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Supplementary information

Part A: Setting up the simulation

Part B: Validation by experimental data

Files: platelet_boolean.xml (for SQUAD), reactions, reactions_notes, metabolites, metabolites_notes, app.para.m and platelet.txt (for CNA), platelet_boolean.jpg (topology), table 1S.xls (literature-based interactions), table 2S.xls (logical rules)

Part A: Setting up the simulation:

As an abstraction based on Table 1S we derived a Boolean model. Table 2S shows the applied logical rules and the phases in which the respective reactions become active. Compared to the full cytoscape (figure 1), our Boolean model represents a simplification. We concentrated on nodes that are functionally well analysed and approved to play a tremendous role in platelet signal-transduction. The final model topology was evaluated and confirmed by experts of platelet biochemistry. We used CellNetAnalyzer for implementation. (see for algorithm details: (a) S. Klamt, J. Saez-Rodriguez, E. D. Gilles, *BMC Syst Biol*, 2007, **1,** 2 (b) S. Klamt, J. Saez-Rodriguez, J. A. Lindquist, L. Simeoni, E. D. Gilles, *BMC Bioinformatics,* 2006, **7,** 56).

CellNetAnalyzer is an extension of the former *FluxAnalyzer*. (Klamt S, Stelling J, Ginkel M and Gilles ED (2003) FluxAnalyzer: exploring structure, pathways, and flux distributions in metabolic networks on interactive flux maps. *Bioinformatics* **19(2):** 261-269.) and hence also further interactions such as signalling interactions are described by a matrix composed of reactions and metabolites (both given as files and with metabolite notes and reaction notes, respectively). CNA has previously been used to describe and analyze large-scale Boolean models of biological networks. This tool is also useful to predict and verify experimental data, examine the structure and the hierarchy of the system as well as the relevance of its components. In opposition to standard Boolean approaches, CNA offers the possibility to include basal stochiometry in the established network.

The requirements for using *CellNetAnalyzer* (CNA) are:

- MATLAB version 7.1 (R14) or higher
- Some functions require the optimization toolbox of MATLAB (or/and GLPKMEX) with GLPK library

An English manual is available as an online manual at

http://www.mpi-magdeburg.mpg.de/projects/cna/manual/toc_frame.htm

Several ASCII files stored in the project directory are used by CNA for representing mass-flow (MF) and signal flow (SF) networks. These files are in a special format interpretable by CNA and required for both mass- and signal-flow networks.
To set up the simulation, both respective reactions and metabolites files, as well as the files app_para.m and platelet_boolean.jpg have to be saved in a subdirectory of the unpacked

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CellNetAnalyzer folder. The software is started by typing "startcna" in the Matlab command line. Next, a new project has to be created via clicking on the projects menu in the main window. In the newly appearing window, the project name, the network type (in this case signal-flow) and the name of the subfolder containing the platelet files has to be entered (see manual, chapter 1 and 2). Additionally, the corresponding graphic file needs to be specified in the network map section. Here, we use the file platelet_boolean.jpg. After saving the project (app_para.m may not be overwritten), it can be started from the main window. Simulation and analyzation tools are applied as stated in the manual.

Dynamic simulations were performed after loading the file xml file into the software SQUAD, as described in: Alessandro Di Cara, Abhishek Garg, Giovanni De Micheli, Ioannis Xenarios and Luis Mendoza, *BMC Bioinformatics* 2007, **8**:462. It is freely available at: http://www.enfin.org/wiki/overview

Boolean operators

Boolean approaches can be applied to biological systems, and signal flow networks can be described reasonable by a logical approach (40). The Boolean formalism is especially useful for qualitative representation of signalling and regulatory networks where activation and inhibition are the essential processes (50). In a Boolean representation, the biological active state of a species can be translated into the “on” state whereas the inactive state is represented by the “off” state. Enzymes play the role of switching other enzymes and genes “on” and “off”. Applying Boolean algebra to a signalling network results in an interaction network, analogous to electrical circuits, which can be conveniently represented by logical interaction graphs.
Assignment rules contain the basic Boolean operators AND (conjuction), OR (disjunction) and NOT (complement). This will be explained for the example of two variables A and B. A numerical multiplication is analogous to a logical conjunction expressed by (A Λ B) or (A AND B). A conjunction of two statements is true when both statements are true. A numerical addition of A and B is expressed in Boolean algebra as a disjunction (A V B) or (A OR B). A disjunction of two statements is true when one of the statements is true (inclusive disjunction). In the presented logical platelet model disjunctions are not notated explicitly but are represented by several interactions which can lead to the same result. A numerical negation (–A) is expressed by (NOT A) or (!A) in Boolean algebra. The complement of a statement is true when the statement is false.

SQUAD parameters

The parameters incorporated in the ODE for a given node represent the strength of its respective activators and inhibitors, and the value of its gain. The sigmoid shape of the mathematical equations establishes a monotonic and bounded behaviour within the closed interval [0,1].

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Part B: Validation by experimental data

In the paper, in particular Figure 4 (experimental data according to platelet web including validation of different activation phases by phosphorylation data, kinase and substrate information) as well as Figure 5 (direct experiments for validation Boolean processing steps regarding output parameters such as calcium flux) show that there is a lot of supporting experimental evidence for the different activation steps and protein interactions discussed in our model. We give here furthermore in Table 3S detailed information with individual literature references for all nodes and interactions modelled in Figure 4 including modulating influence by drugs. This includes also information on additional nodes left out in the Boolean model (Fig. 2 in the manuscript).

Table 3S. Interactions (including drug modulation) and protein nodes involved in our Boolean model and as shown in Figure 4 of the paper.

Gene id	*Gene symbol*	*Interactant id*	*Interactant gene symbol*	*Publication*
5592	PRKG1	5592	PRKG1	1
5592	PRKG1	6915	TBXA2R	2
5578	PRKCA	207	AKT1	3
5579	PRKCB	207	AKT1	3
5578	PRKCA	6915	TBXA2R	4
5566	PRKACA	6915	TBXA2R	2, 5
5566	PRKACA	6011	GRK1	6
5588	PRKCQ	10125	RASGRP1	7
5578	PRKCA	5581	PRKCE	8-10
5578	PRKCA	9368	SLC9A3R1	11-13
5581	PRKCE	2771	GNAI2	14
6714	SRC	5580	PRKCD	15
207	AKT1	6788	STK3	16, 17
6714	SRC	2983	GUCY1B3	18
6714	SRC	7048	TGFBR2	19
5578	PRKCA	7408	VASP	20
5566	PRKACA	5566	PRKACA	21
5594	MAPK1	5321	PLA2G4A	22
5578	PRKCA	5139	PDE3A	23, 24
5566	PRKACA	5139	PDE3A	24
5566	PRKACA	8654	PDE5A	25-27
5578	PRKCA	5770	PTPN1	28
207	AKT1	5590	PRKCZ	29-31
2534	FYN	5588	PRKCQ	32
2776	GNAQ	5739	PTGIR	33, 34
5590	PRKCZ	6714	SRC	35

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Gene id	*Gene symbol*	*Interactant id*	*Interactant gene symbol*	*Publication*
207	AKT1	3690	ITGB3	36, 37
4067	LYN	5580	PRKCD	38, 39
2771	GNAI2	3480	IGF1R	40
2770	GNAI1	3480	IGF1R	41
23136	EPB41L3	5320	PLA2G2A	42
2770	GNAI1	5147	PDE6D	43
113	ADCY7	5580	PRKCD	44
5592	PRKG1	5908	RAP1B	45
5330	PLCB2	7222	TRPC3	46
9368	SLC9A3R1	5330	PLCB2	47
5578	PRKCA	5578	PRKCA	48
7048	TGFBR2	7048	TGFBR2	49-53
5581	PRKCE	5594	MAPK1	54
5580	PRKCD	5580	PRKCD	8, 9, 55-59
4067	LYN	5588	PRKCQ	60
5580	PRKCD	5590	PRKCZ	61, 62
207	AKT1	5588	PRKCQ	63
207	AKT1	6714	SRC	64
6714	SRC	207	AKT1	64
1195	CLK1	5770	PTPN1	8, 65, 66
207	AKT1	5770	PTPN1	8, 65
6714	SRC	5584	PRKCI	67
5584	PRKCI	6714	SRC	67
3690	ITGB3	6714	SRC	68
6714	SRC	3690	ITGB3	68, 69
2776	GNAQ	5330	PLCB2	70
5147	PDE6D	5906	RAP1A	71
5581	PRKCE	6714	SRC	72
3480	IGF1R	5580	PRKCD	73
3690	ITGB3	7094	TLN1	74-76
4067	LYN	51206	GP6	77, 78
2534	FYN	51206	GP6	77, 78
4067	LYN	4067	LYN	8, 69, 77, 79-82
5594	MAPK1	5770	PTPN1	83
5770	PTPN1	5594	MAPK1	83, 84
5566	PRKACA	5908	RAP1B	85
3480	IGF1R	3480	IGF1R	86, 87
5578	PRKCA	5590	PRKCZ	62, 88, 89
5590	PRKCZ	5578	PRKCA	8, 62, 82, 88, 89

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Gene id	*Gene symbol*	*Interactant id*	*Interactant gene symbol*	*Publication*
2776	GNAQ	9368	SLC9A3R1	90
5583	PRKCH	5583	PRKCH	91
5770	PTPN1	6714	SRC	92-95
2778	GNAS	5739	PTGIR	96
6788	STK3	6788	STK3	97
5578	PRKCA	5592	PRKG1	98
5581	PRKCE	5581	PRKCE	8, 99-102
2778	GNAS	5729	PTGDR	103
5580	PRKCD	5594	MAPK1	104
5566	PRKACA	9351	SLC9A3R2	105
5592	PRKG1	7222	TRPC3	106
6011	GRK1	6011	GRK1	107
5590	PRKCZ	5580	PRKCD	8, 9, 61, 82, 108-110
5580	PRKCD	6714	SRC	111
2982	GUCY1A3	116987	AGAP1	112
2983	GUCY1B3	116987	AGAP1	112
5566	PRKACA	6714	SRC	58, 59, 69, 113, 114
3710	ITPR3	7222	TRPC3	46, 115
5590	PRKCZ	5594	MAPK1	116
5588	PRKCQ	5588	PRKCQ	117
5147	PDE6D	6011	GRK1	118
5147	PDE6D	5739	PTGIR	119
5592	PRKG1	8654	PDE5A	120
5578	PRKCA	6714	SRC	121
2534	FYN	2534	FYN	82, 108, 122-125
207	AKT1	207	AKT1	126, 127
5592	PRKG1	7408	VASP	59, 108, 128-132
5566	PRKACA	7408	VASP	59, 108, 128-132
5579	PRKCB	5579	PRKCB	133
818	CAMK2G	818	CAMK2G	134
2771	GNAI2	64805	P2RY12	135
2534	FYN	5580	PRKCD	136
2534	FYN	5590	PRKCZ	136
5583	PRKCH	6714	SRC	136
2534	FYN	5583	PRKCH	136
2534	FYN	5581	PRKCE	136
2212	FCGR2A	2534	FYN	137
2212	FCGR2A	4067	LYN	137
4067	LYN	2212	FCGR2A	137

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Gene id	*Gene symbol*	*Interactant id*	*Interactant gene symbol*	*Publication*
2534	FYN	2212	FCGR2A	137
818	CAMK2G	109	ADCY3	138, 139
3480	IGF1R	6714	SRC	140
6714	SRC	3480	IGF1R	8, 82, 140-142
3480	IGF1R	5770	PTPN1	143
2776	GNAQ	6915	TBXA2R	90, 144
4067	LYN	6714	SRC	145
2534	FYN	6714	SRC	145
6281	S100A10	8605	PLA2G4C	146
2212	FCGR2A	51206	GP6	147, 148
7846	TUBA1A	7941	PLA2G7	149
5028	P2RY1	9368	SLC9A3R1	150
5028	P2RY1	9351	SLC9A3R2	150
5578	PRKCA	5739	PTGIR	151
5590	PRKCZ	5590	PRKCZ	9, 152
5578	PRKCA	7222	TRPC3	153
5594	MAPK1	5594	MAPK1	8, 9, 37, 58, 81, 82, 109, 122, 141, 142, 154-161
5566	PRKACA	5906	RAP1A	162
6714	SRC	6714	SRC	113, 141, 142, 163-165
Drug	Abciximab	3690	ITGB3	166
Drug	Ticagrelor	64805	P2RY12	167

1. J. L. Busch, E. P. Bessay, S. H. Francis and J. D. Corbin, *The Journal of biological chemistry*, 2002, **277**, 34048-34054.
2. H. M. Reid and B. T. Kinsella, *The Journal of biological chemistry*, 2003, **278**, 51190-51202.
3. C. Kroner, K. Eybrechts and J. W. Akkerman, *The Journal of biological chemistry*, 2000, **275**, 27790-27798.
4. L. P. Kelley-Hickie and B. T. Kinsella, *British journal of pharmacology*, 2004, **142**, 203-221.
5. S. Yamamoto, F. Yan, H. Zhou and H. H. Tai, *Biochemical pharmacology*, 2002, **64**, 375-383.
6. T. J. Horner, S. Osawa, M. D. Schaller and E. R. Weiss, *The Journal of biological chemistry*, 2005, **280**, 28241-28250.
7. Y. Zheng, H. Liu, J. Coughlin, J. Zheng, L. Li and J. C. Stone, *Blood*, 2005, **105**, 3648-3654.
8. H. Daub, J. V. Olsen, M. Bairlein, F. Gnad, F. S. Oppermann, R. Korner, Z. Greff, G. Keri, O. Stemmann and M. Mann, *Molecular cell*, 2008, **31**, 438-448.
9. N. Dephoure, C. Zhou, J. Villen, S. A. Beausoleil, C. E. Bakalarski, S. J. Elledge and S. P. Gygi, *Proceedings of the National Academy of Sciences of the United States of America*, 2008, **105**, 10762-10767.
10. J. Durgan, A. J. Cameron, A. T. Saurin, S. Hanrahan, N. Totty, R. O. Messing and P. J. Parker, *The Biochemical journal*, 2008, **411**, 319-331.

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11. E. J. Weinman, D. Steplock, Y. Zhang, R. Biswas, R. J. Bloch and S. Shenolikar, *The Journal of biological chemistry*, 2010, **285**, 25134-25138.
12. J. Li, P. I. Poulikakos, Z. Dai, J. R. Testa, D. J. Callaway and Z. Bu, *The Journal of biological chemistry*, 2007, **282**, 27086-27099.
13. V. Raghuram, H. Hormuth and J. K. Foskett, *Proceedings of the National Academy of Sciences of the United States of America*, 2003, **100**, 9620-9625.
14. J. Chu, H. Zheng, Y. Zhang, H. H. Loh and P. Y. Law, *Cellular signalling*, 2010, **22**, 684-696.
15. V. O. Rybin, J. Guo, E. Harleton, S. J. Feinmark and S. F. Steinberg, *Biochemistry*, 2009, **48**, 4642-4651.
16. D. Kim, S. Shu, M. D. Coppola, S. Kaneko, Z. Q. Yuan and J. Q. Cheng, *PloS one*, 2010, **5**, e9616.
17. D. Romano, D. Matallanas, G. Weitsman, C. Preisinger, T. Ng and W. Kolch, *Cancer research*, 2010, **70**, 1195-1203.
18. S. Meurer, S. Pioch, S. Gross and W. Muller-Esterl, *The Journal of biological chemistry*, 2005, **280**, 33149-33156.
19. A. J. Galliher and W. P. Schiemann, *Cancer research*, 2007, **67**, 3752-3758.
20. O. Knauer, N. A. Binai, G. Carra, T. Beckhaus, K. M. Hanschmann, T. Renne, S. Backert, M. Karas and S. Wessler, *Cellular microbiology*, 2008, **10**, 2285-2296.
21. A. Girod, V. Kinzel and D. Bossemeyer, *FEBS letters*, 1996, **391**, 121-125.
22. A. G. Borsch-Haubold, F. Bartoli, J. Asselin, T. Dudler, R. M. Kramer, R. Apitz-Castro, S. P. Watson and M. H. Gelb, *The Journal of biological chemistry*, 1998, **273**, 4449-4458.
23. R. W. Hunter, C. Mackintosh and I. Hers, *The Journal of biological chemistry*, 2009, **284**, 12339-12348.
24. M. Pozuelo Rubio, D. G. Campbell, N. A. Morrice and C. Mackintosh, *The Biochemical journal*, 2005, **392**, 163-172.
25. S. Bruder, A. Schultz and J. E. Schultz, *The Journal of biological chemistry*, 2006, **281**, 19969-19976.
26. S. H. Francis, E. P. Bessay, J. Kotera, K. A. Grimes, L. Liu, W. J. Thompson and J. D. Corbin, *The Journal of biological chemistry*, 2002, **277**, 47581-47587.
27. S. D. Rybalkin, I. G. Rybalkina, R. Feil, F. Hofmann and J. A. Beavo, *The Journal of biological chemistry*, 2002, **277**, 3310-3317.
28. A. J. Flint, M. F. Gebbink, B. R. Franza, Jr., D. E. Hill and N. K. Tonks, *The EMBO journal*, 1993, **12**, 1937-1946.
29. R. P. Doornbos, M. Theelen, P. C. van der Hoeven, W. J. van Blitterswijk, A. J. Verkleij and P. M. van Bergen en Henegouwen, *The Journal of biological chemistry*, 1999, **274**, 8589-8596.
30. N. A. Bourbon, L. Sandirasegarane and M. Kester, *The Journal of biological chemistry*, 2002, **277**, 3286-3292.
31. D. J. Powell, E. Hajduch, G. Kular and H. S. Hundal, *Molecular and cellular biology*, 2003, **23**, 7794-7808.
32. D. Ron, E. W. Napolitano, A. Voronova, N. J. Vasquez, D. N. Roberts, B. L. Calio, R. H. Caothien, S. M. Pettiford, S. Wellik, J. B. Mandac and L. M. Kauvar, *The Journal of biological chemistry*, 1999, **274**, 19003-19010.
33. J. S. Hayes, O. A. Lawler, M. T. Walsh and B. T. Kinsella, *The Journal of biological chemistry*, 1999, **274**, 23707-23718.
34. O. A. Lawler, S. M. Miggin and B. T. Kinsella, *The Journal of biological chemistry*, 2001, **276**, 33596-33607.
35. M. L. Seibenhener, J. Roehm, W. O. White, K. B. Neidigh, M. L. Vandenplas and M. W. Wooten, *Molecular cell biology research communications : MCBRC*, 1999, **2**, 28-31.
36. R. I. Kirk, M. R. Sanderson and K. M. Lerea, *The Journal of biological chemistry*, 2000, **275**, 30901-30906.
37. T. E. Thingholm, M. R. Larsen, C. R. Ingrell, M. Kassem and O. N. Jensen, *Journal of proteome research*, 2008, **7**, 3304-3313.
38. I. Kronfeld, G. Kazimirsky, P. S. Lorenzo, S. H. Garfield, P. M. Blumberg and C. Brodie, *The Journal of biological chemistry*, 2000, **275**, 35491-35498.

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39. Z. Szallasi, M. F. Denning, E. Y. Chang, J. Rivera, S. H. Yuspa, C. Lehel, Z. Olah, W. B. Anderson and P. M. Blumberg, *Biochemical and biophysical research communications*, 1995, **214**, 888-894.
40. J. F. Kuemmerle and K. S. Murthy, *The Journal of biological chemistry*, 2001, **276**, 7187-7194.
41. H. Hallak, A. E. Seiler, J. S. Green, B. N. Ross and R. Rubin, *The Journal of biological chemistry*, 2000, **275**, 2255-2258.
42. V. A. Robb, M. A. Gerber, E. K. Hart-Mahon and D. H. Gutmann, *Oncogene*, 2005, **24**, 1946-1957.
43. M. Hanzal-Bayer, L. Renault, P. Roversi, A. Wittinghofer and R. C. Hillig, *The EMBO journal*, 2002, **21**, 2095-2106.
44. E. J. Nelson, K. Hellevuo, M. Yoshimura and B. Tabakoff, *The Journal of biological chemistry*, 2003, **278**, 4552-4560.
45. Y. Miura, K. Kaibuchi, T. Itoh, J. D. Corbin, S. H. Francis and Y. Takai, *FEBS letters*, 1992, **297**, 171-174.
46. B. C. Bandyopadhyay, W. D. Swaim, X. Liu, R. S. Redman, R. L. Patterson and I. S. Ambudkar, *The Journal of biological chemistry*, 2005, **280**, 12908-12916.
47. Y. Tang, J. Tang, Z. Chen, C. Trost, V. Flockerzi, M. Li, V. Ramesh and M. X. Zhu, *The Journal of biological chemistry*, 2000, **275**, 37559-37564.
48. W. Bin, M. O. Aksoy, Y. Yang and S. G. Kelsen, *American journal of physiology. Lung cellular and molecular physiology*, 2001, **280**, L675-679.
49. W. T. Parks, D. B. Frank, C. Huff, C. Renfrew Haft, J. Martin, X. Meng, M. P. de Caestecker, J. G. McNally, A. Reddi, S. I. Taylor, A. B. Roberts, T. Wang and R. J. Lechleider, *The Journal of biological chemistry*, 2001, **276**, 19332-19339.
50. P. Kavsak, R. K. Rasmussen, C. G. Causing, S. Bonni, H. Zhu, G. H. Thomsen and J. L. Wrana, *Molecular cell*, 2000, **6**, 1365-1375.
51. M. Kawabata, A. Chytil and H. L. Moses, *The Journal of biological chemistry*, 1995, **270**, 5625-5630.
52. S. Lawler, X. H. Feng, R. H. Chen, E. M. Maruoka, C. W. Turck, I. Griswold-Prenner and R. Derynck, *The Journal of biological chemistry*, 1997, **272**, 14850-14859.
53. K. Luo and H. F. Lodish, *The EMBO journal*, 1997, **16**, 1970-1981.
54. N. A. Bourbon, J. Yun, D. Berkey, Y. Wang and M. Kester, *American journal of physiology. Cell physiology*, 2001, **280**, C1403-1411.
55. R. W. Wrenn, *Biochemical and biophysical research communications*, 2001, **282**, 882-886.
56. W. Li, J. Zhang, D. P. Bottaro and J. H. Pierce, *The Journal of biological chemistry*, 1997, **272**, 24550-24555.
57. N. Sugiyama, T. Masuda, K. Shinoda, A. Nakamura, M. Tomita and Y. Ishihama, *Molecular & cellular proteomics : MCP*, 2007, **6**, 1103-1109.
58. C. Pan, J. V. Olsen, H. Daub and M. Mann, *Molecular & cellular proteomics : MCP*, 2009, **8**, 2796-2808.
59. G. Han, M. Ye, H. Liu, C. Song, D. Sun, Y. Wu, X. Jiang, R. Chen, C. Wang, L. Wang and H. Zou, *Electrophoresis*, 2010, **31**, 1080-1089.
60. Y. Liu, C. Graham, V. Parravicini, M. J. Brown, J. Rivera and S. Shaw, *Journal of leukocyte biology*, 2001, **69**, 831-840.
61. H. Konishi, E. Yamauchi, H. Taniguchi, T. Yamamoto, H. Matsuzaki, Y. Takemura, K. Ohmae, U. Kikkawa and Y. Nishizuka, *Proceedings of the National Academy of Sciences of the United States of America*, 2001, **98**, 6587-6592.
62. C. P. Hodgkinson, E. M. Sale and G. J. Sale, *Biochemistry*, 2002, **41**, 10351-10359.
63. B. Bauer, N. Krumbock, F. Fresser, F. Hochholdinger, M. Spitaler, A. Simm, F. Uberall, B. Schraven and G. Baier, *The Journal of biological chemistry*, 2001, **276**, 31627-31634.
64. R. Chen, O. Kim, J. Yang, K. Sato, K. M. Eisenmann, J. McCarthy, H. Chen and Y. Qiu, *The Journal of biological chemistry*, 2001, **276**, 31858-31862.
65. L. V. Ravichandran, H. Chen, Y. Li and M. J. Quon, *Mol Endocrinol*, 2001, **15**, 1768-1780.

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66. F. M. Moeslein, M. P. Myers and G. E. Landreth, *The Journal of biological chemistry*, 1999, **274**, 26697-26704.
67. M. W. Wooten, M. L. Vandenplas, M. L. Seibenhener, T. Geetha and M. T. Diaz-Meco, *Molecular and cellular biology*, 2001, **21**, 8414-8427.
68. A. Datta, F. Huber and D. Boettiger, *The Journal of biological chemistry*, 2002, **277**, 3943-3949.
69. R. P. Zahedi, U. Lewandrowski, J. Wiesner, S. Wortelkamp, J. Moebius, C. Schutz, U. Walter, S. Gambaryan and A. Sickmann, *Journal of proteome research*, 2008, **7**, 526-534.
70. A. U. Singer, G. L. Waldo, T. K. Harden and J. Sondek, *Nature structural biology*, 2002, **9**, 32-36.
71. V. Nancy, I. Callebaut, A. El Marjou and J. de Gunzburg, *The Journal of biological chemistry*, 2002, **277**, 15076-15084.
72. C. Song, T. M. Vondriska, G. W. Wang, J. B. Klein, X. Cao, J. Zhang, Y. J. Kang, S. D'Souza and P. Ping, *American journal of physiology. Heart and circulatory physiology*, 2002, **282**, H1166-1171.
73. U. Hermanto, C. S. Zong, W. Li and L. H. Wang, *Molecular and cellular biology*, 2002, **22**, 2345-2365.
74. D. A. Calderwood, B. Yan, J. M. de Pereda, B. G. Alvarez, Y. Fujioka, R. C. Liddington and M. H. Ginsberg, *The Journal of biological chemistry*, 2002, **277**, 21749-21758.
75. S. Patil, A. Jedsadayanmata, J. D. Wencel-Drake, W. Wang, I. Knezevic and S. C. Lam, *The Journal of biological chemistry*, 1999, **274**, 28575-28583.
76. D. A. Calderwood, Y. Fujioka, J. M. de Pereda, B. Garcia-Alvarez, T. Nakamoto, B. Margolis, C. J. McGlade, R. C. Liddington and M. H. Ginsberg, *Proceedings of the National Academy of Sciences of the United States of America*, 2003, **100**, 2272-2277.
77. K. Suzuki-Inoue, D. Tulasne, Y. Shen, T. Bori-Sanz, O. Inoue, S. M. Jung, M. Moroi, R. K. Andrews, M. C. Berndt and S. P. Watson, *The Journal of biological chemistry*, 2002, **277**, 21561-21566.
78. M. M. Huang, J. B. Bolen, J. W. Barnwell, S. J. Shattil and J. S. Brugge, *Proceedings of the National Academy of Sciences of the United States of America*, 1991, **88**, 7844-7848.
79. A. Negro, A. M. Brunati, A. Donella-Deana, M. L. Massimino and L. A. Pinna, *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, 2002, **16**, 210-212.
80. A. Hirao, I. Hamaguchi, T. Suda and N. Yamaguchi, *The EMBO journal*, 1997, **16**, 2342-2351.
81. J. R. St-Germain, P. Taylor, J. Tong, L. L. Jin, A. Nikolic, Stewart, II, R. M. Ewing, M. Dharsee, Z. Li, S. Trudel and M. F. Moran, *Proceedings of the National Academy of Sciences of the United States of America*, 2009, **106**, 20127-20132.
82. J. V. Olsen, M. Vermeulen, A. Santamaria, C. Kumar, M. L. Miller, L. J. Jensen, F. Gnad, J. Cox, T. S. Jensen, E. A. Nigg, S. Brunak and M. Mann, *Science signaling*, 2010, **3**, ra3.
83. B. Zhou, Z. X. Wang, Y. Zhao, D. L. Brautigan and Z. Y. Zhang, *The Journal of biological chemistry*, 2002, **277**, 31818-31825.
84. C. H. Charles, H. Sun, L. F. Lau and N. K. Tonks, *Proceedings of the National Academy of Sciences of the United States of America*, 1993, **90**, 5292-5296.
85. L. Lou, J. Urbani, F. Ribeiro-Neto and D. L. Altschuler, *The Journal of biological chemistry*, 2002, **277**, 32799-32806.
86. S. Munshi, M. Kornienko, D. L. Hall, J. C. Reid, L. Waxman, S. M. Stirdivant, P. L. Darke and L. C. Kuo, *The Journal of biological chemistry*, 2002, **277**, 38797-38802.
87. A. Pautsch, A. Zoephel, H. Ahorn, W. Spevak, R. Hauptmann and H. Nar, *Structure*, 2001, **9**, 955-965.
88. W. H. Ziegler, D. B. Parekh, J. A. Le Good, R. D. Whelan, J. J. Kelly, M. Frech, B. A. Hemmings and P. J. Parker, *Current biology : CB*, 1999, **9**, 522-529.
89. S. Gysin and R. Imber, *European journal of biochemistry / FEBS*, 1996, **240**, 747-750.
90. M. D. Rochdi, V. Watier, C. La Madeleine, H. Nakata, T. Kozasa and J. L. Parent, *The Journal of biological chemistry*, 2002, **277**, 40751-40759.

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91. I. Brandlin, T. Eiseler, R. Salowsky and F. J. Johannes, *The Journal of biological chemistry*, 2002, **277**, 45451-45457.
92. Y. Yamamoto, T. Maruyama, N. Sakai, R. Sakurai, A. Shimizu, T. Hamatani, H. Masuda, H. Uchida, H. Sabe and Y. Yoshimura, *Molecular human reproduction*, 2002, **8**, 1117-1124.
93. J. D. Bjorge, A. Pang and D. J. Fujita, *The Journal of biological chemistry*, 2000, **275**, 41439-41446.
94. A. K. Somani, J. S. Bignon, G. B. Mills, K. A. Siminovitch and D. R. Branch, *The Journal of biological chemistry*, 1997, **272**, 21113-21119.
95. D. R. Stover, P. Furet and N. B. Lydon, *The Journal of biological chemistry*, 1996, **271**, 12481-12487.
96. S. M. Miggin, O. A. Lawler and B. T. Kinsella, *The Journal of biological chemistry*, 2003, **278**, 6947-6958.
97. Y. Deng, A. Pang and J. H. Wang, *The Journal of biological chemistry*, 2003, **278**, 11760-11767.
98. Y. Hou, J. Lascola, N. O. Dulin, R. D. Ye and D. D. Browning, *The Journal of biological chemistry*, 2003, **278**, 16706-16712.
99. O. E. Pardo, C. Wellbrock, U. K. Khanzada, M. Aubert, I. Arozarena, S. Davidson, F. Bowen, P. J. Parker, V. V. Filonenko, I. T. Gout, N. Sebire, R. Marais, J. Downward and M. J. Seckl, *The EMBO journal*, 2006, **25**, 3078-3088.
100. J. Ivaska, L. Bosca and P. J. Parker, *Nature cell biology*, 2003, **5**, 363-369.
101. K. England and M. G. Rumsby, *The Biochemical journal*, 2000, **352 Pt 1**, 19-26.
102. M. Takahashi, H. Mukai, K. Oishi, T. Isagawa and Y. Ono, *The Journal of biological chemistry*, 2000, **275**, 34592-34596.
103. C. Faveeuw, P. Gosset, F. Bureau, V. Angeli, H. Hirai, T. Maruyama, S. Narumiya, M. Capron and F. Trottein, *European journal of immunology*, 2003, **33**, 889-898.
104. I. S. Kim, Y. S. Ryang, Y. S. Kim, S. W. Jang, H. J. Sung, Y. H. Lee, J. Kim, D. S. Na and J. Ko, *Life sciences*, 2003, **73**, 447-459.
105. W. Lee-Kwon, J. H. Kim, J. W. Choi, K. Kawano, B. Cha, D. A. Dartt, D. Zoukhri and M. Donowitz, *American journal of physiology. Cell physiology*, 2003, **285**, C1527-1536.
106. H. Y. Kwan, Y. Huang and X. Yao, *Proceedings of the National Academy of Sciences of the United States of America*, 2004, **101**, 2625-2630.
107. K. Palczewski, J. Buczylko, P. Van Hooser, S. A. Carr, M. J. Huddleston and J. W. Crabb, *The Journal of biological chemistry*, 1992, **267**, 18991-18998.
108. R. Raijmakers, K. Kraiczek, A. P. de Jong, S. Mohammed and A. J. Heck, *Analytical chemistry*, 2010, **82**, 824-832.
109. C. I. Ruse, D. B. McClatchy, B. Lu, D. Cociorva, A. Motoyama, S. K. Park and J. R. Yates, 3rd, *Journal of proteome research*, 2008, **7**, 2140-2150.
110. S. A. Beausoleil, M. Jedrychowski, D. Schwartz, J. E. Elias, J. Villen, J. Li, M. A. Cohn, L. C. Cantley and S. P. Gygi, *Proceedings of the National Academy of Sciences of the United States of America*, 2004, **101**, 12130-12135.
111. T. Rosenzweig, S. Aga-Mizrachi, A. Bak and S. R. Sampson, *Cellular signalling*, 2004, **16**, 1299-1308.
112. S. Meurer, S. Pioch, K. Wagner, W. Muller-Esterl and S. Gross, *The Journal of biological chemistry*, 2004, **279**, 49346-49354.
113. L. M. Brill, W. Xiong, K. B. Lee, S. B. Ficarro, A. Crain, Y. Xu, A. Terskikh, E. Y. Snyder and S. Ding, *Cell stem cell*, 2009, **5**, 204-213.
114. Y. Obara, K. Labudda, T. J. Dillon and P. J. Stork, *Journal of cell science*, 2004, **117**, 6085-6094.
115. T. Lockwich, B. B. Singh, X. Liu and I. S. Ambudkar, *The Journal of biological chemistry*, 2001, **276**, 42401-42408.
116. Y. Zhao, J. Liu, L. Li, L. Liu and L. Wu, *Regulatory peptides*, 2005, **128**, 43-50.
117. N. Thuille, I. Heit, F. Fresser, N. Krumbock, B. Bauer, S. Leuthaeusser, S. Dammeier, C. Graham, T. D. Copeland, S. Shaw and G. Baier, *The EMBO journal*, 2005, **24**, 3869-3880.
118. H. Zhang, S. Hosier, J. M. Terew, K. Zhang, R. H. Cote and W. Baehr, *Methods in enzymology*, 2005, **403**, 42-56.

This journal is © The Royal Society of Chemistry 2013

119. S. J. Wilson and E. M. Smyth, *The Journal of biological chemistry*, 2006, **281**, 11780-11786.
120. M. K. Thomas, S. H. Francis and J. D. Corbin, *The Journal of biological chemistry*, 1990, **265**, 14971-14978.
121. K. L. Gould, J. R. Woodgett, J. A. Cooper, J. E. Buss, D. Shalloway and T. Hunter, *Cell*, 1985, **42**, 849-857.
122. V. L. Goss, K. A. Lee, A. Moritz, J. Nardone, E. J. Spek, J. MacNeill, J. Rush, M. J. Comb and R. D. Polakiewicz, *Blood*, 2006, **107**, 4888-4897.
123. K. Hansen, G. Alonso, S. A. Courtneidge, L. Ronnstrand and C. H. Heldin, *Biochemical and biophysical research communications*, 1997, **241**, 355-362.
124. M. E. Noble, A. Musacchio, M. Saraste, S. A. Courtneidge and R. K. Wierenga, *The EMBO journal*, 1993, **12**, 2617-2624.
125. S. H. Cheng, P. C. Espino, J. Marshall, R. Harvey, J. Merrill and A. E. Smith, *Journal of virology*, 1991, **65**, 170-179.
126. M. Andjelkovic, D. R. Alessi, R. Meier, A. Fernandez, N. J. Lamb, M. Frech, P. Cron, P. Cohen, J. M. Lucocq and B. A. Hemmings, *The Journal of biological chemistry*, 1997, **272**, 31515-31524.
127. K. Datta, T. F. Franke, T. O. Chan, A. Makris, S. I. Yang, D. R. Kaplan, D. K. Morrison, E. A. Golemis and P. N. Tsichlis, *Molecular and cellular biology*, 1995, **15**, 2304-2310.
128. H. Molina, D. M. Horn, N. Tang, S. Mathivanan and A. Pandey, *Proceedings of the National Academy of Sciences of the United States of America*, 2007, **104**, 2199-2204.
129. Z. Li, J. Ajdic, M. Eigenthaler and X. Du, *Blood*, 2003, **101**, 4423-4429.
130. M. Burkhardt, M. Glazova, S. Gambaryan, T. Vollkommer, E. Butt, B. Bader, K. Heermeier, T. M. Lincoln, U. Walter and A. Palmetshofer, *The Journal of biological chemistry*, 2000, **275**, 33536-33541.
131. A. Smolenski, W. Poller, U. Walter and S. M. Lohmann, *The Journal of biological chemistry*, 2000, **275**, 25723-25732.
132. E. Butt, K. Abel, M. Krieger, D. Palm, V. Hoppe, J. Hoppe and U. Walter, *The Journal of biological chemistry*, 1994, **269**, 14509-14517.
133. J. Zhang, L. Wang, J. Petrin, W. R. Bishop and R. W. Bond, *Proceedings of the National Academy of Sciences of the United States of America*, 1993, **90**, 6130-6134.
134. P. Nghiem, S. M. Saati, C. L. Martens, P. Gardner and H. Schulman, *The Journal of biological chemistry*, 1993, **268**, 5471-5479.
135. P. Ohlmann, K. L. Laugwitz, B. Nurnberg, K. Spicher, G. Schultz, J. P. Cazenave and C. Gachet, *The Biochemical journal*, 1995, **312 (Pt 3)**, 775-779.
136. M. F. Denning, A. A. Dlugosz, D. W. Threadgill, T. Magnuson and S. H. Yuspa, *The Journal of biological chemistry*, 1996, **271**, 5325-5331.
137. N. Bewarder, V. Weinrich, P. Budde, D. Hartmann, H. Flaswinkel, M. Reth and J. Frey, *Molecular and cellular biology*, 1996, **16**, 4735-4743.
138. J. Wei, A. Z. Zhao, G. C. Chan, L. P. Baker, S. Impey, J. A. Beavo and D. R. Storm, *Neuron*, 1998, **21**, 495-504.
139. J. Wei, G. Wayman and D. R. Storm, *The Journal of biological chemistry*, 1996, **271**, 24231-24235.
140. J. E. Peterson, G. Kulik, T. Jelinek, C. W. Reuter, J. A. Shannon and M. J. Weber, *The Journal of biological chemistry*, 1996, **271**, 31562-31571.
141. A. Wolf-Yadlin, S. Hautaniemi, D. A. Lauffenburger and F. M. White, *Proceedings of the National Academy of Sciences of the United States of America*, 2007, **104**, 5860-5865.
142. A. Wolf-Yadlin, N. Kumar, Y. Zhang, S. Hautaniemi, M. Zaman, H. D. Kim, V. Grantcharova, D. A. Lauffenburger and F. M. White, *Molecular systems biology*, 2006, **2**, 54.
143. D. Bandyopadhyay, A. Kusari, K. A. Kenner, F. Liu, J. Chernoff, T. A. Gustafson and J. Kusari, *The Journal of biological chemistry*, 1997, **272**, 1639-1645.
144. B. T. Kinsella, D. J. O'Mahony and G. A. Fitzgerald, *The Journal of pharmacology and experimental therapeutics*, 1997, **281**, 957-964.
145. G. Pirozzi, S. J. McConnell, A. J. Uveges, J. M. Carter, A. B. Sparks, B. K. Kay and D. M. Fowlkes, *The Journal of biological chemistry*, 1997, **272**, 14611-14616.

This journal is © The Royal Society of Chemistry 2013

146. T. Wu, C. W. Angus, X. L. Yao, C. Logun and J. H. Shelhamer, *The Journal of biological chemistry*, 1997, **272**, 17145-17153.
147. M. Tsuji, Y. Ezumi, M. Arai and H. Takayama, *The Journal of biological chemistry*, 1997, **272**, 23528-23531.
148. J. M. Gibbins, M. Okuma, R. Farndale, M. Barnes and S. P. Watson, *FEBS letters*, 1997, **413**, 255-259.
149. T. Sapir, M. Elbaum and O. Reiner, *The EMBO journal*, 1997, **16**, 6977-6984.
150. R. A. Hall, L. S. Ostedgaard, R. T. Premont, J. T. Blitzer, N. Rahman, M. J. Welsh and R. J. Lefkowitz, *Proceedings of the National Academy of Sciences of the United States of America*, 1998, **95**, 8496-8501.
151. E. M. Smyth, W. H. Li and G. A. FitzGerald, *The Journal of biological chemistry*, 1998, **273**, 23258-23266.
152. J. A. Le Good, W. H. Ziegler, D. B. Parekh, D. R. Alessi, P. Cohen and P. J. Parker, *Science*, 1998, **281**, 2042-2045.
153. K. Kiselyov, X. Xu, G. Mozhayeva, T. Kuo, I. Pessah, G. Mignery, X. Zhu, L. Birnbaumer and S. Muallem, *Nature*, 1998, **396**, 478-482.
154. K. Nagano, T. Shinkawa, H. Mutoh, O. Kondoh, S. Morimoto, N. Inomata, M. Ashihara, N. Ishii, Y. Aoki and M. Haramura, *Proteomics*, 2009, **9**, 2861-2874.
155. C. F. Tsai, Y. T. Wang, Y. R. Chen, C. Y. Lai, P. Y. Lin, K. T. Pan, J. Y. Chen, K. H. Khoo and Y. J. Chen, *Journal of proteome research*, 2008, **7**, 4058-4069.
156. G. R. Panta, L. Du, F. E. Nwariaku and L. T. Kim, *Surgery*, 2005, **138**, 269-274.
157. R. Pulido, A. Zuniga and A. Ullrich, *The EMBO journal*, 1998, **17**, 7337-7350.
158. A. V. Khokhlatchev, B. Canagarajah, J. Wilsbacher, M. Robinson, M. Atkinson, E. Goldsmith and M. H. Cobb, *Cell*, 1998, **93**, 605-615.
159. M. Muda, A. Theodosiou, C. Gillieron, A. Smith, C. Chabert, M. Camps, U. Boschert, N. Rodrigues, K. Davies, A. Ashworth and S. Arkinstall, *The Journal of biological chemistry*, 1998, **273**, 9323-9329.
160. A. J. Rossomando, J. Wu, H. Michel, J. Shabanowitz, D. F. Hunt, M. J. Weber and T. W. Sturgill, *Proceedings of the National Academy of Sciences of the United States of America*, 1992, **89**, 5779-5783.
161. R. Seger, N. G. Ahn, T. G. Boulton, G. D. Yancopoulos, N. Panayotatos, E. Radziejewska, L. Ericsson, R. L. Bratlien, M. H. Cobb and E. G. Krebs, *Proceedings of the National Academy of Sciences of the United States of America*, 1991, **88**, 6142-6146.
162. C. D. Hu, K. Kariya, T. Okada, X. Qi, C. Song and T. Kataoka, *The Journal of biological chemistry*, 1999, **274**, 48-51.
163. E. Unni, S. Sun, B. Nan, M. J. McPhaul, B. Cheskis, M. A. Mancini and M. Marcelli, *Cancer research*, 2004, **64**, 7156-7168.
164. M. Kim, T. Tezuka, K. Tanaka and T. Yamamoto, *Oncogene*, 2004, **23**, 1645-1655.
165. R. B. Irby, W. Mao, D. Coppola, J. Kang, J. M. Loubeau, W. Trudeau, R. Karl, D. J. Fujita, R. Jove and T. J. Yeatman, *Nature genetics*, 1999, **21**, 187-190.
166. G. Amoroso, A. J. van Boven, D. J. van Veldhuisen, R. A. Tio, C. P. Balje-Volkers, A. S. Petronio and W. van Oeveren, *Journal of cardiovascular pharmacology*, 2001, **38**, 633-641.
167. M. M. Marczewski, M. Postula and D. Kosior, *Vascular health and risk management*, 2010, **6**, 419-429.