Targeting of PKCzeta and PKB to caveolin-enriched microdomains represents a crucial step underpinning the disruption in PKB-directed signalling by ceramide.

Titre	Targeting of PKCzeta and PKB to caveolin-enriched microdomains represents a crucial step underpinning the disruption in PKB-directed signalling by ceramide.
Type de publication	Article de revue
Auteur	Hajduch, Eric [1], Turban, Sophie [2], Le Liepvre, Xavier [3], Le Lay, Soazig [4], Lipina, Christopher [5], Dimopoulos, Nikolaos [6], Dugail, Isabelle [7], Hundal, Harinder S [8]
Editeur	Portland Press
Type	Article scientifique dans une revue à comité de lecture
Année	2008
Langue	Anglais
Date	01/03/2008
Pagination	369-79
Volume	410
Titre de la revue	Biochemical Journal
ISSN	1470-8728
Mots-clés	3T3 Cells [9], Adipocytes [10], Animals [11], Caveolin 1 [12], Ceramides [13], Cholesterol [14], Enzyme Activation [15], Humans [16], Insulin [17], Mice [18], Mice, Knockout [19], Muscle, Skeletal [20], Protein Kinase C [21], Proto-Oncogene Proteins c-akt [22], Signal Transduction [23]
Résumé en anglais	Elevated ceramide concentrations in adipocytes and skeletal muscle impair PKB (protein kinase B; also known as Akt)-directed insulin signalling to key hormonal end points. An important feature of this inhibition involves the ceramide-induced activation of atypical PKCzeta (protein kinase C-zeta), which associates with and negatively regulates PKB. In the present study, we demonstrate that this inhibition is critically dependent on the targeting and subsequent retention of PKCzeta-PKB within CEM (caveolin-enriched microdomains), which is facilitated by kinase interactions with caveolin. Ceramide also recruits PTEN (phosphatase and tensin homologue detected on chromosome 10), a 3'-phosphoinositide phosphatase, thereby creating a repressive membrane microenvironment from which PKB cannot signal. Disrupting the structural integrity of caveolae by cholesterol depletion prevented caveolar targeting of PKCzeta and PKB and suppressed kinase-caveolin association, but, importantly, also ameliorated ceramide-induced inhibition of PKB. Consistent with this, adipocytes from caveolin-1-/- mice, which lack functional caveolae, exhibit greater resistance to ceramide compared with caveolin-1+/+ adipocytes. We conclude that the recruitment and retention of PKB within CEM contribute significantly to ceramide-induced inhibition of PKB-directed signalling.
URL de la notice	http://okina.univ-angers.fr/publications/ua7122 [24]

DOI	10.1042/BJ20070936 [25]
Lien vers le document	http://dx.doi.org/10.1042/BJ20070936 [25]
Autre titre	Biochem. J.
Identifiant (ID) PubMed	17983354 [26]

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[26] http://www.ncbi.nlm.nih.gov/pubmed/17983354?dopt=Abstract