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Role of Galphaq Containing Protein in Immune Regulation

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ABSTRACT

G proteins, one of the most important transmembrane signal transducers, contain four subfamilies. $G_{\alpha q}$ is the α subunit of G_q protein subfamily. The $G_{\alpha q}$ containing protein initially attracted attention for its physiological significance is in cardiovascular system. In recent years, its role in immune regulation has been indicated. Studies domenstrated that $G_{\alpha q}$ plays crucial role in regulating both innate and adaptive immune cells function and it is involved in the development of autoimmune disease. In this review, we summarized recent data in the role of $G_{\alpha q}$ containing protein in regulating immune cells function and the possible mechanisms.

Keywords: $G_{\alpha q}$, Heterotrimeric G Proteins, Immune Cells, Autoimmune Disease

1. INTRODUCTION

$G_{\alpha q}$, the α subunit of G_q protein, is ubiquitously expressed in mammalian cells and couples a huge variety of receptors to channel proteins, enzymes and other effector molecules (Wettschureck and Offermanns, 2005; Mizuno and Itoh, 2009). The heterotrimeric G-proteins, are one of the most important transmembrane signal transducers. There are a large number of heterotrimeric guanine nucleotide-binding proteins which interact with the cytoplasmic domains of membrane embedded receptors (G Protein-Coupled Receptors, GPCR). They transduce extracellular signals that affect many biological actions. G-proteins consist of an α-subunit that binds and hydrolyses GTP as well as a β- and a γ-subunit that form an undissociable complex. Based on the types of their α subunits, G proteins can be grouped into four subfamilies, they are $G_{\alpha i}$, $G_{\alpha s}$, $G_{\alpha q/11}$ and $G_{12/13}$, each subfamily contents several member of G proteins. The $G_{\alpha q/11}$ subfamily consists of four members designated $G_{\alpha q}$, $G_{\alpha 11}$, $G_{\alpha 14}$, $G\alpha_{15/16}$, these G-proteins couple a large number of GPCRs for activation of PLC-β (Oldham and Hamm, 2008).

The $G_{\alpha q}$ containing protein initially attracted attention for its physiological significance in cardiovascular system in 1990s (D'Angelo *et al*., 1997; Adams *et al*., 1998). In recent years, studies have indicated the important roles of G_q in regulating both innate and adaptive immunity, which supply us a new insight into the mechanism of immune regulation and autoimmune disease. This review aims to provide a brief review on the role of $G_{\alpha q}$ containing protein in regulating immune cell function and the possible mechanisms involved in the regulation.

1.1. Basic Principles of Mammalian $G_{\alpha q}$ Protein

The $G_{\alpha q/11}$ family members were first identified by affinity purification (Pang and Sternweis, 1990) and molecular cloning strategies (Pang and Sternweis, 1989; Strathmann and Simon, 1991). The $G_{\alpha q}$ protein is the product of Gnaq gene and composed of a GTPase domain and an α-helical domain. The GTPase domain of $G_{\alpha q}$ participates in the hydrolysis of GTP to GDP. The domain has three flexible loops, named switch regions I, II and III, whose conformations are dependent upon GDP or GTP binding. The helical domain contains six helices and is unique to G protein α subunit, but the function of helical domain in G protein signaling remains to be fully clarified (Oldham and Hamm, 2008).

The $G_{\alpha q}$ couples receptors to activate PLC-β (β-isoforms of phospholipase C) (Rhee, 2001). To dynamically couple activated receptors to effectors, it shares the same activation-inactivation cycle with all of the four families of the heterotrimeric G proteins. In the basal state, the GDP-bound α-subunit is associated with the βγ-complex. When the G protein-coupled receptors bind to its appropriate ligands (physiological ligands of $G_{\alpha q}$ protein-coupled receptors are summarized in

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Table 1), the activated receptor couples to the heterotrimeric G protein and promotes the exchange of GDP to GTP on the α-subunit. Then the GTP-bound α-subunit dissociates from the other subunits and becomes an activated α-subunit and a βγ-complex, which transduces signals individually. Signaling is terminated upon the hydrolysis of GTP mediated by the GTPase activity, which is inherent to the G protein α-subunit. The resulting GDP-bound α-subunit reassociates with the βγ-complex to enter a new cycle if activated receptors are present (Wettschureck and Offermanns, 2005).

1.2. $G_{\alpha q}$ in Regulating Innate Immune Cell Function

The innate immune system is a universal and ancient form of host defense against infection. It provides the first line of host defense and controls the initiation and determination of the effector classes of the adaptive immune response. Cells involved in innate immune system include macrophages/monocytes, dendritic cell, granulocytes and natural killer cells.

The best known about G proteins in the innate immune system is its role in the chemokine receptor signaling pathway. Directed cell movement in response to an increased concentration of chemokines underlies the correct targeting of leukocytes to lymphatic organs during antigen surveillance and also allows them to migrate to sites of infection or inflammation (Vicente-Manzanares and Sanchez-Madrid, 2004). Many of the key intracellular proteins and second messengers that control cell migrations have been identified and a consensus chemokine receptor signal transduction model has been proposed. One of the critical components of this chemokine receptor signaling model is the heterotrimeric G protein complex. It directly associates with chemokine receptors and transduces signals from these receptors to other key intracellular signaling molecules. Many studies have elucidated the essential role of Gαi in the chemokine receptor signaling pathway. Despite the critical importance of $G_{\alpha i}$ in chemokine induced cell trafficking, it has been known for many years that chemokine receptors can also couple to $G_{\alpha q}$ family members (Amatruda *et al*., 1993; 1995; Arai and Charo, 1996; Wittmann *et al*., 2002). Arai and Charo (1996) proved that type A and type B Monocyte Chemoattractant Protein-1 (MCP-1) receptors and macrophage inflammatory protein-1alpha/RANTES receptor (C-CR1) coupled to $G_{\alpha q}$ in COS-7 cells and HEK-293 cells via cotransfection experiments. Using selectively Gnaq knockout mice, Borchers and his colleague have shown that $G_{\alpha q}$ subunit was required in allergen-induced recruitment of eosinophils to the lung. However, this effect was not dependent on $G_{\alpha q}$ signaling in eosinophils themselves, because murine eosinophils did not express $G_{\alpha q}$ detected by Western blot or sequencing of RT-PCR products using degenerate primers for Gnaq transcripts. The unique loss of GM-CSF production in the lung of Gnaq-/- mice was responsible for the recruitment of eosinophils. However, the potential effects of the Gnaq deficiency in the target cell have not been resolved, T cells and/or alveolar macrophages might be involved (Borchers *et al*., 2002). In one of our previous study, we have proved that $G_{\alpha q}$ is as important as $G_{\alpha i}$ in some chemokine receptors signaling, such as mFPR1 and CCR1. In those chemokine receptor activation induced neutrophil and DC migration, although $G_{\alpha i2}$ was necessary, but it was not sufficient to induce chemotaxis of primary leukocytes to a large array of chemoattractants and alternative $G_{\alpha q}$-coupled pathway must be engaged in the migration of primary neutrophils and DCs (Shi *et al*., 2007). $G_{\alpha q}$ and CD38 coordinately sustained the calcium response by activating calcium entry. This novel alternative chemokine receptor signaling pathway appeared to be critically important for the initiation of inflammatory responses, as $G_{\alpha q}$ was required for the migration of DCs from the skin to draining lymph nodes after fluorescein isothiocyanate sensitization and the emigration of monocytes from the bone marrow into inflamed skin after contact sensitization (Shi *et al*., 2007). Chemokine receptors dependent on $G_{\alpha q}$ are summarized in **Table 2**.

1.3. $G_{\alpha q}$ in Regulating the Function of T and B Cells

The adaptive immune response is a specific immune response. Adaptive immune responses depend on lymphocytes including T lymphocytes and B lymphocytes. To participate in an adaptive immune response, T cells need to proliferate and differentiate into active $CD4^+$ helper T cells (Th) and $CD8^+$ cytotoxic cells from their naïve states after encountering antigen.

1.4. $G_{\alpha q}$ and B Cell

Studies on the regulation of $G_{\alpha q}$ in B cell are quite few. Bence and his colleagues showed that $G_{\alpha q}$ involved in the activation of Bruton's tyrosine kinase, a protein that is required for normal B-cell development and activation (Bence *et al*., 1997), suggesting that $G_{\alpha q}$ may be involved in B cell development and activation regulation. Our previous study directly demonstrated that $G_{\alpha q}$-containing G protein regulates B cell selection and survival and it was required to prevent B cell-dependent autoimmunity (Misra *et al*., 2010). $G_{\alpha q}$ was not required for B cell development in the bone marrow, However, $G_{\alpha q}$ did modulate the development of peripheral B cell. $G_{\alpha q}$ appeared to control the numbers of transitional T1 B cells (T1 cell), T1-derived Marginal Zone B cell (MZB) precursors, as well as mature MZB and Follicular B cells (FOB). The proliferation between WT B cell and Gnaq-/- B cells showed no difference under the sitimulation of anti-IgM or anti-CD40 Abs.

Table 1. Physiological ligands of $G_{\alpha q}$ protein-coupled receptors

Endogenous Ligand	Receptor	Coupling to G protein subclass	References
Glutamate	mGluR1, 5	$G_{\alpha q}$	(Conn and Pin, 1997)
α-Ketoglutarate	GPR99	$G_{q/11}$	(He *et al*., 2004)
Succinate	GPR91	$G_{q/11}$	(He *et al*., 2004)
L-Arginine, L-lysine	GPRC6A	$G_{q/11}$?	(Wellendorph *et al*., 2005)
Acetylcholine	M1,M3,M5	$G_{\alpha q}$	(Wess, 2004)
Epinephrine,norepinephrine	α1A,α1B,α1D	$G_{q/11}$	(Wu *et al*., 1992)
Histamine	H1	$G_{q/11}$	(Bakker *et al*., 2001)
Serotonin	5-HT2A/B/C	$G_{\alpha q}$	(Tanis *et al*., 2008)
Ca2+	CaSR	$G_{q/11}$	(Goodman, 2004)
ADP/ATP	P2Y1	$G_{q/11}$	(Fredholm *et al*., 1997)
ATP	P2Y11	$G_{q/11}$	(Fredholm *et al*., 1997)
UDP	P2Y6	$G_{q/11}$	(Fredholm *et al*., 1997)
UTP/ATP	P2Y2, P2Y4	$G_{q/11}$	(Fredholm *et al*., 1997)
Fatty acids	GPR40,GPR41	$G_{\alpha q}$	(Lee *et al*., 2008)
	GPR43	$G_{q/11}$	(Brown *et al*., 2003)
	GPR120	$G_{q/11}$	(Hirasawa *et al*., 2004)
LTC4, LTD4	CysLT1	$G_{\alpha q}$	(Parmentier *et al*., 2012)
Lysophosphatidic acid	LPA1/2/3	$G_{\alpha q}$	(Lynch, 2002)
Platelet-activating factor	PAF	$G_{\alpha q}$	(Prescott *et al*., 2000)
Prostaglandin F2α (PGF)	FP	$G_{\alpha q}$	(Liu and Clipstone, 2007)
Prostaglandin E2 (PGE2)	EP1,EP3	$G_{q/11}$	(Hata and Breyer, 2004)
Thromboxane A2 (TxA2)	TP	$G_{\alpha q}$	(Narumiya *et al*., 1999; Hata and Breyer, 2004)
Angiotensin II	AT1	$G_{\alpha q}$	(Gasparo *et al*., 2000)
Bradykinin	B1, B2	$G_{\alpha q}$	(Leeb-Lundberg *et al*., 2005)
Calcitonin	CT	$G_{q/11}$	(Poyner *et al*., 2002)
Calcitonin gene-related peptide (CGRP)	CGRP1	$G_{q/11}$	(Poyner *et al*., 2002)
Cholecyctokinin (CCK-8)	CCK1, CCK2	$G_{q/11}$	(Shulkes and Baldwin, 1997)
Endothelin-1, -2, -3	ETA , ETB	$G_{\alpha q}$	(Cramer *et al*., 2001)
Gastrin	CCK2	$G_{\alpha q}$	(Shulkes and Baldwin, 1997)
Gastrin-releasing peptide (GRP), bombesin	BB2	$G_{\alpha q}$	(Battey and Wada, 1991)
Ghrelin	GHS-R	$G_{q/11}$	(Kojima *et al*., 1999)
Gonadotropin-releasing hormone	GnRH	$G_{\alpha q}$	(Millar *et al*., 2004)
Kisspeptins, metastin	GPR54	$G_{\alpha q}$	(Roux *et al*., 2003; Seminara *et al*., 2003)
Melanin-concentrating hormone	MCHR1	$G_{\alpha q}$	(Fry *et al*., 2006)
Motilin	GPR38	$G_{\alpha q}$	(Feighner *et al*., 1999)
Neurokinin-A/-B	NK2, NK3	$G_{\alpha q}$	(Pennefather *et al*., 2004)
Neuromedin-B	NMB-R	$G_{\alpha q}$	(Shapira *et al*., 1994)
Orexin A/B	OX1, OX2	$G_{q/11}$	(Mieda and Yanagisawa, 2002)
Oxytocin	OT	$G_{\alpha q}$	(Qian *et al*., 1998)
Parathyroid hormone (related peptide)	PTH/PTHrP	$G_{\alpha q}$	(Offermanns *et al*., 1996)
Prokineticin-1,2	PKR1, PKR2	$G_{q/11}$	(Soga *et al*., 2002)
Prolactin-releasing peptide	PrRP (GPR10)	$G_{q/11}$	(Sun *et al*., 2005)
Substance P (SP)	NK1	$G_{\alpha q}$	(Macdonald *et al*., 1996)
Thyrotropin (TSH)	TSHR	$G_{q/11}$	(Vassart and Pardo, 2004)
Thyrotropin-releasing hormone (TRH)	TRHR	$G_{\alpha q}$	(Aragay *et al*., 1992)
Urotensin II	UT-II (GPR14)	$G_{\alpha q}$	(Russell, 2004)
Thrombin	PAR-1, PAR-3, PAR-4	$G_{\alpha q}$	(Vaidyula and Rao, 2003)
Trypsin	Trypsin receptor	$G_{q/11}$	(Shapira *et al*., 1998)
Estrogen	mER	$G_{\alpha q}$	(Qiu *et al*., 2003)

Table 2.Chemokine receptors coupled to $G_{\alpha q}$

Recpetor	Cell type	$G_{\alpha q}$ dependent	References
MCP-1 receptor	COS-7 and HEK-293 cell	Y	(Arai and Charo, 1996)
CCR1	COS-7 and HEK-293 cell	Y	(Arai and Charo, 1996)
	BM neutrophil(mice)	Y	(Shi *et al*., 2007)
CCR2	Immature DC(mice)	?	(Shi *et al*., 2007)
CCR7	DC(mice)	Y	(Shi *et al*., 2007)
CXCR4	DC(mice)	Y	(Shi *et al*., 2007)
mFPR1	BM neutrophil(mice)	Y	(Shi *et al*., 2007)
mFPR2	BM neutrophil(mice)	Y	(Shi *et al*., 2007)

However, Gnaq-/- B cells proliferated more strongly in response to LPS than their WT counterparts, suggesting that either a higher proportion of Gnaq-/- B cells were responsive to LPS or that Gnaq-/- B cells were hyperresponsive to TLR4 ligands. The survival rate of Gnaq-/- B cells was far greater than the survival rate of wide type B cells at all stages of transitional and mature B cells. Gnaq-deficient B cells was more resistant to BAFF withdrawal. Furthermore, Gnaq-deficient B cells constitutively expressed higher levels of activated Akt, PLCγ2 and ERK, suggesting the increased activation of BCR-mediated signaling in Gnaq-/- B cells. Most importantly, Gnaq-deficient mice rapidly developed an autoreactive B cell repertoire and systemic autoimmunity. These data showed that $G_{\alpha q}$-containing G proteins, working in concert with the BCR and BAFFR signaling networks, regulate B cell development and peripheral tolerance induction (Misra *et al*., 2010).

1.5. $G_{\alpha q}$ and T Cell

Role of $G_{\alpha q}$ in lymphocyte migration seems contrary to that in innate immune cells. Data from one of our previous study showed that $G_{\alpha q}$ regulates CCR7 and CXCR4 signaling in DCs but not in T cells. Chemotaxis of Gnaq-/- T cells to these two chemokines was completely normal (Shi *et al*., 2007). However, Ngai reported that Gnaq knockdown T cells showed significantly enhanced migration induced by CXCL12 and the signals conveyed by $G_{\alpha q}$ appear to be mediated through a SHP-1 pathway (Ngai *et al*., 2009). These data suggest that the role of $G_{\alpha q}$ in chemokine receptor signaling regulation is cell type and chemokine receptor specific.

Members of G_q/G_{11} family are repeatedly to be indicated in T cell activation. Activation of primary T cells with anti-CD3/anti-CD28 leads to recruitment of $G_{\alpha q}$ to lipid rafts indicate that $G_{\alpha q}$ may be involved in T cells activation (Abrahamsen *et al*., 2004). Another study using Gnaq knockout mice demonstrated a role of $G_{\alpha q}$ in proximal TCR signaling at the level of Lck (Ngai *et al*., 2008). Jurkat TAg T cells with Gnaq knockdown displayed reduced activation of Lck and LAT phosphorylation, but paradoxically showed sustained ERK1/2 phosphorylation and increased NFAT-AP-1-reporter activity implicating $G_{\alpha q}$ in the negative control of downstream signaling and IL-2-promoter activity. Primary T cells isolated from Gnaq-deficient mice have a similar TCR signaling response with reduced proximal LAT phosphorylation, sustained ERK1/2 phosphorylation and augmented immune responses, including increased secretion of IL-2, IL-5, IL-12 and TNF-α. The effects on NFAT-AP-1-reporter activity were sensitive to the Src family kinase inhibitor PP2 and were reversed by transient expression of constitutively active Lck. Furthermore, expression of constitutively active $G_{\alpha q}$ Q209L elevated Lck activity and Zap-70 phosphorylation. These data indicated the role of $G_{\alpha q}$ in the fine-tuning of proximal TCR signals at the level of Lck and a negative regulatory role of $G_{\alpha q}$ in transcriptional activation of cytokine responses (Ngai *et al*., 2008). These signals conveyed by $G_{\alpha q}$ appear to be mediated through a SHP-1 pathway (Ngai *et al*., 2009).

1.6. $G_{\alpha q}$ and Autoimmune Disease

In 2010, we first demonstrated the role of $G_{\alpha q}$ in autoimmune disease in Gnaq-/- chimeric mice by reconstituting lethally irradiated C57BL/6J recipient mice with Gnaq-/- bone marrow. Gnaq-/- chimeric mice spontaneously developed autoimmunity with multi-organ involvement and joints swelling (Misra *et al*., 2010). Furthermore, we found that $G_{\alpha q}$ expressions at mRNA and protein levels in the peripheral blood lymphocytes (PBLs) from patients with rheumatoid arthritis (RA) were significantly decreased in comparison of which in healthy individuals. The expression levels of $G_{\alpha q}$ mRNA in PBLs from patients with RA were correlated with RA Disease Activity (DAS28), anti-cyclic citrullinated protein antibodies, C-reactive protein and rheumatoid factor. These data suggest that $G_{\alpha q}$ might be involved in the pathogenesis of RA (Wang *et al*., 2011).

1.7. The Molecular Mechanisms of $G_{\alpha q}$ in Regulatint Immune Cell Functions

1.8. $G_{\alpha q}$ and PI3K/Akt Pathway

Phosphatidylinositol 3-Kinase (PI3K) mediates many of the cellular actions of receptor tyrosine kinases, including effects on glucose metabolism, cell survival and cytoskeletal rearrangements (Katso *et al*., 2001). The serine/threonine protein kinase Akt, also termed Protein Kinase B (PKB), an important downstream effector of PI3K, is involved in regulating a similarly wide array of cellular processes as PI3K (Brazil *et al*., 2004). The PI3K/Akt pathway has broad and distinct roles in both innate and adaptive immune cells, it is activated by a broad array of different stimuli via specific receptors, including the BCR, TCR, cytokine receptors (e.g., interleukin 2), insulin receptor, insulin-like growth factor I receptor, as well as Toll-Like Receptors (TLRs) (Weichhart and Saemann, 2008).

Table 3. Role of Mitogen-Activated Protein (MAP) kinase family in immune cells regulation

MAPK members	Immune cells	Effect	References
ERK	Macrophages	mice with selective ERK activation deficits exhibited deficient in LPS-induced TNF-α production, ERK inhibitor PD98059 had a similar effect	(Dumitru *et al*., 2000)
	T cell	ERK1-deficient mice exhibited defective thymocyte maturation	(Pages *et al*., 1999)
		Regulate T cell activation, deficient ERK activation exist in clones that are anergized	(Li *et al*., 1996; Kane *et al*., 2000)
		Regulate Th2 differentiation	
		Study using dominant H-RAS transgenic mice and inhibitors against MEKs showed that ERK pathway is required for Th2 differentiation	(Yamashita *et al*., 1999)
JNK	T cell	Required in negative selection	Rincon *et al*., 1998a)
		T cell activation and IL-2 expression	
		No effect	(Dong *et al*., 1998; Yang *et al*., 1998)
		IL-2 expression defect in mixed lymphocyte	(Sabapathy *et al*., 1999;
		of Jnk1-/- mice and Jnk2-/- mice, absence of JNK2 alone can result in resistance to anti-CD3-induced thymocyte apoptosis and defective mature T cell proliferation.	Sabapathy and Kallunki, 2001)
		Regulate apoptosis, JNK1-/- T cells exhibited reduced activation-induced cell death	(Dong *et al*., 1998)
		JNK1 inhibit Th2 differentiation by using Jnk1-/- mice	(Dong *et al*., 1998)
		JNK2 is required for Th1 differentiation by using Jnk2-/- mice	(Yang *et al*., 1998)
p38	Macrophages Dendritic cells	p38-specific inhibitors reduced LPS-induced IL-12 and IL-1 production, genetic disruption of MKK3-p38 pathway resulted in a selective defect in IL-12 production	(Lu *et al*., 1999)
	T cell	Regulates activation-induced cell death, activation of the p38MAPkinase pathway in vivo induces apoptosis in CD8+ T cells, but not in CD4+ T cell	(Merritt *et al*., 2000)
		Required for Th1 differentiation inhibitors of the p38 kinases block IFN-γ production by Th1 cells in a dose-dependent manner and transgenic mice in which a dominant negative p38αshowed reduced IFN-γ cytokine	(Rincon *et al*., 1998b)
		T cells from mice deficient in the p38 upstream kinase MKK3 have a defect in IFN-γ production	(Lu *et al*., 1999)
		Regulates IFN-γ production in CD8+ T cells	(Merritt *et al*., 2000)

Studies regarding regulation of PI3K and/or Akt by $G_{\alpha q}$ coupled receptors are somewhat controversial. Some studies suggest that $G_{\alpha q}$ can activate PI3K/Akt by using ligands of $G_{\alpha q}$ coupled receptors, summarized in **Table 1**. Graness suggest that receptor of bradykinin might couple to $G_{\alpha q}$ to activate PI3K (Graness *et al*., 1998). Endothelin-1 was also proved to activate PI3K via $G_{\alpha q/11}$ (Imamura *et al*., 1999). Saward proved another ligand of $G_{\alpha q}$ coupled receptor, angiotensin II, can activate PI3K in vascular smooth muscle cells (Saward and Zahradka, 1997) and it can also activate Akt in vascular smooth muscle cells (Eguchi *et al*., 1999; Takahashi *et al*., 1999). Tang *et al*. (2002) showed that muscarinic receptor is coupled to $G_{\alpha q}$ to activate Akt in 1321N1 astrocytoma cells.

There are also some evidences suggested that activated $G_{\alpha q}$ inhibit rather than activate PI3K/Akt activity. Folli *et al*. (1997) proved that angiotensin II can inhibit PI3K activity in aortic smooth muscle cells. Jiang *et al*. (1999) proved that endothelin-1 inhibited insulin-stimulated PI3-kinase activity associated with IRS-2 by 50-60% and inhibited the association of p85 subunit of PI3-kinase to IRS-2. To clarify the effects of $G_{\alpha q}$ on the activity of PI3K/Akt, Ballou *et al*. (2003) used a constitutively active $G_{\alpha q}$ (Q209L) mutant to study the role of $G_{\alpha q}$ in Akt activation, they showed that transient expression of $G_{\alpha q}$ (Q209L) in Rat-1 fibroblasts inhibited platelet-derived growth factor- or insulin-induced the activation of Akt. Expression of $G_{\alpha q}$ (Q209L) also attenuated Akt activation promoted by coexpression of constitutively active PI3K in human embryonic kidney 293 cells. The inhibitory effect of $G_{\alpha q}$ on Akt seemed to be independent on phospholipase C activation and might represses P110 alpha PI3K activity via an physically interaction (Ballou *et al*., 2003).

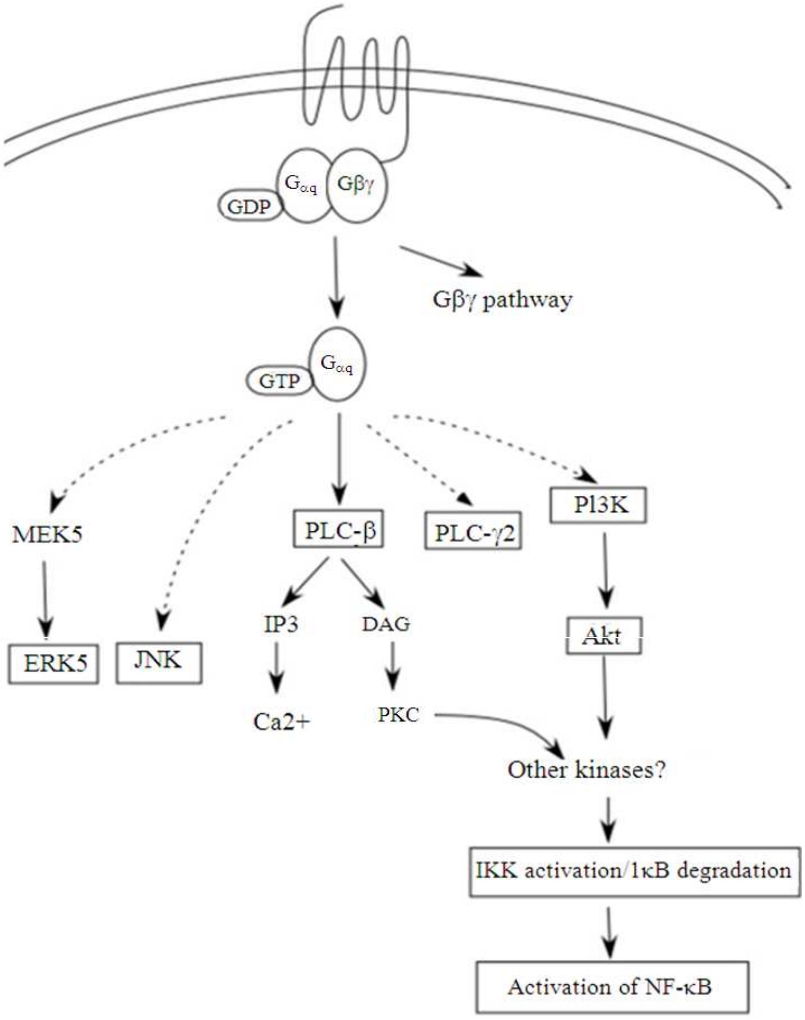

Fig. 1. $G_{\alpha q}$ signaling pathways in immune cells regulation. Activated $G_{\alpha q}$ can directly activate PLC-β, resulting in generating second messengers IP3 and diacyl glycerol. These molecules promote the activation of conventional PKC (cPKC) and the release of Ca2+ from intracellular stores. Activated $G_{\alpha q}$ can regulate the PI3K/Akt activity, this effect seemed to be independent on phospholipase C activation. $G_{\alpha q}$ was also involved in the transduction of signals from GPCR to ERK. Activated $G_{\alpha q}$ can lead to NF-κB activation via PI3K and the PLC-β pathway

1.9. $G_{\alpha q}$ and Mitogen-Activated Protein (MAP) Kinase Family

The Mitogen-Activated Protein (MAP) kinase signaling cascade is one of the most ancient and evolutionarily conserved signaling pathways which respond to a broad range of extracellular and intracellular changes. The MAPK superfamily includes the Extracellular signal-Regulated Kinases (ERK), c-Jun NH2-terminal kinase (JNK1-3) and p38 (α, β, γ and δ) families. In mammalian species, MAP kinases are involved in all aspects of immune responses, from the initiation phase of innate immunity, to activation of adaptive immunity and to cell death when immune function is completed (Dong *et al*., 2002). The main roles of Mitogen-Activated Protein (MAP) kinase family in immune cells are summarized in **Table 3**.

Several studies have indicated the role of $G_{\alpha q}$ in the regulation of Mitogen-Activated Protein (MAP) kinase signaling pathway. Studies on endothelin receptors and gonadotropin-releasing hormone receptors showed that these two types of receptors couple to $G_{\alpha q}$ to activate ERK

(Cramer *et al*., 2001; White *et al*., 2008). Another study showed that $G_{\alpha q}$ was involved in the transduction of signals from GPCR to ERK5 (Fukuhara *et al*., 2000; Marinissen *et al*., 2003). $G_{\alpha q}$ displayed a scaffold-like role in this process via independently interacting with both PKCδ and MEK5 (Garcia-Hoz *et al*., 2010). It was also reported that $G_{\alpha q}$ inhibit TNF alpha-stimulated JNK activation (McIntosh *et al*., 2010).

1.10. $G_{\alpha q}$ and NF-κB

Nuclear Factor (NF) κB is one of the most important transcription factors responsible for the expression of these proinflammatory genes. It s rapid posttranslational activation in response to many pathogenic signals and directly activates the transcription of various genes encoding immunologically relevant proteins. Its properties have been most extensively exploited in cells of the immune system, as reviewed in reference 98 (Baeuerle and Henkel, 1994).

Activated $G_{\alpha q}$ can directly activate PLC-β, resulting in generating second messengers IP3 and diacyl glycerol. These molecules promote the activation of conventional PKC (cPKC) and the release of Ca^{2+} from intracellular stores. Elevation of intracellular Ca^{2+} further activates cPKC. Shahrestanifar *et al*. (1999) have reported that LPA-induced NF-κB activation can be blocked by the rise of intracellular Ca^{2+} and PKC inhibitors. Several PKC isoforms, including cPKC, were known activators of NF-κB based on early studies on the effects of phorbol esters in NF-κB activation (Shahrestanifar *et al*., 1999). Using cell lines with transfected constitutively active mutants of $G_{\alpha q}$, it is demonstrated that a Q209L mutation of $G_{\alpha q}$ lead to activation of NF-κB. Furthermore, based on the inhibitory effects of IkBα repressor, the IkB kinases (IKK), including IKK1 (IKKα) and IKK2 (IKKβ), were involved in the $G_{\alpha q}$-mediated NF-kB activation. Inhibitors for Phosphatidylinositol (PI) 3-kinase (PI3K), as well as dominant negative constructs of PI3K and its downstream effector Akt (PKB) partially block the $G_{\alpha q}$-mediated NF-κB activation (Xie *et al*., 2000). These results suggest that $G_{\alpha q}$ activates NF-κB via PI3K and the PLC-β pathway. The signaling pathway of $G_{\alpha q}$ in immune cells regulation was shown in **Fig. 1**.

2. CONCLUSION

2.1. Conclusion and Future Perspectives

$G_{\alpha q}$ is one of the most important proteins in transducing extracellular signals. Their functions in immune responses are beginning to be revealed with help of $G_{\alpha q}$-specific inhibitors and mouse genetic manipulation. $G_{\alpha q}$ plays crucial role in both innate immune cells and adaptive immune cells function regulation: 1. $G_{\alpha q}$ regulates the migration of neutrophils and DCs induced by a large array of chemokines, it also regulates the allergen-induced recruitment of eosinophils; 2. $G_{\alpha q}$ regulates B cell selection and survival and is required to prevent B cell-dependent autoimmunity; 3. $G_{\alpha q}$ regulates migration of T cell induced by some kinds of chemokines (at least by CXCL12) and it is involved in TCR signaling pathway to regulate T cells activation and some effector function; 4. $G_{\alpha q}$ regulates the development of autoimmune disease, such as RA and the expression levels of $G_{\alpha q}$ mRNA in PBLs from patients with RA were correlated with RA disease activity.

From what we summarized above, we can predict some future directions in the studies of $G_{\alpha q}$:

- Exploring the broader function of $G_{\alpha q}$ in different cell types of the immune system. For instance, the role of $G_{\alpha q}$ in macrophages, Breg, Treg or Th17
- Defining the specific downstream targets of $G_{\alpha q}$ in a given stage and cell type of an immune response. There are multiple substrates of $G_{\alpha q}$, which one mediates is function in a given cell type needs to be carefully characterized
- To clarify the role of $G_{\alpha q}$ in other types of autoimmune disease, such as Systemic lupus erythematosus; Sjogren's syndrome and dermotomyositis. Understanding the signaling mechanisms of $G_{\alpha q}$ in these autoimmune diseases pathogenesis

These results will no doubt advance our knowledge of the mechanisms of $G_{\alpha q}$ signaling in immune responses and may help development of therapeutic agents to selectively modulate $G_{\alpha q}$ activity to treat immune disorders.

3. REFERENCES

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