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. Gαq is the α subunit of Gq protein subfamily. The Gαq containing protein initially attracted attention for its physiological significance in cardiovascular system. In recent years, its role in immune regulation has been indicated. Studies demonstrated that Gαq 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 Gαq containing protein in regulating immune cells function and the possible mechanisms.

Keywords: Gαq, Heterotrimeric G Proteins, Immune Cells, Autoimmune Disease

1. INTRODUCTION

Gαq, the α subunit of Gq 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 Gαs, Gαi, Gαq/11 and G12/13, each subfamily contents several member of G proteins. The Gαq/11 subfamily consists of four members designated Gαq, Gα11, Gα14, Gα15/16, these G-proteins couple a large number of GPCRs for activation of PLC-β (Oldham and Hamm, 2008).

The Gαq 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 Gαq 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 Gαq containing protein in regulating immune cell function and the possible mechanisms involved in the regulation.

1.1. Basic Principles of Mammalian Gαq Protein

The Gαq11 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 Gαq protein is the product of Gnaq gene and composed of a GTPase domain and an α-helical domain. The GTPase domain of Gαq 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 Gαq couples receptors to activate PLC-β (β-isomers 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 Gαq protein-coupled receptors are summarized in
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 (Wettchureck and Offermanns, 2005).

1.2. G_{αq} 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 Gαi in chemokine induced cell trafficking, it has been known for many years that chemokine receptors can also couple to Gαq 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-α-lphalpha/RANTES receptor (C-CR1) coupled to Gαq in COS-7 cells and HEK-293 cells via cotransfection experiments. Using selectively Gnaq knockout mice, Borchers and his colleague have shown that Gαq subunit was required in allergic-induced recruitment of eosinophils to the lung. However, this effect was not dependent on Gαq signaling in eosinophils themselves, because murine eosinophils did not express Gαq 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 Gαq is as important as Gαi in some chemokine receptors signaling, such as mFPR1 and CCR1. In those chemokine receptor activation induced neutrophil and DC migration, although Gαi2 was necessary, but it was not sufficient to induce chemotaxis of primary leukocytes to a large array of chemoattractants and alternative Gαq2-coupled pathway must be engaged in the migration of primary neutrophils and DCs (Shi et al., 2007). Gαq 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 Gαq 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 Gαq are summarized in Table 2.

1.3. G_{αq} 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_{αq} and B Cell

Studies on the regulation of Gαq in B cell are quite few. Bence and his colleagues showed that Gαq 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 Gαq may be involved in B cell development and activation regulation. Our previous study directly demonstrated that Gαq-containing G protein regulates B cell selection and survival and it was required to prevent B cell-dependent autoimmunity (Misra et al., 2010). Gαq was not required for B cell development in the bone marrow. However, Gαq did modulate the development of peripheral B cell. Gαq 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 simulation of anti-IgM or anti-CD40 Abs.
Table 1. Physiological ligands of G\textsubscript{αq} protein-coupled receptors

| Endogenous Ligand | Receptor | Coupling to G\textsubscript{αq} protein subclass | References |
|-------------------|----------|-----------------------------------------------|------------|
| Glutamate         | mGluR1, 5 | G\textsubscript{αq}                        | (Conn and Pin, 1997) |
| α-Ketoglutarate   | GPR99    | G\textsubscript{αq}                        | (He et al., 2004) |
| Succinate         | GPR91    | G\textsubscript{αq}                        | (He et al., 2004) |
| L-Arginine, L-lysine | GPRC6A | G\textsubscript{αq}                        | (Wess, 2004) |
| Acetylcholine     | M1,M3,M5 | G\textsubscript{αq}                        | (Wellendorp et al., 2005) |
| Epinephrine, norepinephrine | α1A, α1B, α1D | G\textsubscript{αq}                        | (Wu et al., 1992) |
| Histamine         | H1       | G\textsubscript{αq}                        | (Bakker et al., 2001) |
| Serotonin         | 5-HT2A/B/C | G\textsubscript{αq}                      | (Tanis et al., 2008) |
| Ca\textsuperscript{2+} | CaSR   | G\textsubscript{αq}                        | (Goodman, 2004) |
| ADP/ATP           | P2Y1     | G\textsubscript{αq}                        | (Fredholm et al., 1997) |
| ATP               | P2Y11    | G\textsubscript{αq}                        | (Fredholm et al., 1997) |
| UDP               | P2Y6     | G\textsubscript{αq}                        | (Fredholm et al., 1997) |
| UTP/ATP           | P2Y2, P2Y4 | G\textsubscript{αq}                       | (Fredholm et al., 1997) |
| Fatty acids       | GPR40, GPR41 | G\textsubscript{αq}                 | (Lee et al., 2008) |
| GPR43             | GPR120   | G\textsubscript{αq}                        | (Brown et al., 2003) |
| LTC4, LTD4        | CysLT1   | G\textsubscript{αq}                        | (Sansone et al., 2012) |
| Lyso phosphatic acid | LPA1/2/3 | G\textsubscript{αq}                      | (Lynch, 2002) |
| Platelet-activating factor | PAF | G\textsubscript{αq}                          | (Prescott et al., 2000) |
| Prostaglandin F2α (PGF) | EP1, EP3 | G\textsubscript{αq}                         | (Liu and Clipstone, 2007) |
| Prostaglandin E2 (PGE2) | EP1, EP3 | G\textsubscript{αq}                         | (Hata and Breyer, 2004) |
| Thromboxane A2 (TXA2) | TP   | G\textsubscript{αq}                        | (Barbey and Wada, 1991) |
| Angiotensin II    | AT1      | G\textsubscript{αq}                        | (Gasparo et al., 2000) |
| Bradykinin        | B1, B2   | G\textsubscript{αq}                        | (Leeb-Lundberg et al., 2005) |
| Calcitonin        | CT       | G\textsubscript{αq}                        | (Poyner et al., 2002) |
| Calcitonin gene-related peptide (CGRP) | CGRP1 | G\textsubscript{αq}                       | (Shapira et al., 1994) |
| Cholecystokinin (CCK-8) | CCK1, CCK2 | G\textsubscript{αq}                 | (Shulkes and Baldwin, 1997) |
| Endothelin-1, -2, -3 | ETA, ETB | G\textsubscript{αq}                        | (Cramer et al., 2001) |
| Gastrin           | CCK2     | G\textsubscript{αq}                        | (Shulkes and Baldwin, 1997) |
| Gastrin-releasing peptide (GRP), bombesin | BB2 | G\textsubscript{αq}                          | (Kojima et al., 1999) |
| Ghrelin           | GHS-R    | G\textsubscript{αq}                        | (Milla et al., 2004) |
| Gonadotropin-releasing hormone | GnRH | G\textsubscript{αq}                           | (Roux et al., 2003) |
| Kisspeptins, metasin | GPR54 | G\textsubscript{αq}                        | (Seminara et al., 2003) |
| Melanin-concentrating hormone | MCHR1 | G\textsubscript{αq}                          | (Fry et al., 2006) |
| Motilin           | GPR38    | G\textsubscript{αq}                        | (Feighner et al., 1999) |
| Neurokinin-A/-B   | NK2, NK3 | G\textsubscript{αq}                        | (Pennefather et al., 2004) |
| Neurokinin-B      | NKB      | G\textsubscript{αq}                        | (Shapira et al., 1994) |
| Orexin A/B        | OX1, OX2 | G\textsubscript{αq}                        | (Mieda and Yanagisawa, 2002) |
| Oxytocin          | OT       | G\textsubscript{αq}                        | (Qian et al., 1998) |
| Parathyroid hormone (related peptide) | PTH/PTHrP | G\textsubscript{αq}                       | (Offermanns et al., 1996) |
| Prokineticin-1,2  | PKR1, PKR2 | G\textsubscript{αq}                      | (Soga et al., 2002) |
| Prolactin-releasing peptide | PrRP (GPR10) | G\textsubscript{αq}                  | (Sun et al., 2005) |
| Substance P        | NK1      | G\textsubscript{αq}                        | (Macdonald et al., 1996) |
| Thyrotropin (TSH)  | TSHR     | G\textsubscript{αq}                        | (Vassart and Pardo, 2004) |
| Thyrotropin-releasing hormone (TRH) | TRHR | G\textsubscript{αq}                         | (Argay et al., 1992) |
| Urotensin II      | UT-II (GPR14) | G\textsubscript{αq}                     | (Russell, 2004) |
| Thrombin          | PAR-1, PAR-3, PAR-4 | G\textsubscript{αq}                     | (Vaidyula and Rao, 2003) |
| Tryptase          | Trypsin receptor | G\textsubscript{αq}               | (Shapira et al., 1998) |
| Estrogen          | mER      | G\textsubscript{αq}                        | (Qiu et al., 2003) |

Table 2. Chemokine receptors coupled to G\textsubscript{αq}

| Receptor | Cell type | G\textsubscript{αq} 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) |
| CCR2     | BM neutrophil(mice) | Y | (Shi et al., 2007) |
| CCR7     | Immature DC(mice) | ? | (Shi et al., 2007) |
| CXC4     | 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 Gnaq-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. Gnaq and T Cell

Role of Gnaq in lymphocyte migration seems contrary to that in innate immune cells. Data from one of our previous study showed that Gnaq 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 Gnaq appear to be mediated through a SHP-1 pathway (Ngai et al., 2009). These data suggest that the role of Gnaq in chemokine receptor signaling regulation is cell type and chemokine receptor specific.

Members of Gαq/G11 family are repeatedly to be indicated in T cell activation. Data from one of our previous study showed that Gnaq regulates ERK1/2 phosphorylation and increased immune responses, including increased secretion of IL-2, IL-5, IL-12 and TNF-α. The effects on NFAT-AP1 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 Gnaq Q209L elevated Lck activity and Zap-70 phosphorylation. These data indicated the role of Gnaq in the fine-tuning of proximal TCR signals at the level of Lck and a negative regulatory role of Gnaq in transcriptional activation of cytokine TCR signaling (Ngai et al., 2008). These signals conveyed by Gnaq appear to be mediated through a SHP-1 pathway (Ngai et al., 2009).

1.6. Gnaq and Autoimmune Disease

In 2010, we first demonstrated the role of Gnaq 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 Gnaq 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 Gnaq 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 Gnaq might be involved in the pathogenesis of RA (Wang et al., 2011).

1.7. The Molecular Mechanisms of Gnaq in Regulating Immune Cell Functions

1.8. Gnaq 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 1 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 | (Yamashita et al., 1999) |
|              | T cell       | Study using dominant H-RAS transgenic mice and inhibitors against MEKs showed that ERK pathway is required for Th2 differentiation | |
| JNK          | T cell       | Required in negative selection | Rincon et al., 1998a) |
|              | T cell       | T cell activation and IL-2 expression | Dong et al., 1998; Yang et al., 1998 |
|              | T cell       | IL-2 expression defect in mixed lymphocyte 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) |
|              | T cell       | Regulate apoptosis, JNK1-/- T cells exhibited reduced activation-induced cell death | Hong et al., 1998 |
|              | T cell       | JNK1 inhibit Th2 differentiation by using Jnk1-/- mice | Dong et al., 1998 |
|              | T cell       | JNK2 is required for Th1 differentiation by using Jnk2-/- mice | Dong et al., 1998 |
| p38          | Macrophages  | 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) |
|              | Dendritic cells | 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) |
|              | T cell       | 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 p38 showed reduced IFN-γ cytokine T cells from mice deficient in the p38 upstream kinase MKK3 have a defect in IFN-γ production | (Rincon et al., 1998b) |
|              |              | Regulates IFN-γ production in CD8+ T cells | (Merritt et al., 2000) |

Studies regarding regulation of PI3K and/or Akt by G<sub>αq</sub> coupled receptors are somewhat controversial. Some studies suggest that G<sub>αq</sub> can activate PI3K/Akt by using ligands of G<sub>αq</sub> coupled receptors, summarized in Table 1. Graness suggest that receptor of bradykinin might couple to G<sub>αq</sub> to activate PI3K (Graness et al., 1998). Endothelin-1 was also proved to activate PI3K via G<sub>αq</sub> (Imamura et al., 1999). Saward proved another ligand of G<sub>αq</sub> 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<sub>αq</sub> to activate Akt in 1321N1 astrocytoma cells.

There are also some evidences suggested that activated G<sub>αq</sub> 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 PI3K kinase activity associated with IRS-2 by 50-60% and inhibited the association of p85 subunit of PI3k-kinase to IRS-2. To clarify the effects of G<sub>αq</sub> on the activity of PI3K/Akt, Ballou et al. (2003) used a constitutively active G<sub>αq</sub> (Q209L) mutant to study the role of G<sub>αq</sub> in Akt activation, they showed that transient expression of G<sub>αq</sub> (Q209L) in Rat-1 fibroblasts inhibited platelet-derived growth factor- or insulin-induced the activation of Akt. Expression of G<sub>αq</sub> (Q209L) also attenuated Akt activation promoted by coexpression of constitutively active PI3K in human embryonic kidney 293 cells. The inhibitory effect of G<sub>αq</sub> 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\textsubscript{aq} signaling pathways in immune cells regulation. Activated G\textsubscript{aq} 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\textsuperscript{2+} from intracellular stores. Activated G\textsubscript{aq} can regulate the PI3K/Akt activity, this effect seemed to be independent on phospholipase C activation. G\textsubscript{aq} was also involved in the transduction of signals from GPCR to ERK. Activated G\textsubscript{aq} can lead to NF-κB activation via PI3K and the PLC-β pathway

1.9. G\textsubscript{aq} 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\textsubscript{aq} 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\textsubscript{aq} to activate ERK
properties have been most extensively exploited in cells blocked by the rise of intracellular Ca\textsuperscript{2+}. G\textsubscript{αq} signals from GPCR to ERK5 (Fukuhara et al., 2000; Marinissen et al., 2003). G\textsubscript{αq} 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\textsubscript{αq} inhibit TNF alpha-stimulated JNK activation (McIntosh et al., 2010).

1.10. G\textsubscript{αq} and NF-κB

Nuclear Factor (NF) κB is one of the most important transcription factors responsible for the expression of these proinflammatory genes. Its 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\textsubscript{αq} 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\textsuperscript{2+} from intracellular stores. Elevation of intracellular Ca\textsuperscript{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\textsuperscript{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\textsubscript{αq}, it is demonstrated that a Q209L mutation of G\textsubscript{αq} lead to activation of NF-κB. Furthermore, based on the inhibitory effects of IkBa repressor, the IkB kinases (IKK), including IKK1 (IKKa) and IKK2 (IKKB), were involved in the G\textsubscript{αq}-mediated NF-κB 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\textsubscript{αq}-mediated NF-κB activation (Xie et al., 2000). These results suggest that G\textsubscript{αq} activates NF-κB via PI3K and the PLC-β pathway. The signaling pathway of G\textsubscript{αq} in immune cells regulation was shown in Fig. 1.

2. CONCLUSION

2.1. Conclusion and Future Perspectives

G\textsubscript{αq} 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\textsubscript{αq}-specific inhibitors and mouse genetic manipulation. G\textsubscript{αq} plays crucial role in both innate immune cells and adaptive immune cells function regulation: 1. G\textsubscript{αq} 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\textsubscript{αq} regulates B cell selection and survival and is required to prevent B cell-dependent autoimmunity; 3. G\textsubscript{αq} 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\textsubscript{αq} regulates the development of autoimmune disease, such as RA and the expression levels of G\textsubscript{αq} 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\textsubscript{αq}:

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

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

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