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Protein Kinase C (PKC) expression is deregulated in chronic lymphocytic leukemia

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Running title: PKC in chronic lymphocytic leukemia

"Letter to the Editor"

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The mammalian genome encodes more than 500 of protein kinases [1,2] which play diverse roles in cell signaling and disease. Protein kinase C (PKC) is a family of protein serine/threonine kinases encoded by nine genes [3]. This family of proteins is of importance in cell signaling through multiple pathways including the MAPK pathways [4]. Recently PKC-mediated signal transduction pathways have been implicated in acute myeloid leukemia [5]. However, the role of different PKC isoforms in chronic lymphocytic leukemia (CLL) is by and large unknown. CLL is the most common type of leukemia which develops through a multistep process involving both genetic and epigenetic alterations of oncogenes and tumor suppressor genes [6,7]. Several prognostic markers have been identified for CLL over the last couple of decades [8]. In this communication we describe the expression patterns of different PKC isoforms in CLL as well as different other cancers.

We analyzed 693 micro-array samples from different cancer patients and the corresponding tissues from healthy donors for expression of PKC isoforms (Table 1). The mRNA expression data were downloaded from NCBI Gene Expression Omnibus (GEO) and were then normalized using the median scale normalization method. This method allows for showing data from different platforms in the same scale.

PKC isoforms play differential roles in several types of cancers. For example both PKCδ and PKCε exhibit oncogenic functions in breast cancers while PKCδ acts as a tumor suppressor in colon cancer [9,10]. We observed that PKCα expression was down-regulated in glioblastoma, CLL and colon

cancer while it remained unchanged in other cancers (Fig. 1A). Although expression of PKCβ2 has been found to be down-regulated in most types of cancers, it was found to be significantly up-regulated in CML, breast cancer and CLL (Fig. 1B). PKCγ was down-regulated only in glioblastoma and in lung cancer (Fig. 1C), and expression of PKCδ was increased in myeloma and prostate cancer while it was decreased in AML, glioblastoma and colon cancer (Fig. 1D). PKCε might play a role in T-PLL as its expression was significantly increased in this type of leukemia (Fig. 1E).

A decrease of PKCη expression was observed in AML and colon cancer (Fig. 1F) and PKCθ expression was upregulated in CML but was downregulated in glioblastoma, WM myeloma and lung cancer (Fig. 1G). Similar to PKCβ2, PKCς expression was also increased in CLL (Fig. 1H). In addition this PKC isoform was found to be deregulated in many other cancers (Fig. 1H). PKCι expression was only increased in AML and myeloma suggesting its importance in these cancers.

Since we observed an increase expression of PKCβ2 and PKCς in CLL and since also another study has suggested that PKC activation is important for CLL cell survival [11], we further analyzed expression using the same normalized dataset. PKCβ2 regulates B-cell antigen receptor (BCR)-induced Ca^{2+} fluxes in CLL patients [12] and is constitutively expressed in ZAP-70 expressing CLL cells [13]. PKCβ2 displayed the highest expression of all nine isoforms of PKC and its expression further significantly increased indicating a role in CLL (Fig. 1J). This observation was further supported by the observation that PKCβ was indispensable for CLL development in a mouse model [14]. In addition a

PKCβ-specific inhibitor inhibited PMA-induced Akt phosphorylation in B-CLL cells [15].

We further analyzed PKCβ2 expression from three different sets of micro-array data of CLL patients which were also downloaded from NCBI GEO. As shown in figure 1K, there was no significant difference in PKCβ2 expression in CD38 positive and negative population as well as in indolent or progressive CLL while a decreased PKCβ2 expression displayed a correlation with poor prognosis. Thus we suggest that although PKCβ2 expression was significantly increased in CLL, and further studies are required to define its exact role.

Potential conflict of interest: The authors declared no conflict of interest.

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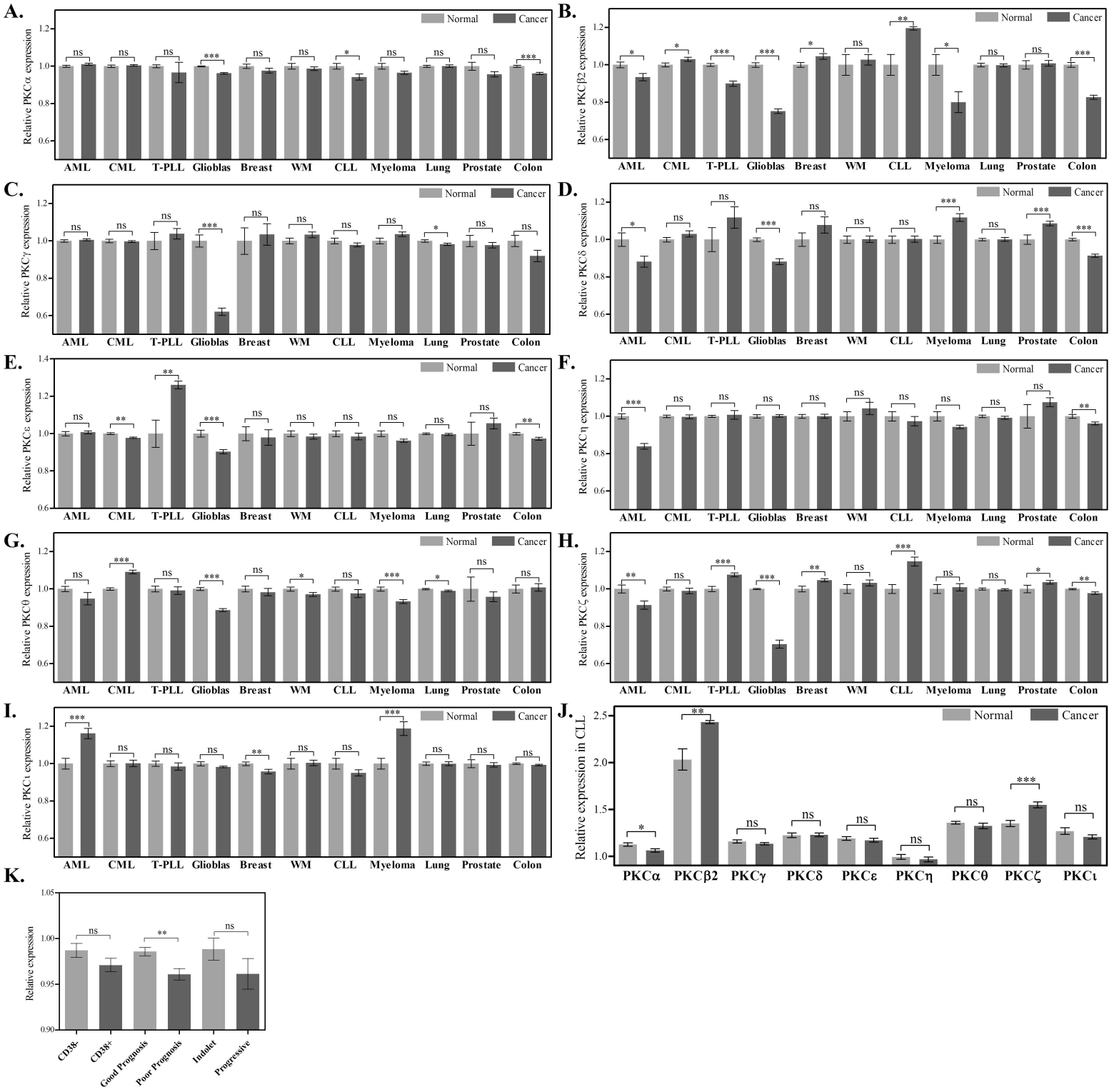
Figure Legend

Fig. 1. The mRNA expression was analyzed from microarray data of different patient samples and corresponding healthy donors. Expression data was downloaded from NCBI Gene Expression Omnibus (GEO) and then normalized using median scale normalization. Error bars show SEM, and t-test was performed to determine significance. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; AML, Acute myeloid leukemia; CML, Chronic myeloid leukemia; T-PLL, T-cell-prolymphocytic leukemia; WM, Waldenström's macroglobulinemia; CLL, Chronic lymphocytic leukemia.


A.
B.
C.
D.
E.
F.
G.
H.
I.
J.
K.
Normal
Cancer
Relative PKCα expression
Relative PKCβ2 expression
Relative PKCγ expression
Relative PKCδ expression
Relative PKCε expression
Relative PKCη expression
Relative PKCθ expression
Relative PKCζ expression
Relative PKCι expression
Relative expression in CLL
Relative expression
AML
CML
T-PLL
Glioblas
Breast
WM
CLL
Myeloma
Lung
Prostate
Colon
PKCα
PKCβ2
PKCγ
PKCδ
PKCε
PKCη
PKCθ
PKCζ
PKCι
CD38-
CD38+
Good Prognosis
Poor Prognosis
Indolet
Progressive
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