS – Importin A – Importin B complex interacts with the elements of the NPC, more exactly with the FG - Nups, binding to FG, GLFG or FXFG nucleoporins temporarily. Not all FG - Nups have the same affinity to the importin (especially importin B), existing FG - Nups called clusters with more binding power (Bayliss et al. 2000; Ribbeck and Görlich 2002). At the nuclear basket, the transport complex interacts with the nucleoporin Nup50. Nup50 binds to Nup135

and has three domains, namely a C - terminal extreme, a FG domain and a N - terminal extreme. Importin B binds to the FG domain of Nup50 and separates from Cargo NLS – Importin A complex. Then Importin A binds to the N - terminal extreme of Nup50, releasing the cargo (Stewart 2007). It is fundamental for Nup50 to be phosphorylated at serine-221 and serine-315 in order to function properly (Kosako et al. 2010).

Parallel to this process, RanGDP, the energy carrier in nucleocytoplasmic transport, comes back to the nucleus. RanGDP is carried by the protein NTF2, a dedicated nuclear-import factor for Ran (Stewart 2000).

Importin A and importin B are back to the cytoplasm with different mechanisms of transport. Importin A is transported by cellular apoptosis susceptibility (CAS) and RanGTP, while importin B is only carried by RanGTP (Kutay et al. 1997; Ström and Weis 2001).

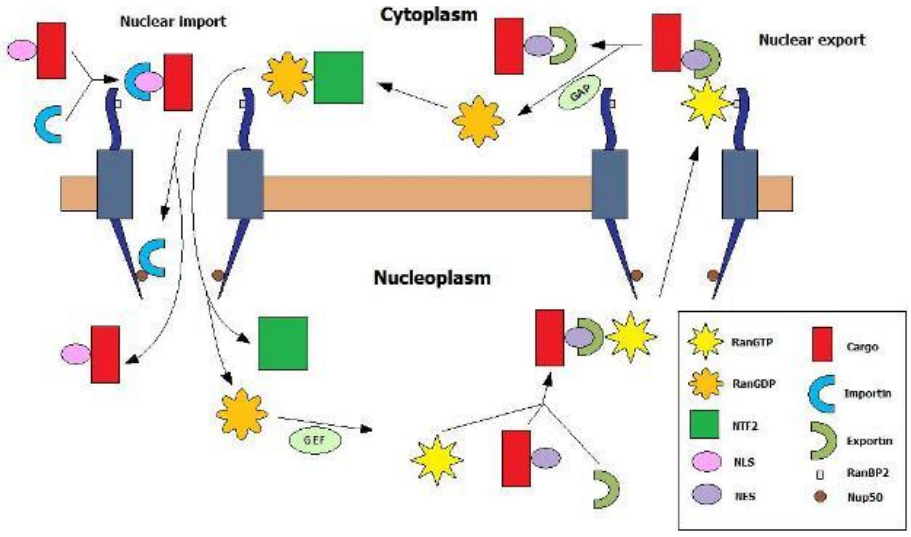

Figure 2. Nuclear import, export and Ran cycle. This picture shows these processes and the elements that are involved in them. The legend identify each element of the nucleocytoplasmic transport in the picture. All of the proteins and the process shown are fully explained in the main text.

Nuclear export

Nuclear export begins with a nuclear protein that contains a NES. This peptide sequence is recognized by exportins which also bind to RanGTP. This Cargo NES – Exportin – RanGTP complex travels from the nucleus to the cytoplasm. The exportin interacts with the nucleoporins (FG – Nups) on the same way as importins. In the cytoplasm, RanGTP binds to RanBP1 and RanBP2, and releases the Cargo – Exportin complex, which subsequently disassembles (Goldberg 2004).

Ran cycle

Nucleocytoplasmic transport would not proceed without Ran, a protein which provides the energy needed in this process. It is a cycle that begins with a Ran binding to a GTP molecule. Afterwards, this GTP is hydrolyzed and appears RanGDP. Finally, new RanGTP is formed from RanGDP. This cycle happens in the nucleus and the cytoplasm, creating a Ran gradient that occurs from nucleus to cytoplasm because RanGTP is in a higher concentration in nucleus than in the cytoplasm. This gradient aids to transport molecules.

Ran cycle starts with a RanGTP that binds to a Cargo - NES – Exportin complex inside the nucleus. As RanGTP is in a higher concentration in the nucleus than in the cytoplasm, the complex is exported outside the nucleus. In the cytoplasm, Ran is separated from the complex and binds to RanBP1 and RanBP2. An enzyme called GAP degrades the GTP to GDP. RanGDP is returned back to the nucleus by NFT2. Both separate with the involvement of Nup50, because RanGDP binds to the C – terminal extreme of Nup50, also called the Ran binding domain (RBD) (Sazer and Dasso 2000; Yoneda et al. 1999).

In the nucleus, an enzyme called GEF (guanine nucleotide exchange factor) transforms GDP into GTP, synthesizing new RanGTP, so that a new cycle begins (Sazer and Dasso 2000; Yoneda *et al.* 1999) (Figure 2).

Biophysics of nucleocytoplasmic transport

In order to explain the function of FG – Nups there are some discrepancy among the authors. In fact, there are four models in order to explain it called the "virtual gating/polymer brush model", the "reduction of dimensionality model", the "selective phase/hydrogel model" and the "forest model". The first one proposes that non - interacting FG – Nups create an entropic barrier that can only be crossed when the cargo attaches to them. The second model suggests that FG – Nups configure a small hole that permits the passive diffusion of small molecules and the transport of large ones by translocation . The third one hypothesizes that FG – Nups have big interactions which contribute to the creation of a hydrogel inside the pore. When transport complexes bind to the FG – Nups, the hydrogel disappears and transport can occur. Finally, the fourth model proposes that there are two fragments in FG – Nups, namely, the globular domains, that create a central channel for the transport of small molecules, and the extended coils, which configure a peripheral zone for the transport of larger molecules (Yang et al. 2011).

In any case, Moussavi et al. (2011) demonstrated that this transport is not lineal but follows a Brownian movement, employing between 5 and 10 ms.

Transport of messenger RNA from the nucleus

Messenger RNA (mRNA) is exported by a complex process that varies with respect to the standard explanation. First of all, DNA

is transcribed by RNA polymerase II. At the same time, SAGA, a protein associated to the gene in transcription, binds the DNA chain to the NPC so that the transcription process happens near the NPC. SAGA specifically attaches to a complex called TREX – 2 which binds to the NPC. RNA polymerase II also binds to a complex called THO/TREX that joins with TREX – 2. The synthesized mRNA joins with the protein UAP56. Afterwards, during splicing mRNA also binds with Aly protein. Aly interacts with the complex TAP/NXT1 which transports the mRNA along the nuclear pore hole. During this transit is very important the interaction of mRNA with two nucleoporins, Nup98 and Nup153. The energy required for this process is provided by the protein Dbp5. This protein is a part of the DEAD – box and anchors to another protein called Gle1, which is located at the cytoplasmic filaments. But, the most important thing is that this protein needs inositol hexa – phosphate (IP6) in order to make the export of mRNA possible (Hocine et al. 2010; Ling et al. 2010; Stewart 2010) (Figure 3).

Other roles of the nuclear pore complex

NPC is not only involved in nucleocytoplasmic transport, but also plays a key role in other cellular functions.

NPC serves as an anchoring place for the enzymes kinesin - 1 and dynein. Kinesin – 1 binds to Ran BP2 and microtubules and carries the nucleus to a cell pole. Dynein binds to Ran BP2 and BICD2, an adaptor protein of the SUN – KASH family, and transports the nucleus to a central position

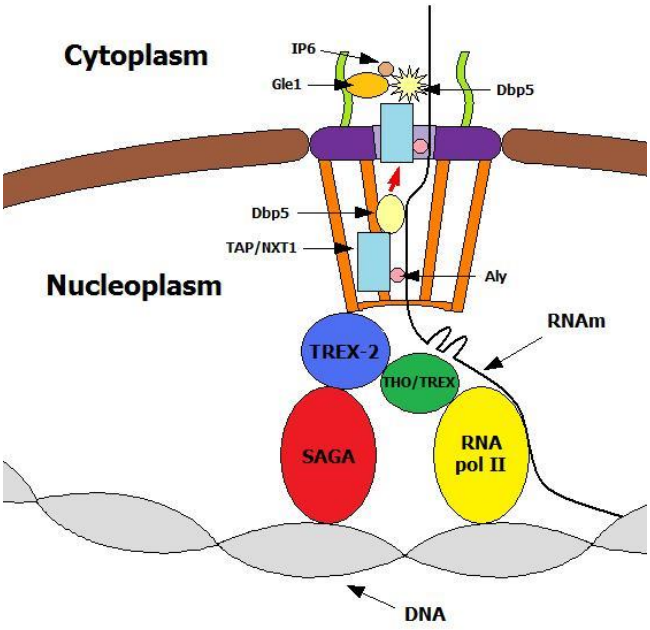

Figure 3. mRNA export. This image explains the process of mRNA export, since it is transcribed until it is taken out from the nucleus. RNAm transcription, as recent investigations demonstrate, starts near NPC because RNA polymerase II (in yellow) is anchored to NPC by a complex comprised of THO/TREX (in green) and TREX-2 (in blue). Then, the transcribed mRNA binds to other proteins (TAP/NXT1, Dbp5, Aly) that transport mRNA to the cytoplasm via NPC. All of the proteins and the process shown are fully explained in the main text.

(Tanenbaum et al. 2011).

In addition, NPC mediates the import of the steroids hormones and its receptor, allowing them to carry out their function as a transcription factor. This complex process starts with the steroid receptor (SR) which is anchored to a complex of transporter proteins that is made up of hsp90, hsp70, hsp40, Hop and p23. Afterwards, the steroid hormone binds to the receptor. Subsequently, Hop is replaced for TPR protein. The complex is then carried to the NPC by dynein and NPC transports it to the nucleoplasm. There, the hormone – receptor complex is released and acts as a transcription factor (Galigniana et al. 2010).

Finally, it is important to mention that some nuclear basket proteins like Tpr develop specifics functions. For example, this protein regulates Mad 1 and Mad 2, two proteins which are very important in the cell cycle (metaphase) and anchors some activated genes and silenced telomeres (Lee et al. 2010).

Biosynthesis of the nuclear pore complex

There are three occasions within the cell cycle in which NPCs are synthesized, including interphase, G2 phase, and after anaphase when nuclear envelope begins to configure (Fernández – Martínez et al. 2009; Maeshima et al. 2011).

NPC biogenesis starts when Pom121 migrates through the nuclear envelope from the outer membrane to the inner membrane. Pom121 is a transmembrane protein which possesses a luminal domain (cadherin - like domain) and a nucleoplasmic domain. This last, known as LBR domain, recognizes regions in the nuclear lamina with lamina B. So, the biosynthesis of new NPC occurs mainly in rich lamina B regions. The places where Pom121 concentrates are also determined by Heh1p and Heh2p, two proteins from the LEM - domain family (a family of proteins that are located within the inner nuclear membrane and nucleus). These proteins are located in determined regions of the nuclear envelope and bind Pom121 by the cadherin like luminal domain. SUN1 protein is also implicated in Pom121 distribution along the nuclear envelope. Pom121 activates alcalin - phosphatase 5 and the Nup133 enzyme. This nucleoporin activates Nup155 and Nup35, which fuse the two nuclear layers (the inner and the outer layer of the nuclear envelope). In these zones Pom121 and ELYS recruit the complex Nup107 – 160 (Nup84) which attracts other nucleoporins, ending the construction of the NPC.

Regulation of the expression of the NPC components

NPC expression differs depending on the cell type. Cells that are able to proliferate have a higher number of NPC and increased NPC turnover. Moreover, the phase of the cell cycle has an important determining role in NPC expression. For example, in G2 cell cycle phase, NPC number increases (Maeshima et al. 2011).

Moreover, some genes like HEH1 and HEH2 determine the level of expression of the nucleoporins. HEH1 affects the expression of Nup153, Nup50, Pom121, Ndc1 and RTN1 (reticulon 1). HEH2 determines the level of expression of Nup160, Nup107, Nup155 and Nup188. Some nucleoporins, namely Nup35, Nup133, Nup59, gp210 and APQ12, interact

simultaneously with HEH1 and HEH2 (Yewdell et al. 2011).

However, not only does the genetic environment determines NPC expression, but the tissue environment, particularly Ras signaling pathway, PIK3 signaling pathway and AMP kinase, does as well. Ras signaling pathway is responsible for cell proliferation and the PIK3 signaling pathway is responsible for cell growing. So, both cell proliferation and cell growing are processes that regulate NPC expression. In the Ras signaling pathway, mitogens activate Ras and Raf, Mek, Erk and Rsk proteins. Erk phosphorylates Nup50 (its phosphorylation diminishes the binding with importin B), Nup153 and Nup214, while Rsk phosphorylates RanBP3, which determines the Ran – GTP gradient (Kodiha et al. 2010; Kosako and Imamoto 2010; Maeshima et al. 2011). In the PIK3 signaling pathway, growing factors stimulates PIK3 which phosphorylates and GlcNAcetylates Nup50, Nup62, Nup88, Nup153, Nup214, CAS, Importin – A and RanBP3. Moreover, AMP has an important role of phosphorylating and acetylating Importin A (Kodiha et al. 2010).

Finally, oxidative stress also affects NPC, particularly, nucleoporins, importins, exportins and Ran nucleocytoplasmic localization and function. Oxidative stress also has a very important relationship with importin A, Importin B1 and Nup153 (Kodiha et al. 2004, 2008). Termical and hiperosmotic shocks also affect Ran gradient (Kelley and Paschal 2007; Kodiha et al. 2004). Moreover, ceramide provokes the mislocalization of CAS and Importin A (Faustino et al. 2008). Furthermore, aging deregulates Importin A, CAS and RanBP1 (Pujol et al. 2002). Finally, some immune molecules like interferon gamma upregulate the expression of Nup98 and Nup96 (Enniga et al. 2002).

Role in gene expression

As recent investigations show, NPC could be an important cellular element in the regulation of gene expression. According to the evidences, this mechanism could take place in two ways, either by regulating epigenetic enzymes or affecting the nucleocytoplasmic balance of transcription factors and small nuclear RNAs (snRNAs) (Griffis et al. 2004; Kasper et al. 1999; Kataoka et al. 1999; Mingot et al. 2001; Neuman de Vegvar and Dahlberg 1990; Petit et al. 2008; Ploski et al. 2004; Takahashi et al. 2008; Turner and Sullivan 2008; Wang et al. 2007; Wiermer et al. 2010).

Gene expression is determined by epigenetic regulation. NPC interacts with CBP/p300, a histone acetil – transferase, and with NSD1, a histone metil transferase, which affect the transcription either positively or negatively (Kasper et al. 1999; Petit et al. 2008; Wang et al. 2007). NPC has also an important role as a transcription factor and involves nucleoporins Nup1, Nup2, Nup60, Nup88, Nup98, Nup153 and Nup157 (Griffis et al. 2004).

Moreover, NPC regulates gene expression in other way: by determining the proportion of concrete transcription factors in the nucleus and cytoplasm. IPO13 imports the transcription factor Pax6 and releases elF1A (Mingot *et al.* 2001; Ploski *et al.* 2004). XPO1 or CRM1 determines the nucleocytoplasmic balance of NFAT, cyclin B and AP – 1 (Turner and Sullivan 2008). Nup88 determines the quantity of NFkB that accumulates in the nucleoplasm (Takahashi *et al.* 2008). Nup88 and Nup214 are extremely important for keeping the transcription factor Cactus – Dorsal/Dif in nucleus, which is the responsible for transcribing genes related to innate immune response (Wiermer et al. 2010). IPO12 imports splicing factors like SFRS1 and SFRS2 (Kataoka *et al.* 1999).

NPC complex also controls the import of snRNAs. These molecules act as regulators of transcription factors, participate in mRNA splicing and maintaining the telomeres (Neuman de Vegvar and Dahlberg 1990).

Role in pathology

NPCs are altered in many diseases such as cancer, neurodegeneration, viral infections and cardiovascular pathologies.

NPC and its role in cancer

NPC number has been demonstrated to be increased in cancer (Maul et al. 1980). Moreover, some mutations of NPC proteins are characteristic in some types of cancer. For example, Nup88 is over expressed in tumors of advanced state. Some authors even expose that Nup88 has an important role in their invasive character. It is found to be over expressed in breast, colon and hepatic cancer (Agudo et al. 2004; Zhang et al. 2004). Another mutation that involves the translocation of Nup98 with HOXA9 occurs in leukemia. This mutation determines the expression of oncogenes and stops the differentiation of hematopoietic cells (Kasper et al. 1999). Another protein called Nup214 translocates with Dek and Set. This translocation is also involved in leukemia

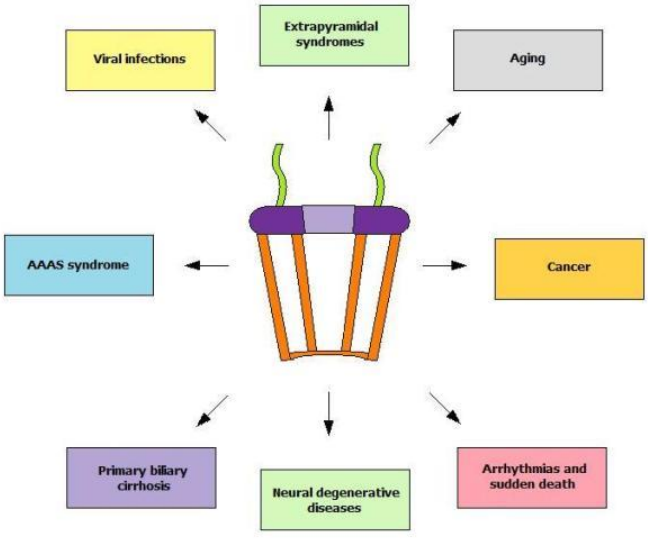

Figure 4. Diseases and nuclear pore complex. This picture indicates some pathological processes demonstrated to have NPC involvement.

(Ageberg et al. 2008; Boer et al. 1998). Tpr, a nuclear basket protein, translocates with Met (tirosin kinase of HGF) and this is linked with gastric cancer (Soman et al. 1991). Tpr can also translocate with Ntrk1 (NGF tirosin kinase) which is related to thyroid cancer (Greco et al. 1992; Greco et al. 1997). Ran is also over expressed in cancer, making nuclear protein synthesis faster (Sanderson and Clarke 2003). Finally, it has recently been discovered that mitotic spindle formation in cancer cells depends on a Ran-Survivin complex, something not present in normal cells. The alteration of this complex by inhibition provokes aberrant mitosis and apoptosis of cancer cells (Xia et al. 2008).

NPC and its role in aging

NPC and aging could be linked. Cells without capacity of proliferation do not turnover their NPC. So, aging process would provoke NPC degradation and poor cell and genetic functioning as time goes by (Fernández – Martínez and Rout 2009) .

NPC and its role in neurodegenerative diseases

NPCs are thought to be involved in neuro degenerative diseases because neurons do not proliferate and NPCs are not renewed causing NPCs to degenerate and neurons to die. High levels of ionic calcium are also involved in neural degeneration which is thought to be due to calcium-dependent pore degeneration (Bano et al. 2010a, 2010b).

NPC and its role in viral infections

NPC also plays an important role in viral infections because the nucleocytoplasmic transport of viral molecules depends on NPC. Moreover, some viruses disrupt NPC normal function when they are within the host cell. For example, HIV integrase has a specific NLS and is imported by TNPO3 (an importin) (Ocwieja et al. 2011; Woodward and Chow 2010). Another example is poliomyelitis virus which hydrolyzes Nup153 and impedes normal nucleocytoplasmic transport (Gustin and Sarnow 2001).

NPC and its role in other diseases

Many mutations in genes of nucleoporins provoke severe diseases. For example, a mutation in Nup155 is believed to produce atrial fibrillation and sudden death (Chen et al. 2008). Moreover, mutations in Nup133 are related to poor embryonic neural development (Lupu et al. 2008). ELYS (another NPC protein) mutation inhibits normal development in retina and intestine (de Jong Curtain et al. 2009). Furthermore, some authors link primary biliary cirrhosis with damage in Nup62 (Tartakovsky and Worman 1995).

The role of NPC in disease is an extremely new topic that is beginning to evolve. Nevertheless, scientists and doctors have known one syndrome for many years that was due to a mutation in NPC. It is ”triple A syndrome” comprising of achalasia, adrenocortical insufficiency (addisonianism) and alicrimia. This syndrome produces the mentioned manifestations and it is due to a mutation in the AAAS gene, a gene which normally produces the NPC protein Adracalin or Aladin (Sarathi and Shah 2010). More recently, Basel – Vanagaite et al. (2006) have discovered another genetic syndrome, autosomal recessive infantile bilateral striatal necrosis. This syndrome is due to a mutation in the nucleoporin, Nup62 (Figure 4).

As it has been seen, a lot of pathologies have a relationship with the NPC. Therefore, the structures of the NPC that are affected or involved in these pathologies could be therapeutic targets. In fact, Chahine and Pierce (2009) compile some studies in which pharmacologic targeting at the mechanisms of nuclear import have satisfactory laboratory results for the treatment of several diseases.

Conclusion

The NPC is a cellular structure located in the nuclear envelope, which permits the transport of macromolecules between the nucleus and the cytoplasm. However, recent studies have demonstrated that its function is more complex, having an important role in gene expression and disease.

On the one hand, it has been exposed the role of NPC in the regulation of epigenetic enzymes. So that, NPC might be one of the cell elements responsible for maintaining cellular epigenetic memory and cell phenotype. On the other hand, as it has been explained, concrete NPC proteins play an important role in the nucleocytoplasmic transport of snRNAs and many transcriptions factors. Therefore, the quantity of a determined transcription factor that is located in nucleus might depend on the proportion of the concrete nucleoporins, importins and exportins that compounds the NPC of a cell. Transcriptions factors and snRNAs control gene expression, so NPC might also control gene expression at this level.

Futhermore, many diseases and pathological processes such as cancer, aging, neurodegenerative diseases and viral infections have demonstrated to have a relationship with NPC. As a consequence, NPC could become future therapeutic target to treat these processes.

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