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A brief overview on role of graphene based material in therapeutic management of inflammatory response signalling cascades

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Abstract

Graphene is a novel, sp^2 carbon atoms bonded, two-dimensional nano-material. Due to their favorable electronic, thermal, optical, and mechanical property, graphene and its derivatives, like graphene oxide (GO) and graphene quantum dots (GQDs) are used in widespread applications. The outstanding potentials of these compounds in the field of nanoelectronics, composite materials, sensors, energy technology etc helped in the rapid development in their functionalization, modulatory effects on various systems of our body. GQDs has been suggested as a new nanomaterial with improved biocompatibility, biodegradability, water solubility and considerably low cytotoxic effects in in vivo models, and are applicable for altering immune responses based on quantum confinement and edge effect properties. The review particularly elucidates the mechanistic approach by which graphene and/ or its derivatives and/ or their nano-compound aid in therapeutic management against myriads of immunological perspectives. GQDs have unique physio-chemical properties with carbon sheets showcases out-standing biological response against immunological interventions by altering the activities of t-cell lymphocytes. On the contrary GO plays a vital role in eliciting inflammatory signaling factors by controlling pro-inflammation and an anti-inflammatory response. Therefore, this review shall help the readers to have an overview of the biomedical application of graphene and its derivatives to design target specific drugs to regulate the immune response based prognosis and cure.

Keywords: Anti-inflammatory, graphene, graphene oxide, Graphene quantum dots, signaling factors.

Introduction

Graphene is an allotrope of carbon having a single layer of atoms within a two-dimensional hexagonal lattice where one atom forms each vertex (Bhattarai, 2013; Li et al., 2012; Wang et al., 2011). Carbon is the second most abundant mass within human body marks its importance in the chemical basis of life on earth (Malik et al., 2019). Thus, the physico-chemical property of carbon makes its allotrope, graphene, a potential eco-friendly candidate with a sustainable solution for an almost limitless application.

The oxide form of graphene, i.e., graphene oxide, has been reported to be a biocompatible product having anti-inflammatory activity in their non nano and nano formulation (Ding et al., 2020; Miao et al., 2018). Graphene oxide-based nanomaterials have gained broad interests in recent research because of their unique physico-chemical properties specially based on their 2D allotropic structure making them more acceptable in different biological fields (Wang et al., 2011; Priyadarsini et al., 2018). Aside from showing cytotoxicity in the cancer cell (Priyadarsini et al., 2018; Banerjee et al., 2019) it has also been reported that graphene oxide nanoparticle (GONP) has exceptional bio-distribution and cell interaction properties (Liu et al., 2012; Mu et al., 2012; Yang et al., 2013; Tonelli et al., 2015; Podolska et al., 2020).

Graphene quantum dots (GQDs) are edge-bound nanometer-size graphene pieces. They have fascinating optical and electronic properties, showcasing excellent biological and physico-chemical properties which regulate the physiology of various system of our body making them a potential candidate for biomedical applications (Chen et al., 2017; Tian et al., 2018, Kumar et al., 2020). Small size, high photostable nature,exceptional biocompatibility properties with an added antioxidant efficacy in the biological system makes GQD a potential therapeutic agent for treating myriads of diseases including cancer (Tian et al., 2018; Li et al., 2018; Fan et al., 2019; Kumar et al., 2020), diabetes (Faridi, et al., 2019; Du et al., 2020), diseases related to inflammation (Tosic et al., 2019; Lee et al., 2020) etc.

Therefore, the present review focuses a brief perspective focusing on the anti-inflammatory response of Graphene in their GO and GQD which have been found to play a key role in optimizing the signaling cascades for anti-inflammatory or pro-inflammatory responses depending on the individual disease concerned.

Role of graphene oxide (GO) to initiate anti-inflammatory response through polarization of macrophage

Innate immunity of the biological system acts as 1st line defence against pathogens, damage tissue and toxicants (Mukherjee et al., 2017). Inflammation is a major part of innate immunity. Although acute inflammation is good for our biological system, however, it becomes hazardous when acute inflammation is converted to chronic inflammation (Sansbury et al., 2016; Chen et al., 2017) Inflammation is the outcome of activation of different types of immune- signalling cascades (Chen et al., 2017).

Graphene oxide (GO) has been reported to contain hydroxyl, carbonyl, carboxyl and epoxide functional groups on the surfaces of each sheet in their structure (Yang et al., 2016). These reactive functional groups thereby impart tremendous aqueous solubility, biocompatibility and multi-functionalities, of GO which is an essential factor for the smooth targeted delivery of drugs (Pei et al., 2020).

In response to inflammatory dysfunction GO has played a vital role in maintaining a balance in activating upstream and/ or downstream signalling cascades (Feito et al., 2019) GO activates the M2 phenotype of macrophage which is secreting anti-inflammatory cytokines like interleukin 4 (IL-4) and interleukin 10 (IL-10). At the infection site, first M1 initiates secretion of the pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6) and inflammation occurs. After 1st phage of inflammation is done, M1 converts into M2 macrophage which starts the 2nd phage of inflammation. In 2nd phage of inflammation, damaged tissue undergoes a repair system [Ma et al., 2015]. A longer period of extension of the 1st phase of inflammatory effect causes impairment of tissue reconstruction. Therefore, M2 macrophages act as a potential candidate for application for the treatment for M1 induced inflammation (Ding et al., 2020). Recently GO is used as an anti-inflammatory drug that can shift M1 macrophages to the M2 macrophages with the help of the polarization process [Miao et al., 2018]. On the other hand, GO causes cytotoxicity by the production of excess amounts of ROS generation [Zhan et al., 2020]; macrophage targeting polarized GO complex reduces the ROS generation (Han et al., 2018). Further, IL-4 is known to plays a vital role in 2nd phase inflammation (Daseke et al., 2020) where it can upregulate the expression of anti-inflammatory biomarkers with MGC like IL10, mannose receptor (Woodward et al., 2010). It has also been reported that IL-1ra, IL-10 and transforming growth factor (TGF)-β released from M2 macrophages promote the signalling pathways of anti-inflammation thereby inducing tissue repair and cure of injuries (Atri et al., 2018). Additionally, the lipopolysaccharides activated monocytes release tumour necrosis factor (TNF)-α and IL-1β which are responsible for inflammation (Tucureanu et al., 2017). Thus, IL-4 cytokines down regulate these inflammatory biomarkers along with induction of peroxisome proliferator-activated receptors (PPARs) protein with their 2 subset PPAR-γ and PPAR-δ which reduces the expression of IL-6 and IL-12 (pro-inflammatory cytokines) (Natarajan et al., 2002; Croasdell et al., 2015; Khajebishak et al., 2019). Hence without PPARs, IL-4 cannot participates in the reduction of the expression of IL-6 and IL-12 [Kytikova et al., 2020: Cunard et al., 2002]. Further, IL-10 also suppresses the TNF α ,IL-6 and IL-12 expression and prevents the cytokines overproduction (D'Andrea et al., 1993; Schülke 2018) Moreover, IL-4, IL-10 and PPAR protein are suppressed NF – κβ signalling pathways. NF – κβ being the transcription factor that binds with the nuclear binding sites of the inflammatory gene (Driessler et al., 2004; Woodward et al., 2010; Liu et al., 2017; Lin et al., 2017 ; Wierzbicki et al., 2018; Korbecki et al., 2019; Ju et al., 2020) therefore plays a pivotal role in the regulation of inflammation (Farmer et al., 2000; Martins et al., 2016).

Graphene oxide has been an effective scavenger of hydroxyl radicals and superoxide and therefore can act as an antioxidant (Qui et al., 2014). Thus GO has a dual role in the inflammatory response which can induce both pro and anti-inflammatory responses (Ma et al., 2015; Dudek et al., 2016; Han et al., 2018, Diez-Orejas et al., 2018; Feito et al., 2019) and aid in regulating ROS generation through selective pathways. Thus, it may be stated that when GO is uptaken by macrophages, it shows pro-inflammation with M1 macrophages, thereby ensuing their capability to polarize the M1 to M2 macrophages or vice versa signalling

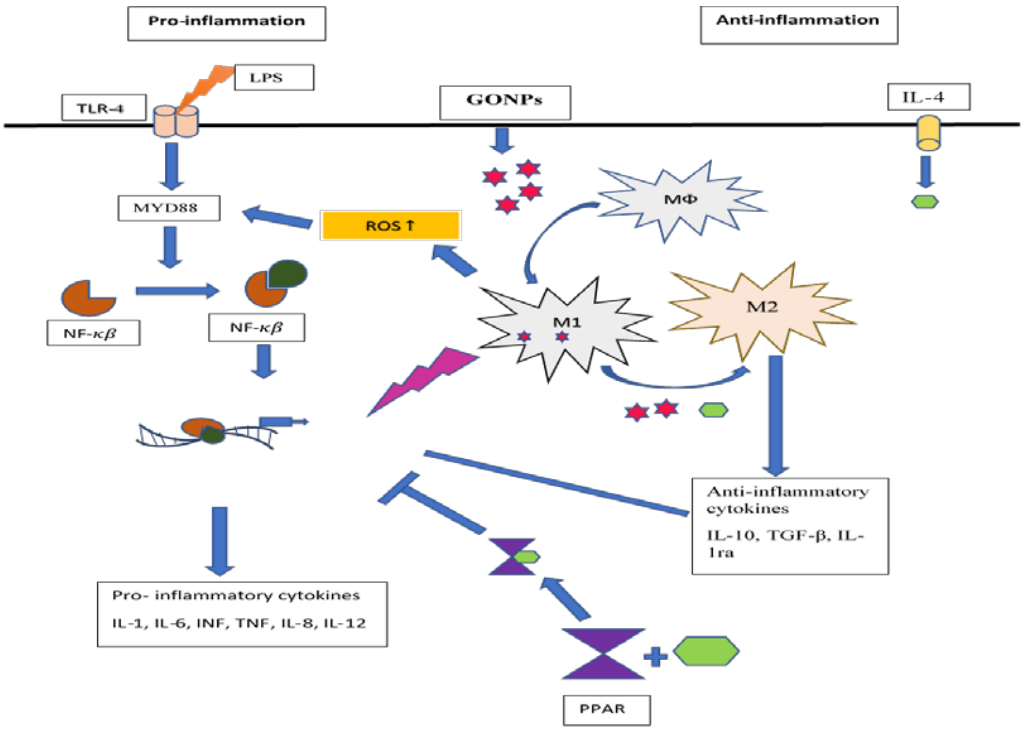

Fig. 1. Diagram of crosstalk signaling between pro-inflammation and anti-inflammation regulated by graphene oxide nanoparticle.

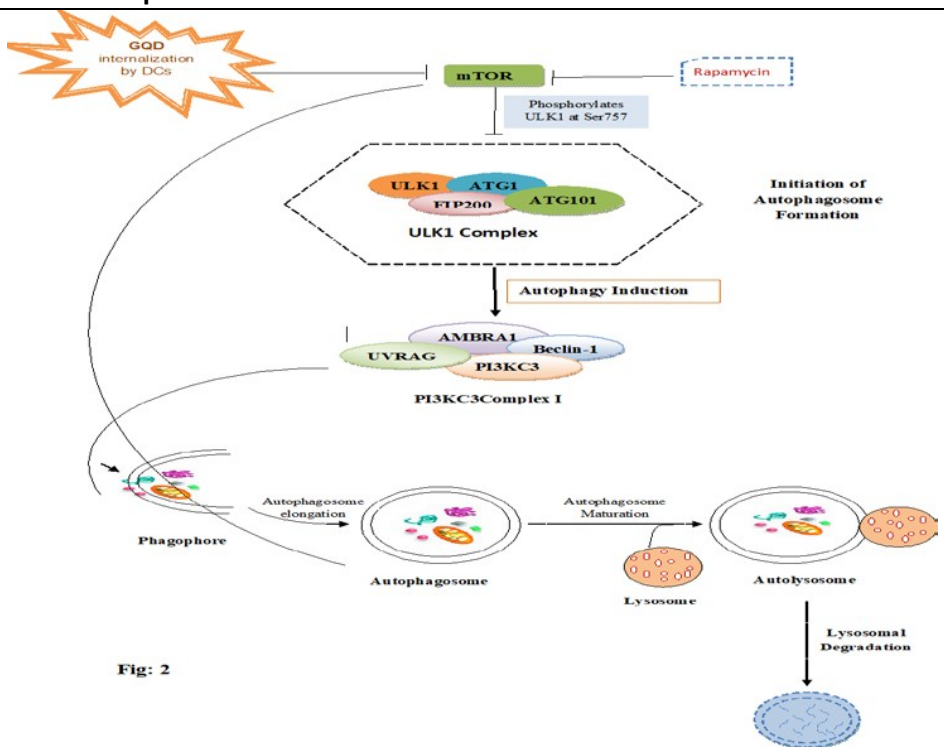

Fig. 2. Graphene Quantum Dots (GQDs) internalization by DCs (Dendritic Cells) promotes Autophagy in them and thus induces Autophagy.

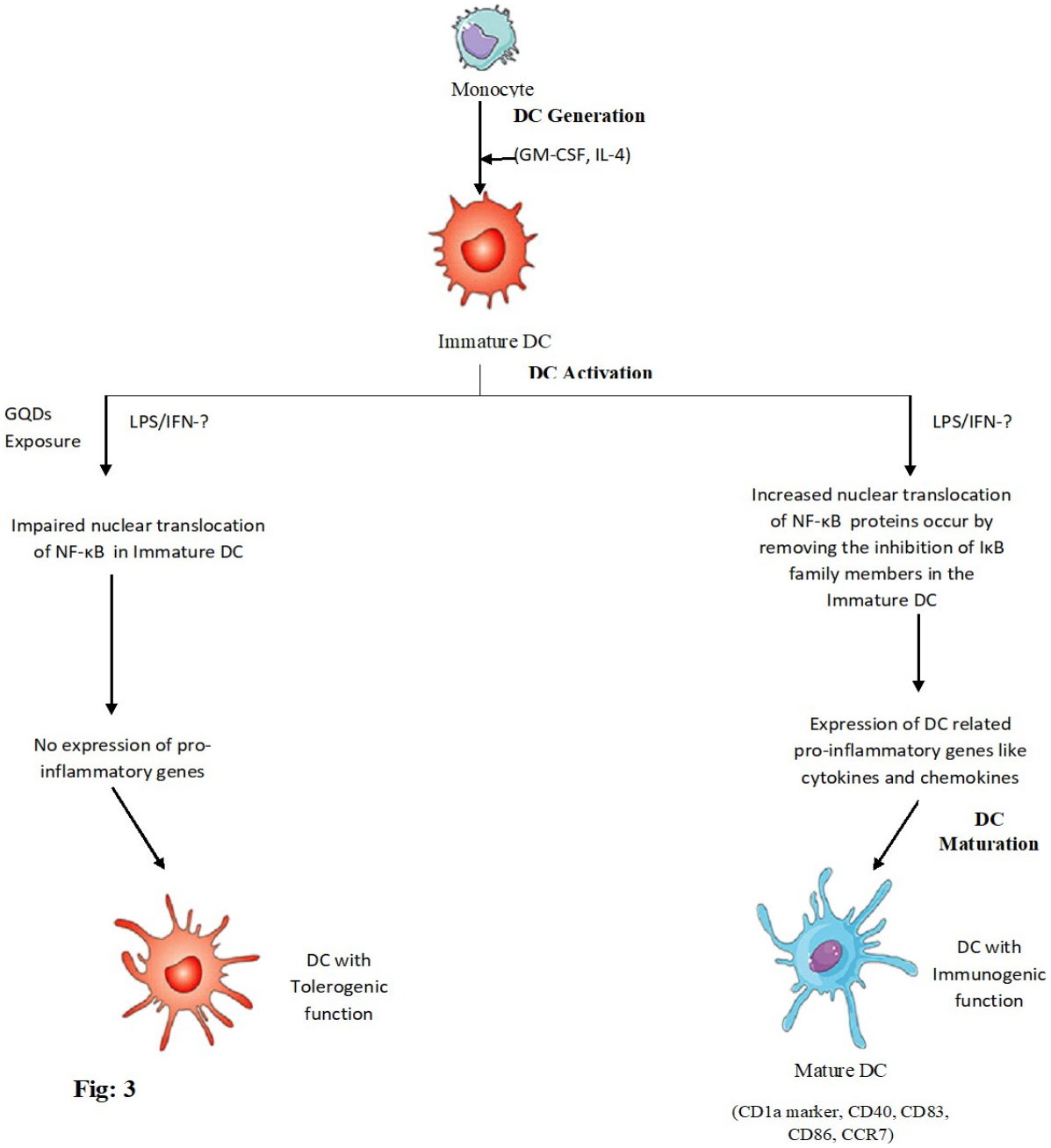

Fig: 3

Fig. 3: Graphene Quantum Dots (GQDs) inducing tolerogenic functionality of DCs (Dendritic Cells) by inhibiting the translocation of NF-κB transcription factors into the nucleus as compared to controlled maturation of DCs.

pathways of inflammation (Fig. 1). Hence, GO has both inflammatory and anti-inflammatory response (Hoyle et al., 2018) which switches and crosswalk in between the two depending on the type of initiation and progression of the individual disease prognosis.

Role of GQD inT-cell functionality by regulating inflammatory response

Dendritic Cells (DCs) are the most potent form of APCs capable of activating or tolerizing antigen-specific T cells (Mildner and Jung, 2014) i.e., DCs enable a tight-regulation of immune system by modifying the functions of T cells. On exposure to GQDs, DCs were found to internalize them, and exhibited a kind of altered development, maturation and differentiation (Tomić et al., 2017). Further, studies indicated that increased autophagic gene transcription, lowered ROS generation and nuclear translocation of NF-κB regulated impaired function of DCs (Tomić et al., 2017). Administration of GQDs inhibited the production of pro-inflammatory and T-helper (Th1) cytokines and increase the production of anti-inflammatory and Th2 cytokines using human peripheral blood mononuclear cells (Tomić et al., 2017; Lee et al., 2020). Since, GQD cannot affect the T cells directly by altering the immunogenic responses, GQDs lowers the phenomenon of T cell proliferation, development of Th1 and Th17 cells and T-cell mediated cytotoxicity by targeting the functions of monocyte-derived Dendritic Cells (DCs). GQDs also induces suppressive regulatory T cells i.e. GQDs have a pro-tolerogenic effects on DC (Tomić et al., 2017; Tosic et al., 2018; Lee et al., 2020).

Dendritic Cells can exhibit both inflammatory responses like phenotypic maturation of DCs, production of pro-inflammatory cytokines such as Interleukin (IL)-12, IL-1β, Lymphotoxin (LT)-α, IL-6, IL-8 and differentiation of pro-inflammatory T helper (Th1) and Th17 cells, and Cytotoxic T lymphocytes (CTLs) as well as anti-inflammatory responses by secreting anti-inflammatory cytokines such as IL-10, which permits DCs to induce immunosuppressive regulatory T cells (Treg) and Th1-suppressing Th2 response (Raker and Domogalla, 2015). Thus it can be inferred that DCs become functionally mature to either give rise to an immunostimulatory phenotype (as occurs in case of infections) or to a tolerogenic phenotype which is linked with immune-suppression to self-antigens (also cancer). This dual function of DCs is critical to Autophagy which can reduce antigen presentation, DC maturation and T cell activation.e Autophagy has an inhibitory role in immunogenic maturation of DCs and positive role in tolerogenic maturation of DCs [Ghislat and Lawrence, 2018]. Thus, it can be anticipated that autophagy is triggered by GQD which in turn is responsible for the tolerogenic functions in DCs, which would serve beneficial in the inflammatory T cell-mediated pathologies, but harmful to anti-cancer therapy by GQDs (Tomić et al., 2017; Qin et al., 2015; Ghislat and Lawrence, 2018). Reports suggest that GQDs disrupt the mTOR (mammalian target of rapamycin) mediated cell survival and induces autophagy in DCs and thus suppressing their maturation and inducing the tolerogenic properties of DCs (Fig. 2). The nuclear translocation of NF-κB has also been found to be crucial for the development and induction of tolerogenic DCs (Tomić et al., 2017; Iruretagoyena, 2006; Carreño et al.,

2010) (Fig 3). Several literature reports suggest that ROS production during aerobic activities of the cell can also participate in the induction of autophagy as an effective defence response towards cellular stress [Fang et al., 2017]. The process of DC migration, maturation and its ability to stimulate antigen-specific T cells as well as T cell activation and cytokine production is balanced by autophagy regulated by transcriptionally activated genes or mTOR proteins (Amiel et al., 2012; Sukhbaatar et al., 2016; Tomić et al., 2017). The GQDs induced cytokine generation and activated overall inflammatory signalling factors, induces apoptosis and autophagy of macrophages via activation of p38 MAPK and NF-kB signalling pathway, subsequently intensifying the tolerogenic activity of dendritic cells by stimulation of Treg cells (Qin et al., 2015; Tomić etal., 2017).

Conclusion

The immune system shields the host body by responding to either/ or both external and internal stimuli. In the present review, we tried to elucidate the potential use of graphene in its two form graphene oxide and graphene quantum dots to promote cytokine-induced inflammation, leading to apoptosis and autophagy of macrophages via activation of p38 MAPK and NF-kB signalling cascades thereby maintaining an optimum balance by switching its activity between pro-inflammatory and anti-inflammatory response factor. Thus, GO and/ or GQDs displayed to be the most promising cellular biocompatible and bio-available substance in triggering immune responses through several pathways thereby paving a new insight towards its improved application for therapeutic management of inflammatory disorders and might be used as an adjunct to develop a newer version of vaccines in the near future.

Conflict of interest:

None to declare

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