Common domain structure of Ca^{2+} and lipid-binding proteins

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Received 30 May 1986

The phospholipase A_2 inhibitor, lipocortin, shares common sequences with three abundant Ca^{2+}-regulated membrane binding proteins of unknown function which are present in many cell and tissue types. A two-domain model for the structure of lipocortin is described and it is suggested that the new Ca^{2+}-regulated proteins each contain at least one lipocortin domain. The structural and biochemical properties of each protein indicate that they all directly interact with phospholipids. Potential sites of interaction with the lipocortin domain are identified on the basis of homology with phospholipid transfer proteins and phospholipase A_2.

Lipocortin *Ca^{2+} binding* *Endonexin* *Calelectrin* *Phospholipase A_2* *Membrane binding*

1. INTRODUCTION

Phospholipids play a central role in signal transduction [1]. Inositol phospholipids are the source of two signals. First, inositol trisphosphate, which mobilizes intracellular Ca^{2+}. Second, diacylglycerol, which activates C-kinase. The same lipids, together with phosphatidylcholine, are the source of prostaglandins and leurotrienes via released *cis*-unsaturated fatty acids [2]. We have identified members of a new class of Ca^{2+}-regulated membrane binding proteins, whose membrane targets appear to be lipids [3–6]. Each protein binds to liposomes containing acidic phospholipids at moderate levels of Ca^{2+} (1–10 μM) and aggregates liposomes or membrane vesicles at higher Ca^{2+} levels (>200 μM) [4–6]. Creutz et al. [7] discovered an analogous protein synexin and, independently, the lipid-binding proteins described here. In view of their similar biochemical and biophysical properties, we have coined the generic term 'annexin' for such proteins [8]. Recently, we published amino acid sequence data for four 'annexins'; endonexin, calelectrin, protein II and p36, which established the presence of a common amino acid sequence – the 'endonexin fold' [6,9]. This feature was also found in the sequence of a phospholipase A_2 inhibitor, lipocortin, deduced from cDNA [10]. Lipocortin is present in many cell types and blocks the production of arachidonate and the consequent prostaglandin/leukotriene-mediated inflammatory response [10,11].

Lipocortin and p36 are strongly implicated in signal transduction. Lipocortin is phosphorylated by protein kinase C [12,13]. Lipocortin and p36 are substrates for EGF receptor and $pp60^{src}$ protein tyrosine kinases [13–15]. Each protein binds Ca^{2+} and shares with protein kinase C the property of Ca^{2+}- and lipid-dependent recruitment by membranes. The functions of the annexin group as a whole are not clear. It is therefore important to make a critical comparison of these molecules, to identify the extent to which they are really related in view of their potential role in transduction of the signals described. I report here a model for the domain structure of lipocortin. I hope this will provide a basis for comparison with the complete structures of the other proteins, when they become known.

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00145793/86/$3.50