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Phospo-PKCs in Abeta1-42-Specific Human T Cells from Alzheimer's Disease Patients

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1. Introduction

Alzheimer's Disease is the most common neurodegenerative dementia of older age. Accurate diagnosis of this condition has important prognostic and therapeutic implications. In the latter, Amyloid-Beta is thought to be produced in excess and subsequently deposited in the brain as plaques, forming the pathological hallmark of Alzheimer's Disease. Interestingly, B- and T-lymphocytes have been implicated in the disease processes being responsible of Amyloid-Bata1-42 peptide removal and activation of inflammation response. Amyloid-Baeta1-42-specific T-cells are present in Alzheimer's disease but not in other neurodegenerative conditions. By using multi-colour flow-cytometry it is possible to analyse cytokine production and Phosho-Protein-Kinase C expression of *in vitro* Amyloid-Beta 1-42 stimulated T-cells. It has been demonstrated that a subset of Amyloid-Beta1-42-specific T-cells, characterised by bright expression of Phosphorylated-Protein-Kinase C, distinguishes Alzheimer's Disease from other neurodegenerative conditions. Therefore, such a new marker might provide further prospective to the studies aimed at diagnosis of Alzheimer's disease and its discrimination from other forms of dementia.

2. T cell activation and lipidic-dependent signal transduction

T cells recognize antigen (Ag) as a peptide– major histocompatibility complex (MHC) on Ag-presenting cells (APC) such as dendritic cells (DC) through direct cell–cell interactions. The T cell antigen receptor (TCR) binds to the Ag peptide–MHC complex and triggers T cell activation by recruiting various signaling molecules. Early analysis of the signaling events related to T cell activation revealed that some intracellular proteins, such as phospholipase-C (PLC), are involved (Bunnell et al., 2002). PLC is a member of phosphoinositide family, including phosphoinositide lipids within cellular membranes and soluble inositol phosphates (Ips). In most stimulatory cells, the plasma membrane phosphoinositide, phosphatidylinositol(4,5)bisphosphate (PIP2) is a key precursor for both other phosphoinositides and soluble IPs. Many of these regulate distinct and overlapping

downstream effectors (Irvine & Schell, 2001; Alcazar-Roman & Wente, 2008; Resnick & Saiardi, 2008; Sauer et al., 2009; Shears, 2009; Sauer & Cooke, 2010). In particular, class I phosphoinositide 3-kinases (PI3K) phosphorylate PIP2 at the 3-position of its inositol-ring into phosphatidylinositol(3,4,5)trisphosphate (PIP3) after receptor stimulation (Vanhaesebroeck et al., 2005; Juntilla & Koretzky, 2008; Fruman & Bismuth, 2009). Receptor-induced PIP2-hydrolysis by phospholipases such as PLCg1/2 in lymphocytes generates the lipid diacylglycerol (DAG) and the soluble IP inositol(1,4,5)trisphosphate (IP3). PIP3, DAG, and IP3 have essential second messenger functions in many cells, including lymphocytes. It is now evident the importance of phosphoinositide signaling in T cells and highlight the importance of a recently identified, intriguing molecular interplay between second messenger lipids and their soluble IP counterparts. All phosphoinositides contain a hydrophobic membrane-embedded diacylglyceride and a hydrophilic solvent-exposed IP moiety. The inositol ring hydroxyl groups can be stereo-specifically phosphorylated by phosphoinositidekinases. Most phosphatidylinositol-bisphosphate in the plasma membrane of unstimulated cells is phosphorylated at the inositol 4- and 5-positions. PIP2 is an important second messenger, recruiting and regulating multiple signaling proteins (McLaughlin et al., 2002). Due to the constitutive PIP2 availability in resting cells, these PIP2-associated proteins likely maintain signaling pathways in a preactivation state (Han et al., 1998; Ang et al., 2007; Ceccarelli et al., 2007). Despite the importance of PIP2, much greater attention has been given to the products of PIP2 phosphorylation or PIP2 hydrolysis that are induced following receptor activation. PIP2 phosphorylation is mediated by PI3Ks. PI3Ks phosphorylate phosphatidylinositol (PI) into PIP and PIP2. PI3Ks are activated by most stimulatory receptors on lymphocytes including T- and B-cell antigen receptors (TCR, BCR), and co-stimulatory, Toll-like, and cytokine receptors (Vanhaesebroeck et al., 2005; Buitenhuis & Coffer 2009; Fruman & Bismuth 2009) and have important roles in T cell development and function (Sasaki et al., 2000; Okkenhaug et al., 2002; Okkenhaug et al., 2006; Patton et al., 2006; Swat et al., 2006; Alcazar et al., 2007; Matheu et al., 2007; Liu et al., 2009a; Liu & Uzonna, 2010; Soond et al., 2010). Taken together, immunoreceptor-induced PIP3 gneration is important for lymphocyte proliferation and differentiation (Juntilla & Koretzky, 2008; Buitenhuis & Coffer, 2009; Fruman & Bismuth, 2009). PIP3 mediates the cellular effects of PI3K activation by recruiting effector proteins binding to PIP3 (Haslam et al., 1993; Mayer et al., 1993), such as Akt (Protein kinase B) and Tec protein kinase families (August et al., 1997; Heyeck et al., 1997; Stokoe et al., 1997). In addition, Akt can also bind to PI(3,4)P2 (Cozier et al., 2004; James et al., 1996; Lemmon, 2008). Akt is particularly important during early T cell development (Juntilla et al., 2007; Juntilla & Koretzky, 2008). PIP2 is a substrate for another immunologically important enzyme, phosphatidylinositol-specific phospholipase-Cg (PLCg). PLCg hydrolyzes PIP2 into its hydrophobic and hydrophilic components, the membrane-lipid DAG and soluble IP3. Both are second messengers that regulate proteins through specific binding domains. The two mammalian PLCg isoforms, PLCg1 and 2, have partially overlapping expression patterns and functions (Wilde & Watson, 2001). T cells exclusively express PLCg1. T cell-specific PLCg1-deletion impaired thymocyte positive and negative selection, T regulatory cell development and function, TCR-induced peripheral T cell proliferation and cytokine production. Defective TCR activation of the MAP kinases Erk and Jnk, and of the transcription factors NFAT, AP-1, and NF-kB indicates the broad importance of PLCg1 in TCR signaling through several

pathways. Autoimmune disease symptoms show the physiological importance of PLCg1 in T cells (Fu et al., 2010). Severe blocks in T cell development and late onset autoimmunity in mice expressing a PLCg1-binding-deficient LAT allele indicate the importance of LAT interactions for PLCg1 function (Sommers et al., 2002; Sommers et al., 2005). Finally, severe defects in early hematopoiesis in chimeric mice generated with PLCg1-deficient embryonic stem cells suggest important PLCg1 functions in hematopoietic stem or progenitor cells (Shirane et al., 2001). In contrast, PLCg2-deficient mice are viable with specific defects in B cells, mast cells, dendritic cells, osteoclasts, and neutrophils (Wang et al., 2000; Graham et al., 2007; Cremasco et al., 2008; Epple et al., 2008; Cremasco et al., 2010). The membrane second messenger, DAG, propagates signals via membrane recruitment of cytosolic signaling proteins by binding to their C1 domains, cysteine-rich domains of approximately 50 amino acids. Several well-characterized DAG-effector families include Ras guanine-nucleotide-exchangefactors/releasing proteins (RasGRPs), protein kinase C-related kinases (PKCs, PKD), chimaerin Rho/Rac-GTPase-activating proteins (Yang and Kazanietz, 2007), Munc13 proteins (Betz et al., 1998), and diacylglycerol kinases (DGKs).

3. Protein Kinase C (PKC) and T cells

Noticeable, among different proteins participating to the lipidic-dependent signal transduction, is the role of PKCs involved in TCR activation. PKCs are a family of serine/threonine protein kinases involved in different lipidic-dependent signal transduction events. PKCs were identified, for the first time, by Nishizuka and colleagues in 1977. To date, different PKC isoenzymes have been described in several tissues and with differential cellular localizations (Saito and Shirai 2002). PKCs can be grouped into three categories according to the presence of motifs dictating cofactor requirements for their optimal catalytic activity. Whereas conventional [cPKCs: alpha, beta I-II (spliced variants) and gamma] and novel [nPKCs: delta, epsilon, ni and theta] PKCs bind DAG which stimulates kinase catalytic activity, atypical [aPKCs: zeta, iota/lambda] PKCs do not interact with DAG. cPKCs but not nPKCs also require for their activation Ca^{2+}.

Each PKC contains a highly homologous C-terminal catalytic domain and an N-terminal regulatory domain, which mediates cofactor binding and substrate accessibility. PKCs also are characterised by the presence of a DAG/phorbol-ester-binding C1 domain, defined by the presence of two repeated cysteine-rich zinc-finger motifs (C1A and C1B); it is functional in cPKCs and nPKCs, but not in aPKCs. The C2 domain mediates Ca^{2+} binding in cPKCs but differences in key residues abolish this function in nPKCs. aPKCs have single modified C1 domains. C3 and C4 domains are ATP- and substrate-binding lobes of the kinase core. The auto-inhibitory pseudosubstrate sequence (PS) present in the regulatory domain of all PKC isoenzymes interacts directly with the substrate-binding cavity in the catalytic domain, thereby sterically blocking access of substrates to the active site. The activation of signal transduction pathways, involving PKCs, leads to the hydrolysis of PIP2, and consequently to the formation of DAG and IP3. DAG binds to the PKC C1 domain; PKCs are activated by phosphorilation and can finally phosphorylate protein substrates. PKCs demonstrated broad substrate specificity *in vitro* related to several functions *in vivo*. Distinct roles of different PKC isoforms can be, at least in part, attributed to differences in their structures and to the different mechanisms modulating their activation (Figure 1). These different PKC roles are also evident in the context of intracellular immune cell signalling (Tan and Parker 2003).
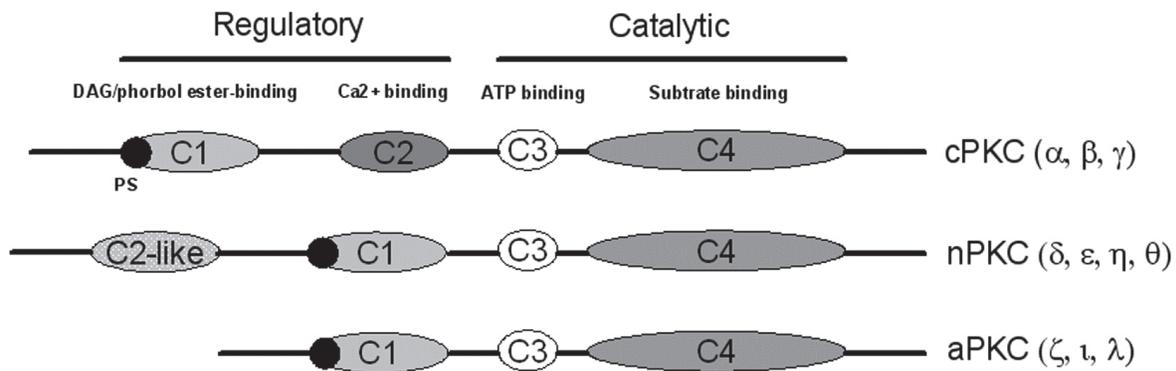
Fig. 1. PKC structure

The role of PKC in regulating T cell activation has been well characterised. The nPKC member PKC-theta which expression is largely restricted to T cells co-localised with the TCR was originally identified to play an important role in TCR-induced T cell activation (Baier 2003) (Isakov and Altman 2002). PKC-theta has also been involved in cell signalling events triggered by TCR engagement both *in vitro* in cell models and *in vivo* in knockout mice (Baier-Bitterlich, Uberall et al. 1996); (Lin, O'Mahony et al. 2000); (Bauer, Krumbock et al. 2000); (Sun, Arendt et al. 2000) (Pfeifhofer, Kofler et al. 2003). In particular PKC-theta mediates activation of the transcription factor activator protein-1 (AP-1) and of the nuclear factor κB (NF-κB) in response to TCR/CD28 co-stimulation in several T cell models (Baier-Bitterlich, Uberall et al. 1996); (Lin, O'Mahony et al. 2000); (Bauer, Krumbock et al. 2000). It has been demonstrated that PKC-theta activation could also be linked to nuclear factor of activated T cells (NFAT) signaling (Pfeifhofer, Kofler et al. 2003) (Figure 2). Beside the well-recognized role of PKC-theta for T cell receptor activation, other PKC isoforms seem to be involved in T cell signalling in an alternative or cooperative fashion.

Among others, PKC-alpha has been suggested to play a potential role in thymocyte developmen. PKC-delta has been reported to be possibly involved in T cell migration (Volkov, Long et al. 1998). Self-reactive B-cells normally undergo either clonal deletion or tolerance to self-antigens (B-cell anergy), which is essential for the prevention of autoimmune disease. The physiological role of PKC-delta, the closest related PKC member to PKC-theta, in the control of B-cell tolerance has recently been uncovered by characterization of PKC-delta-knockout mice generated independently by two laboratories (Miyamoto et al., 2002; Mecklenbrauker et al., 2002). Loss of PKC-delta in mice leads to significant splenomegaly and lymphadenopathy because of increased numbers of peripheral B-cells, although no noteworthy abnormalities are observed in T cells (Miyamoto et al., 2002). The mice die prematurely due to severe autoimmune disease, which is characterized by the detection of autoreactive antibodies, indicates that PKC-delta is essential for the prevention of autoimmune disease. Furthermore, PKC-delta deficiency prevents B-cell anergy, allowing maturation and differentiation of self-reactive B-cells, attributed to a defect in nuclear factor κB (NF-κB) activation, at least as judged by inefficient IκB degradation in the cytoplasm (Mecklenbrauker et al., 2002). Although the above studies suggest that PKC-delta is involved in negative regulation of proliferation, there is no consensus on the mechanism. Mecklenbrauker et al. reported that the B-cells from PKC-delta-deficient mice have normal responses to antigenic stimulation and thereby concluded that PKC-delta −/−

B-cells have a specific defect in the induction of anergy. In contrast, Miyamoto et al. showed that the proliferation of B-cells from PKC-delta −/− mice was increased in response to several mitogenic stimuli, suggesting a generalized enhancement of signalling events. Whereas NF-κB activation remained unaffected, increased production of the growth-promoting cytokine IL-6, as well as the DNA-binding activity of the nuclear factor IL-6 (NFIL-6) transcription factor, was detected in the PKC-delta −/− B-cells, suggesting PKC-delta might negatively regulate B-cell growth through transcriptional regulation of the IL-6 gene.

Intriguingly, PKC-zeta has also been implicated in the T cell-dependent immune response (Duran, Diaz-Meco et al. 2003); (Savkovic, Koutsouris et al. 2003). Targeted disruption of the PKC-zeta gene in mice indicates that the role of this aPKC within the immune system is also specific to B-cell function (Martin et al., 2000). B-cells from PKC-zeta-deficient mice showed increased spontaneous apoptosis, and impaired proliferation and survival in response to IgM cross-linking, whereas both peripheral T cells and thymocytes seemed to develop and proliferate normally. The defective survival of B-cells in these mice correlated with defects in the activation of extracellular-signalregulated kinase (ERK) (but not p38 MAPK or JNK) and the transcription of NF-κB-dependent genes, including Bcl-xL, IκB and IL-6. Furthermore, transcription of these NF-κB-dependent genes, but not NF-κB nuclear translocation, was inhibited in B-cells stimulated with IgM. PKC-zeta-null mice were unable to mount an optimal T cell-dependent immune response, in spite of the fact that, as adults, they exhibited no major defects in the subpopulations of B-cells, indicating that this is a post-B-cell maturation phenomenon. Although the possibility of a PKC cascade involving both PKC-beta and PKC-zeta has not been excluded, recent findings showed that PKC-zeta can regulate NF-κB via an IKK-independent pathway, by directly phosphorylating Ser^{311} of the pHealy et al., 1998 subunit (RelA) (Duran et al., 2003; Savkovic et al., 2003).

Therefore, modulation of the expression and phosphorylation of different PKC isoforms might play critical independent or complementary roles in the context of the better known PKC-theta-driven T cell signalling in different normal and pathological conditions. As far as AD is concerned, while a body of literature refers to a possible involvement of PKC signalling in brain and skin tissues of these patients (Alkon, Sun et al. 2007), scarce or no knowledge is available about the behaviour of the above reported PKCs in peripheral T cells from AD patients. Recently, it was reported that flow cytometric assessment of well defined bright P-PKC-delta and P-PKC-zeta T cell subpopulations (probably CD4+ T cells) after specific Abeta1–42 stimulation in the majority of AD patients, may refer to the development of T cell subpopulations reactive to Abeta1–42 and concomitantly expressing high levels of phosphorylated PKC-delta and PKC-zeta (Miscia, Ciccocioppo et al. 2009).

4. Inflammation and T cells in Alzheimer's disease

Normal aging in humans brings a progressive loss in memory and is often exacerbated by diseases such as Alzheimer's disease (AD). Although many underlying processes have been invoked, one common ground that links many factors associated with cognitive aging is neuroinflammation. Markers of inflammation are associated directly with deficits in cognitive function and with diseases that are risk factors for cognitive decline (Gemma C, 2010). Amelioration of brain inflammation with various treatments has beneficial actions on several indicators of impaired cognitive aging. Understanding how neuroinflammation

affects cognition may provide directions for useful interventions to prevent or treat an aberrant cognitive decline in older adults.
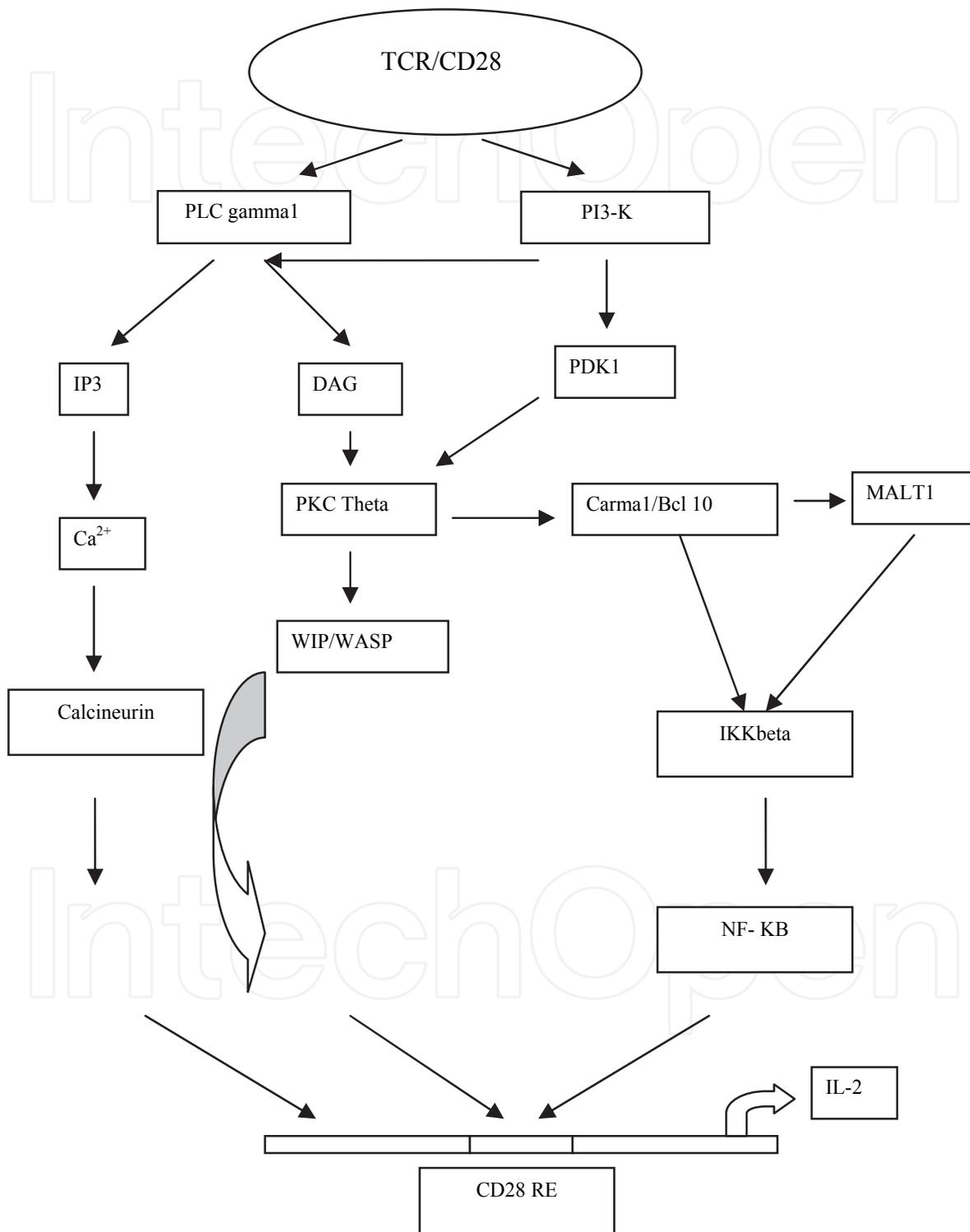
a)
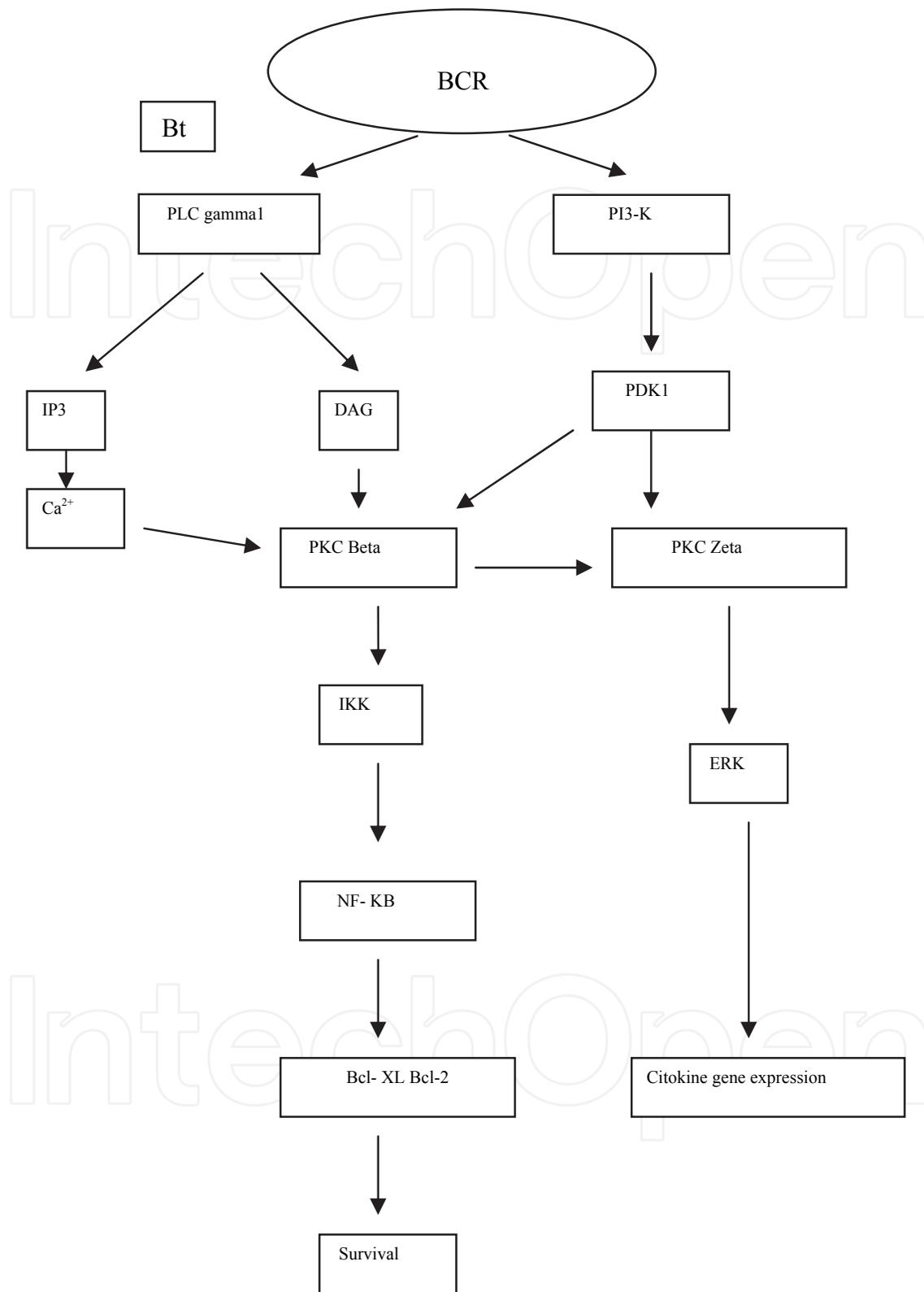
b)

Fig. 2. Signal transduction pathways involving PKC in T (a) and B (b) cells

However, to better understand inflammation's role in disease, it is necessary to recognise that inflammation is a protective response of our body that occurs in response to an insult. In the case of infection, the immune system is activated to identify the foreign agent and neutralize it. This involves a series of events and requires the recruitment of a variety of immune cells. Throughout most of the body, cells known as macrophages, search for invaders, and then engulf and neutralizing them. The recognition of infectious non-self is mediated by a limited number of germline-encoded pattern-recognition receptors (PRRs), which trigger rapid responses. In the brain, supporting cells of the glial family comprise of astrocytes and microglia. Microglial cells, act as scavengers and are considered "the CNS professional macrophages". Microglia are myeloid lineage cells expressing a wide range of PRRs and for this reason they embody the innate immune response of the brain, as they provide the first line of defense whenever there is an injury. They engulf and eliminate dead neurons that have been damaged by injury or illness. However, they also secrete harmful neurotoxins and toxic oxygen free radicals in an attempt to neutralize foreign or undesirable substances. Unfortunately, sometimes the injurious event overwhelms the protective effect and inflammation may become self-perpetuating. This is the case of normal aging, but it is much more rampant in neurodegenerative diseases such as Alzheimer's, Parkinson's, which are characterized by exacerbated microglial activity. To date, the neurotoxic and neuroprotective roles of innate immune reactions in brain injury, ischemia, autoimmune and neurodegenerative disorders of the CNS, altogether solicits an intensively investigated and debated scientific research issue. However, despite considerable work in this area, much more points remain to be elucidated, notably cellular events regarding the early dysregulating events that activate brain inflammatory pathways. If it will be possible to target and harness these inflammatory processes toward therapeutic application, then cognition could be protected during aging and disease by early intervention against the negative consequences of inflammation.

It is now clear that inflammation plays an important pathogenethic role in Alzheimer's disease (AD). At onset of pathology, the inflammatory changes are probably linked to misfolding and the consequent accumulation of Amyloid beta (Abeta) peptide in the limbic and associative cortices of AD brains (Rogers, Webster et al. 1996); (McGeer and McGeer 1999; McGeer and McGeer 1999; McGeer and McGeer 2002). Many studies have demonstrated that such inflammation arises mainly from cellular (glial) sources within the central nervous system (CNS) rather than from external sources such as T cells. However, recent studies have suggested that systemic T cells, and in particular CD4+ T cells, can be recruited to the CNS to modify potential destructive local inflammation (Schwartz and Shechter 2010). As a consequence of increased damage to the blood–brain barrier (BBB) or in response to inflammatory signals T cells might more commonly cross the BBB and accumulate in AD brains (Rogers, Luber-Narod et al. 1988); (Togo, Akiyama et al. 2002). It remains to be determined whether brain penetration of T cells is involved in the etiopathogenesis of AD, or if it is simply an epiphenomenon.

5. Peripheral T cell responses in Alzheimer's Disease

In humans, naïve T cells typically express CD45RA on the surface. When naïve T cells encounter their antigen they become activated and a CD45 isoform switching from RA to RO occurs consequently (Dutton, Bradley et al. 1998). This isoform switching can thus be taken as a marker of human T cell "memory" (Figura 3).

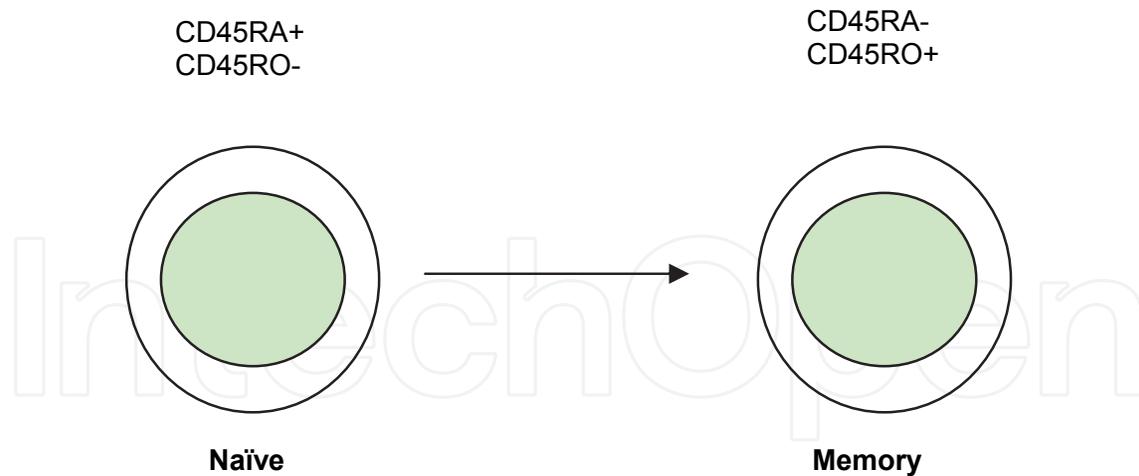CD45RA+
CD45RO-

CD45RA-
CD45RO+

Naïve

Memory

Fig. 3. Cell surface antigens on naïve and memory subsets

It has been demonstrated that CD45RO expression was increased in T cells from AD patients compared to controls, when isolated T cells were placed in culture (Lombardi, Garcia et al. 1999). Interestingly, Togo et al. reported the presence of CD45RO+ T cells in brains of AD patients (Togo, Akiyama et al. 2002). These findings demonstrated that T cells are indeed activated at some point during the clinical progression of AD. In an attempt to address this question, Lombardi et al. (Lombardi, Garcia et al. 1999) found an increase in CD4+ T cells and CD25+ T-regulatory cells in the AD group compared to healthy controls. Additional evidence of systemic T cell activation in AD comes from studies designed to measure Abeta auto-antibodies or Abeta-reactive T cells in AD patients and controls. Although antibody production is a B cell-dependent process, the response is supported by activated T cells. At least three studies to date found increased levels of circulating Abeta auto-antibodies in patients clinically diagnosed with dementia compared to non-demented controls (Nath, Hall et al. 2003) (Gruden, Davudova et al. 2004) (Mruthinti, Buccafusco et al. 2004). Using various peptides and specific assay systems to stimulate peripheral T cells from AD patients, it was also demonstrated that T cells specific for the fragment 1-42 of the Abeta peptide (Abeta1-42) can be detected in peripheral blood (Monsonego, Zota et al. 2003). More recently, by applying a slightly modified system than the one used by Monsonego et al (2003), an increased T cell reactivity to Abeta1–42 peptide in peripheral blood from AD patients respect to control subjects was seen (Miscia, Ciccocioppo et al. 2009).

6. T cell subsets in AD pathogenesis and diagnosis

In vitro studies have shown that IFN-gamma-treated microglia are efficient antigen-presenting cells (APCs) presenting Abeta and triggering Abeta-reactive T cell proliferation. Th1 Abeta-reactive cells become apoptotic after such stimulation, whereas Th2 cells stimulated by Abeta express the cardinal Th2 cytokines (Monsonego, Zota et al. 2003). It has been suggested that Th2-type Abeta-reactive T cells could be beneficial in AD by secreting cytokines which downregulate the proinflammatory environment. To date, the diagnosis of AD is based on neuropsychological examination using criteria such as insidious onset and progressive impairment of memory, as well as loss of other cognitive functions. The presence of plaques and tangles assessed after post mortem examination of brain tissue has been considered a strong marker for AD diagnosis (Hof 1997). Early inflammatory

processes, identified at AD onset, suggest that specific inflammatory biomarkers in the peripheral blood, such as increased levels of TNFalpha, CD40L and other pro-inflammatory cytokines might support the diagnosis (Akiyama, Barger et al. 2000; Speciale, Calabrese et al. 2007;   Schwartz and Shechter 2010). A definitive role of biomarkers in clinical practice has not been unequivocally accepted. As a novel approach to identify specific AD biomarkers, it could be hypothesised that peripheral immune changes could be a suitable and specific AD biomarker. Several reports showed the existence of Abeta1-42-responding T cells in the peripheral blood of AD patients (Monsonego, Zota et al. 2003; Miscia, Ciccocioppo et al. 2009). The up-regulation of some PKC isoforms in T cells from AD patients has also been shown (Ciccocioppo, Lanuti et al. 2008; Miscia, Ciccocioppo et al. 2009). It could be observed that circulating T cells expressing high levels of P-PKC-delta and P-PKC-zeta after Abeta1-42-specific stimulation are present in AD patients. By applying a multicolour flow cytometry method, an association between some activation marker production, such as IL-2, INFgamma, TNFalpha and CD40L and up-regulation of P-PKC-delta and P-PKC-zeta levels following Abeta1-42 stimulation was found in peripheral blood from AD patients but not in healthy subjects. This suggests that T cells expressing bright levels of P-PKC-delta and P-PKC-zeta are Abeta1-42-specific, even if further characterisation of these T cells, in terms of phenotype and memory compartment, has to be addressed in future studies.

7. Discrimating AD from other forms of dementia: possible biomarkers?

After AD, Dementia with Lewy bodies (DLB) is the second most frequent cause of neurodegenerative dementia in the aged population. Neuropathologically, DLB is characterised by an accumulation of inclusion bodies (Lewy bodies) consisting of aggregated alpha-synuclein (Francis 2009). It is generally recognised that the clinical differentiation between AD and DLB is at best difficult (Geser, Wenning et al. 2005; McKeith, O'Brien et al. 2007). Thus, the identification of biomarkers would facilitate the differential diagnosis of AD and DLB. Even though Abeta deposition is identified in DLB brain (Town, Tan et al. 2005), there is no Abeta-triggered inflammatory activity in DLB. It could be postulated that Abeta1-42-specific T cells, expressing bright levels of P-PKC-delta and P-PKC-zeta are absent in DLB. In addition, preliminary experiments were carried out on some patients affected by two other different forms of amyloidopathies, used as controls: inclusion body myositis (IBM; n = 3) and cerebral Amyloid angiopathy (CAA; n = 5) patients. IBM is a rare, chronic and slowly progressing inflammatory myopathy, characterised by T cell invasion of muscle fibres (Askanas and Engel 2002). In IBM the peripheral accumulation of Abeta1-42 plays a critical role in skeletal muscle degeneration (Kitazawa, Green et al. 2006). CAA is instead characterised by predominant deposition of the Abeta1-40 fragment in cerebral blood vessels (Preston, Steart et al. 2003) and it is generally not associated with inflammation. P-PKC-delta and P-PKC-zeta bright T cell subsets were detectable in all IBM patients, while patients with CAA, mainly expressing the fragment Abeta1-40, do not show a similar T cell activation. These data indicate that Abeta1–42 does not induce P-PKC bright subpopulation in T cells from non-AD, neurodegenerative diseases.

8. Conclusion

All thoghether these hypotheses could demontrate that in AD patients, CD4+ Abeta1-42-specific T cells expressing high levels of P-PKC-delta and P-PKC-zeta could represent a

peripheral footprint of an Abeta1-42-mediated inflammation in the brain, related to protein deposition observed in AD. The presence of Abeta1-42-specific T cells, expressing bright levels of P-PKC-delta and P-PKC-zeta, might support clinical diagnosis of AD versus other forms of dementia.

9. Acknowledgements

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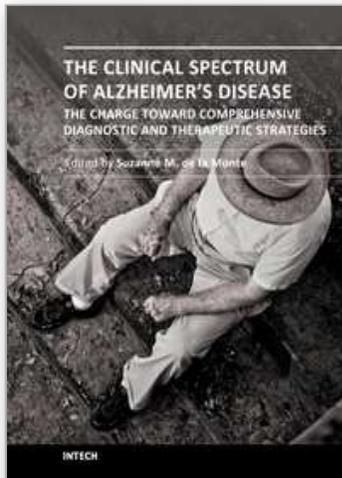
The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies
Edited by Dr. Suzanne De La Monte

The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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