

671 Potential importance of PKC-alpha activity in defining breast tumor luminal/basal phenotype.

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Abstract

We have studied the effects of the protein kinase C (PKC)-activator phorbol 12-myristate 13-acetate (PMA) on gene expression in two highly different breast cancer cell (BCC) lines, the estrogen receptor alpha (ER)-positive, "luminal epithelial-like" MCF-7 and the ERnegative, "fibroblast-like" MDA-MB-231. These express constitutively low and high PKC activities, respectively. After a 24 h exposition to 100 nM PMA, the number of genes showing a altered expression at the 2 fold change level was much higher in MCF-7 (435) than in MDA-MB-231 (18) BCC. Three of these genes, namely CDC2, CENPA, MMP10, were altered in the same way in both cell lines. Two genes were regulated in an opposite way: IDI and EVAL. Many of the genes modulated in MCF-7 BCC (about 22% of total) were cell-cycle associated; they were down-regulated. The ER gene, ESR1, and a series of other genes associated to the ER-positive, "luminal epithelial-like" phenotype of BCC were down regulated. while genes related to a more "fibroblast-like" BCC phenotype were up regulated. Other altered genes were notably linked to cell architecture, supporting profound effects of PMA on cell morphology and motility, and on the interactions between BCC and their neighboring proteins. Of note, all the genes identified as related to proteolysis and their controls were up regulated. In summary, PMA effects suggest that PKC activation may induce, to some extent, a more "fibroblast-like" phenotype in the (ER)-positive, "luminal epithelial-like" MCF-7 BCC and significantly modulate the interactions of these cells with their environment.

hybridizations for each experimental

condition were performed

Material and Methods		chromosome l
00		0 ATP binding (35)
	Molecular Function	DNA binding (28)
MCF7 ER+ MDA-MB-231 ER- (luminal-like) (basal-like)		 hydrolase activity (26)
		receptor activity (16)
* *		 protein serine/threenine kinase activity (15)
PMA 100 nM 24h		# structural molecule activity (8)
		protein-tyrosine kinase activity (8)
+ +		nucleoside binding (6)
pante pante		 apoptosis inhibitor activity (5)
	Statistical algolficant p-0.05 FDB.	 DNA dependent ATPase activity (4)
cDNA 10K (Incyte Genomics)		 protein phosphatase type 2C activity (4)
Two (forward and reverse fluorochrome)		myosin phosphatase 0 activity (4)

a max of 1 or 2 genes per function)

MCF ER+/	7 Luminal (1) 2.0 Venn diagram using ge		MDA-MB-231 ER-/Basal	Biological Process	ENA replication (db) regulation of an optimized experiment of the optimized of	registering of CFN registering of CFN registering to CF	Overlap between PMA regulated gene and NCI 7650 probe- times Mitcroarray transmit Mitcroarray		Hierarchical cluster diagram of 99 BC specimers based on the 221 Pharmaceuter and the 221 Pharma
	Functional p biological pr	rofiles (using Gene O	Ontology terms) for biochen ellular component, molecul ess).	nical function,		P.VALK P.VALK P.VALK	Astastastastastastastastastastastastastas		自然。 一個。 對此一
	ATP binding (35)	magnesium-dependent protein serine/threenline phosphatase activity (4)				1.0003 0.0080 0 1.0007 0.0080 24 1.0072 0.0080 24	10	16	是一次的第三人称单数的 化
n	 DNA binding (28) 	prosphatase activity (4) calcium-dependent protein serine/threeoine phosphatase activity (4)	Cellular Component	nucleus (87)	a intermediate filament				10 M 1 A M
	 hydrolase activity (26) 	CTD phosphatase activity (4)		 cytoplasm (25) 	 DNA replication facto complex (3) 				
	receptor activity (16)	single-stranded DNA binding (4)		 cellular_component unknown (14) 	 synaptic vesicle (3) 	112034 01199 10 112034 01199 10 1173072 012485 10 117007 014214 10			Conclusions
	 protein serine/threenine kinase activity (15) 	protein phosphatase type 2A activity (4)		 soluble fraction (14) 	 DNA replication facto complex (3) 		15		
	# structural molecule activity (8)	protein kinase activity (4)		 microsome (5) 	 focal adhesion (3) 	0.210327 0.07711 43 0.21304 0.077050 20			The sumble of the black designs of the Party
	protein-tyrosine kinase activity (8)	cell adhesion receptor activity (4)		# spindle (5)	alpha DNA polymerase:primase complex (3)	0.22023 0.16220 M 0.22404 0.16224 M 0.25004 0.20278 M		(a)	The number of modulated genes after PMA are higher in MCF7/ER+ BCC compared to MDA-
7	nucleoside binding (6)	glucuronosyliransferase activity (3)		 delta-DNA polymerase cofactor complex (5) 	 insoluble fraction (2) 	8.30531 0.23968 28 8.20776 0.24256 0 8.37569 0.20542 4			MB-231 BCC lines.
	 apoptosis inhibitor activity (5) 	delta DNA polymerase activity (3)		mitschondrion (4)	a nuclear chromosome		10 III	(b)	PMA effects suggest that PKC activation may
	BNA dependent ATPase = activity (4)	cyclin-dependent protein kinase inhibitor activity (7)		 integrin complex (4) 	 spindle microtabale (2)			induce, to some extent, a more "fibroblast-like" phenotype in the (ER)-positive, "luminal
	 protein phosphatase type XC activity (4) 	adenosinetriphosphatase		 chromatin (4) 	0 calcineurin complex (2)			epithelial-like" MCF-7 BCC and significantly modulate the interactions of these cells with their
	a myoyin phosphatase a	activity (3) damaged DNA binding (3)		 microtubule associated complex (4) 	condensin core heterodimer (2)				environment.
	activity (4) other (191 genes : sum of groups w				other (15 genes : sum which include a max i gene per component)				

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