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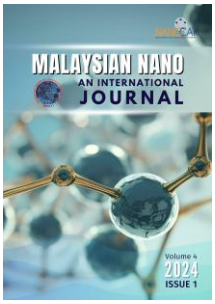

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Advancements in biomimetic nanomaterials in the activation of NF-κb receptors in cancer

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Abstract

Biomimetic nanomaterials are catching up in the field of oncology with the traditional methods of treating cancer. One of the leading causes of cancer is the misregulation of nuclear factor-κB (NF-κB) receptors in the body. They are essential for DNA transcription, cytokine synthesis, and cell survival. This study includes the roles of different biomimetic particles in activating the NF-κB pathway leading to cancer. NF-κB transcription factors involve various physiological processes, including innate and adaptive immunological responses, cell proliferation, cell death, and inflammation. It has been established that abnormal regulation of NF-κB and the signalling pathways that govern its activity play a role in cancer formation, development, and tolerance to chemo- and radiotherapy-future treatment options in nanotech. Cancer treatment includes conjugating nanoparticles and antibodies to suppress the activation of NF-κB receptors and using carbon-based nanomaterials like graphene.

Keywords: Protein, pro-apoptotic, tumour, carbon nanomaterials, immuno-nanomedicines

1. Introduction

The protein complex NF-κB (or NF-kappaB, which stands for "nuclear factor kappa-light-chain-enhancer of activated B cells") regulates DNA transcription, cytokine synthesis, and cell survival. NF-κB is present in virtually all animal cell types and plays a role in cellular responses to stress, cytokines, free radicals, heavy metals, UV irradiation, oxidised LDL, and bacterial or viral antigens, among other things (Gilmore et al., 2006; Brasier et al., 2006; Perkins et al., 2007; Gilmore et al., 1999; Tian et al., 2003). The transcription factor NF-κB is involved in regulating the immunological response to infection. Cancer, inflammatory and autoimmune illnesses, septic shock, viral infection, and incorrect immunological development have all been associated with NF-κB misregulation. The transcription factor NF-κB has also been linked to synaptic plasticity and memory (Albensi et al., 2000; Meffert et al., 2003; Levenson et al., 2004; Freudenthal et al., 1998; Merlo et al., Park et al., 2013).

NF-κB was identified in the lab of Nobel laureate David Baltimore by Ranjan Sen through its interaction with an 11-base pair sequence in the immunoglobulin light-chain enhancer in B cells in 1986 (Sen et al., 1986). It has been discovered in the dormant state in the cytoplasm of every cell and is found in all species, from Drosophila to man. When activated, it translocates to the nucleus, which controls the production of approximately 300 immunological, growth, and inflammatory genes. There are five members of the NF-κB family: NF-κB1 (p50/p105), NF-κB2 (p52/p100), RelA (p65), RelB, and c-Rel. There are two separate NF-κB activation pathways: canonical and non-canonical pathways. NF-κB1 and NF-κB2 are cleaved to the active p50 and p52 subunits before the NF-κB complex is translocated into the nucleus (Aggarwal et al., 2003). NF-κB is a transcription factor that regulates genes that control proliferation and survival in eukaryotic cells. As a result, NF-κB has been misregulated in many different types of human malignancies, resulting in NF-κB being constitutively active. Active NF-κB activates the production of genes that keep the cell growing and protect it from apoptosis-inducing circumstances. Proteins that govern NF-κB signalling are altered or overexpressed in cancer, resulting in a lack of cooperation between the malignant cell and the rest of the body. This is evident in metastasis and the immune system's ineffective tumour eradication (Vlahopoulos et al., 2017). Normal cells die when they are expelled from the tissue they belong to or when their genome fails to work in concert with tissue function: these events depend on NF-κB feedback regulation and fail in cancer (Vlahopoulos et al., 2015).

Defects in NF-κB make cells more susceptible to apoptosis, which leads to cell death. This is because NF-κB inhibits the activity of the caspase family of enzymes, which are essential for most

apoptotic processes, by regulating anti-apoptotic genes such as TRAF1 and TRAF2 (Sheikh et al., 2003). NF-κB activity is increased in tumour cells, as seen in 41% of nasopharyngeal carcinoma (Li et al., 2017), colorectal cancer, prostate cancer, and pancreatic tumours. This is caused by mutations in genes that code for NF-κB transcription factors or genes that control NF-κB activity (such as IκB genes); in addition, some tumour cells release substances that activate NF-κB (Sun et al., 2011; Nouri et al., 2020). By inhibiting NF-κB, tumour cells can cease multiplying, perish, or become more susceptible to anti-tumour drugs (Taniguchi et al., 2018; Sun et al., 2013). As a result, pharmaceutical companies are actively researching NF-κB as a target for anti-cancer therapy (Escárcega et al., 2007). Nonetheless, although convincing experimental data has identified NF-κB as a critical promoter of tumorigenesis, providing a solid rationale for the development of antitumor therapy based on NF-κB activity suppression, caution should be exercised when considering anti-NF-κB activity as a broad therapeutic strategy in cancer treatment, as data has also shown that NF-κB activity enhances tumour cell sensitivity to apoptosis and senescence. Furthermore, the canonical NF-κB is a Fas transcription activator, whereas the alternative NF-κB is a Fas transcription repressor. As a result, NF-κB enhances Fas-mediated apoptosis in cancer cells, while inhibiting NF-κB may limit Fas-mediated apoptosis, impairing tumour suppression by host immune cells (Liu et al., 2012).

The transcription factor NF-κB was first discovered to be required for B cell-specific gene expression. Still, subsequent research has found that it is part of a widely expressed family of Rel-related transcription factors that act as critical regulators for the inducible expression of several genes. The number of stimuli that trigger members of the Rel family is expanding, emphasising their importance in transcriptional responses. The molecular mechanism by which various inputs interact to activate this group of transcription factors is still a mystery (Mercurio et al., 1999).

2. Types of NF-κB receptors activated in cancer

As discussed earlier, five transcription factors make up the NF-κB family (also known as theRel/NF-κB family): p50, p52, RelA (also known as p65), RelB, and c-Rel (Karin et al., 2002; Bonizzi et al., 2004). All of them have a Rel homology domain (RHD), which contains a nuclear localisation signal (NLS) and is involved in homomeric or heteromeric dimer formation, sequence-specific DNA binding, and interaction with ankyrin repeat motifs found in IκB family members, which inhibits NF-κB. IκBα, IκBβ, IκBγ, IκBε, IκBNS, and Bcl-3 are the seven members of the IκB family. IκBζ (Yamamoto et al., 2004), IκBNS (Kuwata et al., 2006) and Bcl-3 (Bours et al., 1994) are nuclear proteins that interact with NF-κB family members in the nucleus to

control transcription. The remaining members of the IκB family engage with NF-κB' sRel homology domain in the cytoplasm and hide the nuclear localisation signal, thus sequestering NF-κB family members in the cytoplasm. As a result, when NF-κB family members form complexes with cytoplasmic IκB family proteins, they become transcriptionally inactive.

The activation of NF-κB in at least two types of cells is required for the formation and progression of cancer. NF-κB activation occurs in cells that are destined to become malignant (premalignant cells) and cells that are recruited to the tumour microenvironment and produce cytokines, growth and angiogenic factors, and proteases that deteriorate the extracellular matrix to assist cancer development and progression (microenvironment cells) (Greten et al., 2004; Pikarsky et al., 2004). Macrophages, dendritic cells, neutrophils, mast cells, T cells, and B cells are among the microenvironment cells. Several inflammatory cytokines, including TNFα, IL-1, and IL-6, are known to be dependent on the IKK-mediated classical NF-κB activation pathway generated by inflammation in some of these cells. TNFα and IL-1 secreted by premalignant cells activate NF-κB, which causes the activation of genes associated with apoptosis blocking, proliferation, and angiogenesis, all of which encourage malignancy. The conventional activation pathway, in which TNFR recruits TRAF2 and TRAF5 (Tada et al., 2001), and TRAF6 is required for IL-1 signalling, is also involved in NF-κB activation by TNFα or IL-1(Kobayashi et al., 2001; Cao et al., 1996).

Cancer metastasis necessitates malignant cells migrating both into and out of vessel walls that convey them to different body parts. Specific chemicals expressed in response to various signals from inflammatory cells, tumour cells, and others allow cells to pass vessel walls. ICAM-1, ELAM-1, and VCAM-1 are three of the unique molecules that have been demonstrated to be controlled by NF-κB activation (van der Saag et al., 1996; Iademarco et al., 1992; Whelan et al., 1991). As a primary target of NF-κB, the gene encoding granulocyte macrophage-colony stimulating factor (GM-CSF) facilitates breast cancer osteolytic bone metastases by increasing osteoclast formation (Park et al., 2007).

Like normal cells, tumour cells require oxygen to function, and a lack of oxygen can slow tumour progression. The production of angiogenic growth factors (e.g., VEGF, MCP-1) from tumour cells and inflammatory cells like macrophages and neutrophils, or in response to pro-inflammatory cytokines, is required for tumour vascularisation (e.g., TNF) (Loch et al., 2001; Oyama et al., 2000; Ueno et al., 2000). NF-κB controls the expression of angiogenesis-related growth factors and cytokines (VEGF, TNF, and MCP-1) (Chiloy et al., 1997; Shakhov et al., 1990; Ueda et al., 1994; Collart et al., 1994). Many genes associated with cancer promotion (e.g., clonal expansion, growth, diversification, angiogenesis, adhesion, extravasation, and extracellular

matrix breakdown) are regulated by NF-κB. For example, the proinflammatory gene COX2, which is highly expressed in a range of malignancies, including colorectal cancer and mesothelioma (Kalgutkar et al., 2001; Marrogi et al., 2000), may be regulated by NF-κB. TNF (Noguchi et al., 1996), IL-1 (Tomimatsu et al., 2001), iNOS (Klotz et al., 1999), matrix metalloproteinase (MMP-9) (Dong et al., 2001), urokinase-type plasminogen activator (uPA) (Pacheco et al., 2001), and many other chemokines have all been found to be regulated by NF-κB in similar research(Scotton et al., 2001; Strieter et al., 2001; Palmer et al., 2001).

In addition to its more well-known anti-apoptotic function, NF-κB has been found to have a pro-apoptotic function. B cells (Abbadie et al., 1993), T cells (Dumont et al., 1999; Kasibhatla et al., 1998), neuronal cells (Schneider et al., 1999; Qin et al., 1999), and endothelial cells (DeMeester et al., 1998) are examples of cells that have pro-apoptotic effects from it. The conflicting effects of NF-κB are assumed to be cell-type specific and reliant on the inducing signal (IL-1, TNF-α, and UV radiation, for example). Different NF-κB activation pathways may result in the expression of apoptosis-promoting (e.g., Fas, c-myc, p53, and IκBα) or apoptosis-inhibiting proteins (e.g., Fas, c-myc, p53, and IκBα) or apoptosis-inhibiting proteins (e.g., TRAF2, IAP proteins, and Bcl-2 like proteins) (Qin et al., 1999; Chan et al., 1999; Stehlik et al., 1998). Furthermore, NF-κB activation regulates cell cycle proteins (e.g., cyclin D1 and CDK2 kinase) (Guttridge et al., 1999; Hinz et al., 1999; Bash et al., 1997) and their interactions with cellular components (e.g., p300 and p53) that promote or induce apoptosis in different ways (Ravi et al., 1998; Yang et al., 1999).

The five types of NF-κB receptors are as follows:

1. **RelA/p65:** Transcription factor p65, also known as nuclear factor NF-κB p65 subunit, is a protein encoded by the RELA gene in humans (Nolan et al., 1991). NF-κB/RELA activation has been linked to cancer development (Vlahopoulos et al., 2019), implying that RELA might be a cancer biomarker (Onishi et al., 2018). Various cancer types have also reported RELA-specific alteration patterns (Ahmed et al., 2019; Ali et al., 2017). The correlation discovered between RELA nuclear localisation and prostate cancer aggressiveness, and biochemical recurrence suggests that RELA may have a potential role as a biomarker for prostate cancer development and metastasis (Gannon et al., 2013). There is a strong association between RELA nuclear localisation and clinicopathological characteristics for papillary thyroid cancer (PTC), suggesting that NF-κB activation plays a role in tumour development and aggressiveness in PTC (Pyo et al., 2013). In addition to

being used as a biomarker, morphoproteomic study shows that serine 536 phosphorylation in RELA is associated with nuclear translocation and the expression of several transactivating genes such as COX-2, IL-8, and GST-pi in follicular thyroid carcinomas (Liu et al., 2012). Mutations in RELA's transactivation domain can reduce transactivation capacity, which has been discovered in lymphoid neoplasia (Trecca et al., 1997). In patients with head and neck squamous cell carcinoma, nuclear NF-B/RELA localisation favourably connects tumour micrometastases into lymph and blood and negatively correlates with patient survival results (Balermpas et al., 2013). This points to NF-B/RELA as a potential target for targeted treatment. RELA and the aryl hydrocarbon receptor (AhR) have a physical and functional interaction, activating c-myc gene transcription in breast cancer cells (Gionet et al., 2009). Another study found connections between oestrogen receptors (ER) and NF-κB members such as p50 and RELA. It has been demonstrated that ERα interacts with both p50 and RELA in vitro and in vivo and that RELA antibodies can inhibit the formation of ER: ERE complexes. According to the article, ER and NF-κB suppress each other.

2. **c-Rel:** In various contexts, abnormal, constitutively active Rel/NF-κB activity has been linked to human malignancies (Gilmore et al., 2002; Karin et al., 2002). Although p50–RelA NF-κB complexes are constitutively nuclear and active in many human tumour cell types (Gilmore et al., 2002), this activity most likely contributes to tumour cell survival (i.e., antiapoptosis) (Barkett and Gilmore et al., 1999). Thus, suppressing NF-κB activity will likely be helpful as adjuvant treatment in these conditions, sensitising tumour cells to the apoptotic impact of typical chemo- or radiotherapeutic drugs. Similarly, although C-terminal truncation of p100 (in the NF-κB2 gene) and overexpression of the p50/p52 coactivator BCL-3 have been found in human B-cell leukaemias/lymphomas (Gilmore et al., 2002; Karin et al., 2002), these proteins have not been shown to have oncogenic activity in lymphoid cells in vitro or transgenic mice. cRel, conversely, appears to have direct and total carcinogenic activity in lymphoid cells, according to many lines of evidence. First, as previously mentioned, human REL overexpression (but not other human Rel/NF-kB family members) can malignantly convert chicken lymphoid cells in vitro (Gilmore et al., 2001; Starczynowski et al., 2003). Second, transgenic mice with v-rel expression driven by a T cell-specific promoter generate T-cell malignancies, although with a 6–10-month latency (Carrasco et al., 1996). Third, c-rel gene expression has been upregulated in B-cell lymphomas through genetic mechanisms: one chicken B-cell

lymphoma cell line has a retroviral integration upstream of c-rel (Kabrun et al., 1990); the REL gene has been translocated near the immunoglobulin light chain gene enhancer in one primary Hodgkin's lymphoma (Barth et al., 2001); and the REL gene is enhanced in human lymphomas.

3. **RelB:** RelB was discovered as a major transcription factor of NF-κB, which affects several biological processes, including cell survival and immunological and inflammatory responses (Guo et al., 2008; Bellet et al., 2012; McMillian et al., 2011). Emerging research suggests that relB has a significant function in the advancement of several forms of cancer. RelB stimulates cancer cell proliferation in prostate cancer while decreasing radiosensitivity (Xu et al., 2009; Zhu et al., 2014). In breast cancer, relB promotes cellular survival and has a propensity for more invasive phenotypes (Mineva et al., 2009). Overexpression of relB in chronic lymphocytic leukaemia (CLL) cells improves susceptibility to the proteasome inhibitor bortezomib (Xu et al., 2014).
4. **NF-κB1:** Although NF-κB1 is most typically associated with cancers associated with inflammation (Didonato et al., 2012), anti-inflammatory p50 homodimers can operate as tumour suppressors in hepatocellular carcinoma (Wilson et al., 2015). NF-κB1 may impart a direct cellular protective response against carcinogens that induce genotoxic damage, such as alkylating chemicals, and its involvement in controlling the inflammatory response. NF-κB1 has been identified as a pathway-specific tumour suppressor that protects against haematological malignancy after alkylator (N-methyl-Nnitrosourea)-mediated cellular damage (Voce et al., 2014). In colorectal cancer cell lines, p50 homodimers have also been shown to attract the anti-apoptotic protein BCL2-associated athanogene (BAG-1) to the promoter of the epidermal growth factor receptor (EGFR) gene. BAG-1 needs p50 to suppress EGFR expression, potentially downregulating an essential signalling pathway in colorectal cancer start and development (Southern et al., 2012).
5. **NF-κB2/p52:** Despite its discovery more than a decade ago, p52 NF-κB (also known as NF-κB2 and Lyt-10) is one of the most poorly understood NF-κB subunits (Neri et al., 1991; Schmid et al., 1991; Bours et al., 1992). p52 is a tumour-promoting transcription factor that is activated by viral oncoprotein production. Increased p52 activation has been seen in the lung (Dimitrakopoulos et al., 2012), breast (Cogswell et al., 2000), prostate (Lessard et al., 2005; Seo et al., 2009) and pancreatic cancers (Wharry et al., 2009); however, research on the impact of p52 activation in epithelial cancers has been limited

due to a lack of adequate in vivo models.

Table 1: Types of NF-κB receptors

Type	Cancer Association	Biomarkers	Pathways	Interactions
RelA/p65	Promotes cancer development and metastasis	Prostate cancer, papillary thyroid cancer	RelA nuclear translocation, serine 536 phosphorylation	Aryl hydrocarbon receptor (AhR), estrogen receptors (ER)
c-Rel	Directly contributes to lymphoid malignancies	Not Established	Not Established	Not Established
RelB	Promotes cancer cell proliferation and survival	Chronic lymphocytic leukaemia (CLL)	Not Established	Not Established
NF-κB1	Can act as a tumor suppressor in some cancers	Hepatocellular carcinoma	p50 homodimer formation	BCL2-associated athanogene (BAG-1)
NF-κB2/p52	Promotes tumorigenesis	Lung, breast, prostate, pancreatic cancers	Not well understood	Viral oncoproteins

3. Role of different biomimeric nanoparticles in activation of NF-κB receptors

Nanoparticles-Antibody Conjugate:

The bulk of NF-κB is found in the cytosol as a heterodimer of p65/p50 Rel proteins bound to inhibitory IκBα proteins. When the IκBα protein is activated, it separates from NF-κB, and p65/p50 translocates into the nucleus to begin gene expression (Kabe et al., 2005; Karin et al., 2002). Because of misregulated signals, several forms of human malignancies have constitutively active NF-κB (Ahn et al., 2005; Pikarsky et al., 2004; Karin et al., 2005). The epithelial malignancies of breast, colon, lung, prostate, and ovarian carcinomas have all been linked to NF-κB signalling (Zeligs et al., 2016). As a result, inhibiting NF-κB activity and its signalling pathways could provide promising novel cancer chemotherapeutic methods. As a targeted therapy,

blocking NF-κB can induce tumour cells to stop multiplying or become more receptive to anti-tumor medicines (Greten et al., 2004).

Understanding the control and function of the NF-κB subunits in cancer is paving the way for developing more effective treatments targeting the NF-κB–IKK pathway (Ahn et al., 2005). Inhibition of NF-κB as a therapeutic target is generally inefficient due to inhibitors with low specificity to a target protein or disruption from other signalling systems in the parallel crosstalk. To prevent off-target effects, siRNA-mediated gene silencing has been created. Despite this, the use of siRNA as a treatment is limited due to their poor chemical stability and the requirement of easily transfectable cells (Kim et al., 2019; Kokkinos et al., 2020). A p65-antibody-nanoparticle construct is used to inhibit the translocation of the particular transcription factor Rel protein p65/p50 near the nuclear pore in the last cytosol phase, which is akin to catching a goal-tending ball in a soccer game (Chen et al., 2020).

In previously described antibody-based nanotechnology, cellular surface antibodies such as human epidermal growth factor receptor 2 (HER2) are coupled onto nanoparticles to block or target surface antigens via immunogenic recognition for detection/diagnosis, imaging, and treatment (Yang et al., 2010; McCarron et al., 2008). There have been no reports of an antibody treatment for preventing the nuclear transduction process in the cytoplasm because antibodies have substantial permeability issues entering cells unless they are coupled with cargo delivery or cell-penetrating peptides (CPP) (Rizzuti et al., 2015). The difficulty is solved by conjugating the p65 antibody to CPP-conjugated nanoparticles. The CPP-nanoparticle design will be an excellent nanocarrier for delivering the p65 antibody into the cell and focusing on the nucleus to capture the Rel protein p65. Mesoporous silica nanoparticle (MSN) (Chen et al., 2013; Chen et al., 2019; Shao et al., 2018; Sun et al., 2019) is chosen for the nanocarrier because of its ease of functionalisation.

In vitro, cell-penetrating peptides such as the transactivator of transcription (TAT) peptide comprising a short section of YGRKKRRQRRR have been studied for their ability to promote cell penetration and nucleus targeting (Rizzuti et al., 2015; Wu et al., 2013). TAT peptides coupled with nanoparticles have been proven to direct nuclear entry into cells. TAT-functionalized tiny MSN has been employed to transport cancer drugs into the nucleus of cells for successful cancer treatment. Using TAT's inherent proclivity for nucleus targeting and p65 antibody's ability to capture p65 in the perinuclear area, we show that this hybrid MSN can successfully block TNF-induced NF-κB p65 activity in HeLa cells and decrease cell proliferation in constitutively NF-κB activated HNSCC cells (Pan et al., 2012, 2013, 2014).

Carbon-Based Nanomaterials:

Carbon nanotubes (CNTs) have been widely studied for their unique physicochemical features thus far. Because of their 1D nature, they are an excellent substrate for biological applications (Battigelli et al., 2013). VanHandel et al. discovered that tumour-associated CNTs took up most Macrophages in one of the first trials employing CNTs to treat glioma, with no substantial systemic damage in animals (VanHandel et al., 2009). Furthermore, in a study using a metastatic brain tumour mouse model, functionalised carbon nanotubes conjugated with CpG via disulfide bonds not only increased CpG uptake by TAMs but also resulted in the elimination of intracranial (i.c.) gliomas, protecting mice from tumour recurrence even at low doses. Furthermore, higher retention of CNT–CpG was detected in TLR-9 positive microglia, leading to TLR (Toll-Like Receptor)-induced activation of NF-κB and AP-1 (Fan et al., 2012).

Graphene is the most recent member of the family of carbon nanomaterials. Because of its physiochemical features and biocompatibility, this carbon allotrope lattice has received much interest in cancer therapy. Graphene strongly stimulates the TLR-mediated NF-κB pathway and increases the production of cytokines such as IL-1a, TNF-α, and IL-10, as well as chemokines such as MCP-1, MIP-1a, and RANTES. These inflammatory stimuli alter the shape and function of naïve macrophages. IL-10 prevents macrophages from developing inflammatory responses, hence preventing macrophages from overactivation following graphene exposure (Zhou et al., 2012). Tao et al. employed PEG and PEI-functionalized Graphene (GO-PEG-PEI) to transport CpG. On the one hand, GO-PEG-PEI increased the number of proinflammatory cytokines and improved the function of CpG. On the other hand, GO-PEG-PEI boosted the immunostimulatory activity of CpG due to its NIR absorbance (Tao et al. 2014). Ma et al. discovered that bigger Graphene particles (750–1300 nm) promoted M1 polarisation more potently than smaller Graphene particles (50–350 nm); in contrast to more minor Graphene moieties, larger Graphene particles may adsorb onto the macrophage membrane and engage vigorously with Toll-like receptors such as TLR2 and TLR4. As a result, bigger Graphene particles more strongly activated the NF-κB pathway and significantly increased M1 polarisation in vitro and in vivo (Ma et al., 2015).

Table 2: Nanoparticles & their effects on NF-κB pathways

Nanoparticle Type	**Function**	**Effect on NF-κB Signaling**	**Mechanism of Action**	**Reference**
Antibody-Nanoparticle Conjugate	Inhibit p65/p50 translocation to nucleus	Blocks NF-κB activation	TAT peptide conjugated nanoparticles deliver p65 antibody to the cytoplasm to capture Rel protein p65	Chen et al., 2020
Mesoporous Silica Nanoparticle (MSN)	Carrier for p65 antibody	Facilitates delivery and targeting of p65 antibody	Chosen for ease of functionalization	Chen et al., 2013
Carbon Nanotubes (CNTs)	Immunostimulant	May activate NF-κB through TLR-9 positive microglia	Increased CpG uptake by TAMs leads to TLR-induced activation	Fan et al., 2012
Graphene Oxide (GO)	Immunostimulant	Promotes TLR-mediated NF-κB pathway activation	Increases proinflammatory cytokines and chemokine production	Zhou et al., 2012
PEGylated and PEI-functionalized Graphene (GO-PEG-PEI)	CpG delivery and immunostimulant	Enhances CpG function and immunostimulatory activity	Delivers CpG and increases NIR absorbance	Tao et al., 2014

4. Future Perspectives & Conclusion

Materials having immunomodulatory properties are being developed for cancer vaccines, cytokine delivery, and TAM regulation. As the use of biomaterials in cancer immunotherapies grows, more emphasis will be placed on directly regulating other kinds of immune cells. The intersection of nanomedicine and imaging will likely represent a potential step forward in developing cancer immuno-nanomedicines shortly. The fundamental criteria needing improvement to achieve maximum clinical efficacy are patients' particular responses, cancer type specificity, and robust targeting. High-throughput library methods, as well as extensive phenotyping, will be critical in the creation of cutting-edge products with the ability to target cancer cells mainly.

Because the behaviour of nanoparticles may differ in vitro and in vivo, substantial validation in animal models is required for reliable clinical translation. To improve anticancer effects, it will be necessary to stimulate both the innate and adaptive immune systems with carefully developed cancer immuno-nanomedicines. To achieve precision administration, better stability, targeted

biodistribution, favourable pharmacokinetics, and minimal systemic toxicity, nanoparticle features such as size, shape, charge, material, surface functionalisation, and antigen and adjuvant selection will require rigorous critical examination (Ovais et al., 2019).

Newer and more complex characterisation approaches, such as pharmacokinetics and long-term toxicity investigations, are also required. The expense of integrating numerous components for co-loading or multifunctional features is another factor to consider for economic feasibility. The requisite regulatory processes are also becoming more difficult due to the multifunctionalities of the nanoparticles, which comprise many extra components and claim various indications with a single nanoparticle. Nonetheless, there is a good chance that multifunctional chemo/gene therapy nanoparticle systems for cancer-specific treatment will be deployed in clinics soon. Multifunctional chemo/gene therapy techniques will aid in meeting unmet medical demands for effective cancer therapies with few side effects (Glasglow et al., 2015).

Conflicts of interest

The authors declare that they have no conflict of interest.

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