Adenylyl cyclases (E.C. 4.6.1.1)

Overview: Adenylyl cyclase (ENSFM00250000000192) converts 5′-ATP to 3′,5′-adenosine monophosphate and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six transmembrane domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, Premont *et al*., 1996) and Gαs (the stimulatory G protein α subunit). Adenosine and its derivatives (e.g. 2′,5′-dideoxyadenosine), acting through the P-site, appears to be a physiological inhibitor of adenylyl cyclase activity (Tesmer *et al*., 2000). Four families of membrane-bound adenylyl cyclase are distinguishable: Ca^{2+}/CaM-stimulated (AC1, AC3 and AC8), Ca^{2+}-inhibitable (AC5 and AC6), Ca^{2+}-insensitive (AC2, AC4 and AC7) forms and the forskolin-insensitive AC9. The soluble adenylyl cyclase activity (Buck *et al*., 1999) is unaffected by either Gα or Gβγ subunits, but stimulated by calcium and bicarbonate ions and has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor (Chen *et al*., 2000).

Nomenclature	AC1	AC2	AC3	AC4	AC5
Other names	AC I	AC II, HBCA2	AC III, olfactory type	AC IV	AC V
Ensembl ID	ENSG00000164742	ENSG00000078295	ENSG00000138031	ENSG00000129467	ENSG00000173175
Endogenous activators	Ca^{2+}/CaM (Tang *et al*., 1991), PKC-evoked phosphorylation (Jacobowitz *et al*., 1993)	Gβγ (Taussig *et al*., 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig *et al*., 1993)	Ca^{2+}/CaM (Choi *et al*., 1992), PKC-evoked phosphorylation (Jacobowitz *et al*., 1993)	Gβγ (Gao and Gilman, 1991)	PKC-evoked phosphorylation (Kawabe *et al*., 1994)
Endogenous inhibitors	Gαi (Taussig *et al*., 1994), Gαo (Taussig *et al*., 1994), Gαz (Kozasa and Gilman, 1995), Gβγ (Taussig *et al*., 1993), CaM kinase IV-evoked phosphorylation (Wayman *et al*., 1996), PAM (Scholich *et al*., 2001)	–	Gαi (Taussig *et al*., 1994), Gβγ (Diel *et al*., 2006), RGS2 (Sinnarajah *et al*., 2001), CaM kinase II-evoked phosphorylation (Wayman *et al*., 1995)	PKC-evoked phosphorylation (Zimmermann and Taussig, 1996)	Gαi (Taussig *et al*., 1994), Gαz (Kozasa and Gilman, 1995), Ca^{2+} (Ishikawa *et al*., 1992), PKA-evoked phosphorylation (Iwami *et al*., 1995), RGS2 (Salim *et al*., 2003), PAM (Scholich *et al*., 2001), Ric8a (Wang *et al*., 2007)

Nomenclature	AC6	AC7	AC8	AC9	SAC
Other names	AC VI	AC VII	AC VIII	AC IX	AC10, soluble AC
Ensembl ID	ENSG00000174233	ENSG00000121281	ENSG00000155897	ENSG00000162104	ENSG00000143199
Endogenous activators	Gβγ (Gao *et al*., 2007), Raf1 (Ding *et al*., 2004)	PKC-evoked phosphorylation (Watson *et al*., 1994)	Ca^{2+}/CaM (Cali *et al*., 1994)	PKC-evoked phosphorylation (Cumbay and Watts, 2004)	$Ca^{2=}$ (Jaiswal and Conti, 2003), bicarbonate (Chen *et al*., 2000)
Endogenous inhibitors	Gαi (Taussig *et al*., 1994), Ca^{2+} (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen *et al*., 1997), PKC-evoked phosphorylation (Lai *et al*., 1999), RGS2 (Roy *et al*., 2003), PAM (Scholich *et al*., 2001)	PAM (Scholich *et al*., 2001)	Gβγ (Steiner *et al*., 2006)	Ca^{2+}/calcineurin (Paterson *et al*., 2000)	–

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively (Hill *et al*., 2000), although it is unclear whether this phenomenon is of physiological significance.

Abbreviations: CaM, calmodulin; **NKH477**, 6-(3-dimethylaminopropionyl) forskolin hydrochloride; **PAM**, protein associated with myc (MYCBP2, ENSG00000005810); **PKA**, protein kinase A or cyclic AMP-dependent protein kinase; **PKC**, protein kinase C; **RGS2**, Regulator of G-protein signalling 2 (ENSG00000116741); **Ric8a**, ENSG00000177963, also known as synembryn A

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