Rate equations and parameters for the IRS-PKR signaling system

Signaling process	Reactions for the interactions	Rate equations	Kinetic parameters	Ref *esti-mated
Insulin-Receptor binding	$Insulin + Receptor \leftrightarrow IR$	$k_1[Insulin][Receptor] - k_{-1}[IR]$	$\mathbf{k_1} = 6 \times 10^7, \mathbf{k_{-1}} = 0.2$	[1]
	$Insulin + IR^P \leftrightarrow I2R^P$	$k_2[IR^P][Insulin] - k_{-2}[I2R^P]$	$\mathbf{k_2} = k_1, \mathbf{k_{-2}} = 100k_{-1}$	[1]
	$IR \leftrightarrow IR^P$	$k_3[IR] - k_{-3}[IR^P]$	$\mathbf{k_3} = 2500, \mathbf{k_{-3}} = k_{-1}$	[2]
	$IR^P \leftrightarrow EN\_IR^P$ $I2R^P \leftrightarrow EN\_I2R^P$	$k_4'[IR^P] - k_{-4}'[EN\_IR^P]$ $k_4'[I2R^P] - k_{-4}'[EN\_I2R^P]$	$\mathbf{k_4'} = 0.0021, \mathbf{k_{-4}'} = 0.00021$	[2]
	$Receptor \leftrightarrow EN\_Receptor$	$k_4[Receptor] - k_{-4}[EN\_Receptor]$	$\mathbf{k_4} = k_{-4}/9, \mathbf{k_{-4}} = 0.003$	[3]
	$\leftrightarrow EN\_Receptor$ (synthesis and degradation)	$k_5 - k_{-5}[EN\_Receptor]$	$\mathbf{k_{-5}} = 1.67 \times 10^{-13}, \mathbf{k_5} = 1.67 \times 10^{-13}$	[3]
	$EN\_IR^P \rightarrow EN\_Receptor$ $EN\_I2R^P \rightarrow EN\_Receptor$	$k_6[EN\_IR^P]$ $k_6[EN\_I2R^P]$	$\mathbf{k_6} = 0.46$	[2]
IRS tyrosine phosphoryla-tion	$IRS1 \leftrightarrow IRS1^{tyrP}$	$k_7[IRS1] - k_{-7}[IRS1^{tyrP}]$	$\mathbf{k_7} = \frac{4.16([IR^P] + [I2R^P])}{6.97 \times 10^{-13}}$ $\mathbf{k_{-7}} = 1.4[PTP] + [IRS1^{serP}] * 10^{13} * a_1$ $[PTP] = 1 - 0.25[AKT^P]\%$	[2]
IRS serine phosphoryla-tion (feedbacks: PKR, AKT)	$IRS1 \leftrightarrow IRS1^{serP}$	$k_7'[IRS1] - k_{-7}'[IRS1^{serP}]$	$\mathbf{k_7'} = 2([IR^P] + [I2R^P])$ $\times \left(1 + \frac{b_2[PKR^P]\%}{50 + [PKR^P]\%}\right)$ $\times \left(1 + \frac{b_1[AKT^P]\%}{50 + [AKT^P]\%}\right)$ $\mathbf{k_{-7}'} = 0.066 \times 6$	*[2,4]
PI3K activation	$IRS1^{tyrP} + PI3K \leftrightarrow PI3K\_IRS1^P$	$k_8[IRS1^{tyrP}][PI3K] - k_{-8}[PI3K\_IRS1^P]$	$\mathbf{k_8} = k_{-8} \times 0.07 \times 10^{13}, \mathbf{k_{-8}} = 10$	[2]
	$PI45P2 \leftrightarrow PI345P3$	$k_9[PI45P2] - k_{-9}[PI345P3]$	$\mathbf{k_9} = (k_{9a} - k_{9b})\left(\frac{[PI3K_{IRS1^P}]}{[PI3K_{total}]}\right) + k_{9b}$ $\mathbf{k_{-9}} = 30k_{9a}; k_{9a} = 1.39, k_{9b} = 0.09k_{9a}$	[2]
	$PI34P2 \leftrightarrow PI345P3$	$k_{10}[PI34P2] - k_{-10}[PI345P3]$	$\mathbf{k_{10}} = 1.1k_{-10}, \mathbf{k_{-10}} = 2.8$	[2]

AKT activation	$AKT \leftrightarrow AKT^P$	$k_{11}[AKT] - k_{-11}[AKT^P]$	$k_{11} = \frac{0.1k_{-11}([PI345P3]\% - 0.31)}{3.1 - 0.31}$ $k_{-11} = 3.0$	[2]
PKR activation	$PKR \leftrightarrow PKR^P$	$k_{12}[PKR] - k_{-12}[PKR^P]$	$k_{12} = 6.9 * 0.001$ $k_{-12} = 0.1 * k_{12} +$ $[AKT^P]\% \times (30k_{12} - 0.1k_{12})$	*[2]
ShGS complex formation	IR^P or $I2R^P + Shc \leftrightarrow IRSh$	$k_{13}([IR^P] + [I2R^P])[Shc] - k_{-13}[IRSh]$	$k_{13} = 0.1, k_{-13} = 1$	[5]
	$IRSh \leftrightarrow IRSh^P$	$k_{14}[IRSh] - k_{-14}[IRSh^P]$	$k_{14} = 20, k_{-14} = 5$	[5]
	$IRSh^P + GS \leftrightarrow IRShGS$	$k_{15}[IRSh^P][GS] - k_{-15}[IRShGS]$	$k_{15} = 60, k_{-15} = 546$	[6]
	$IRShGS \leftrightarrow ShGS + IR^P$	$k_{16}[IRShGS] - k_{-16}[ShGS][IR^P]$	$k_{16} = 2040, k_{-16} = 15700$	[6]
	$ShGS \leftrightarrow GS + Sh^P$	$k_{17}[ShGS] - k_{-17}[GS][Sh^P]$	$k_{17} = 40.8, k_{-17} = 0$	[6]
	$Sh^P \rightarrow Shc$	$V_{18}[Sh^P]/(K_{18} + [Sh^P])$	$V_{18} = 0.0154, K_{18} = 340$	[6,7]
Rac activation (via shGS or PI3K)	$RacGDP \rightarrow RacGTP[ShGS]$	$k_{e1}[ShGS][RasGDP]/(K_{e1} + [RasGDP])$	$k_{e1} = 0.222, K_{e1} = 0.181$	[6]
	$RacGDP \rightarrow RacGTP[PI3K]$	$k_{f1}[PI3K][RasGDP]/(K_{f1} + [RasGDP])$	$k_{f1} = 0.222, K_{f1} = 0.181$	*[6]
	$RacGTP \rightarrow RacGDP$	$V_{f2}[RasGTP]/(K_{f2} + [RasGTP])$	$V_{f2} = 0.289, K_{f2} = 0.0571$	*[6]
MEKK activation	$MEKK \rightarrow MEKK^P$	$k_{f3}[RacGTP][MEKK]/[K_{f3} + [MEKK]]$	$k_{f3} = 3.5, K_{f3} = 317$	* [6,8]
	$MEKK^P \rightarrow MEKK$	$k_{f4}[MEKK^P]/[K_{f4} + [MEKK^P]]$	$k_{f4} = 0.056, K_{f4} = 2200$	[8]
JNK activation crosstalk:	$JNK \rightarrow JNK^P$	$k_{f5}[RacGTP][MEKK]/[K_{f5} + [MEKK]]$	$k_{f5} = 9.5, K_{f5} = 14600$	* [6,8]
	$JNK^P \rightarrow JNK$	$k_{f6}[JNK^P]/[K_{f6} + [JNK^P]]$	$k_{f6} = 0.3, K_{f6} = 160$	* [6,8]

Blue: the parameter's value need to be fitted with experiment.

*The value of the rate constant of PKR activation and feedback to IRS is borrowed from PKC [2], and we use the equation form from [4] to model the combinatory effect of AKT and PKR. The equations and parameters for Rac are borrowed from Raf[6], which is a similar GTP-binding protein that can activate MEKK. MEKK activates both ERK and JNK, so the equations and parameters for JNK activation are borrowed from ERK[6]. The quantitative information of PKR-mediated activation of JNK and the effect of JNK feedback on IRS is currently unknown.

Component in the signaling process	Initial concentrations	ref
Insulin	Based on experimental treatment	
Receptor	9×10^{-13}M	[2]
EN_Receptor	10^{-13}M	[2]
IRS1	10^{-12}M	[2]
PI3K	10nM	[6]
PI45P2	99.4%	[2]
PI34P2	0.29%	[2]
PI345P3	0.31%	[2]
AKT	10nM	[6]
PKR	?	
Shc	1000nM	[6]
GS	10nM	[6]
RacGDP	120nM	*[6]
MEKK	120nM	[6]
JNK	1000nM	*[6]

* The initial concentration of Rac are borrowed from Raf[6], which is a similar GTP-binding protein that can activate MEKK. The initial concentration of JNK is considered similar to that of ERK [6].

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