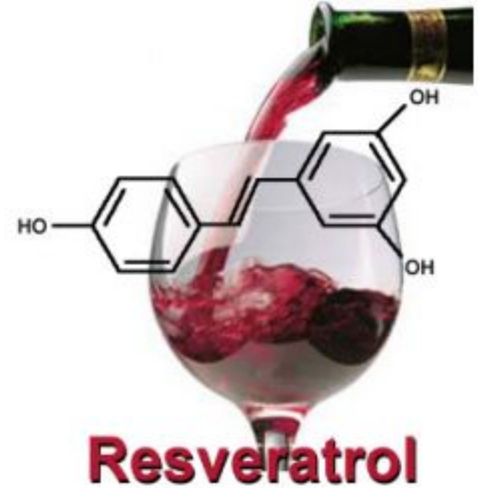


Resveratrol Ameliorates Aging-Related Metabolic Phenotypes by Inhibiting cAMP Phosphodiesterases.

Sung-Jun Park et al., Cell, 2012

Why did people start to have much interest in 'Resveratrol'?

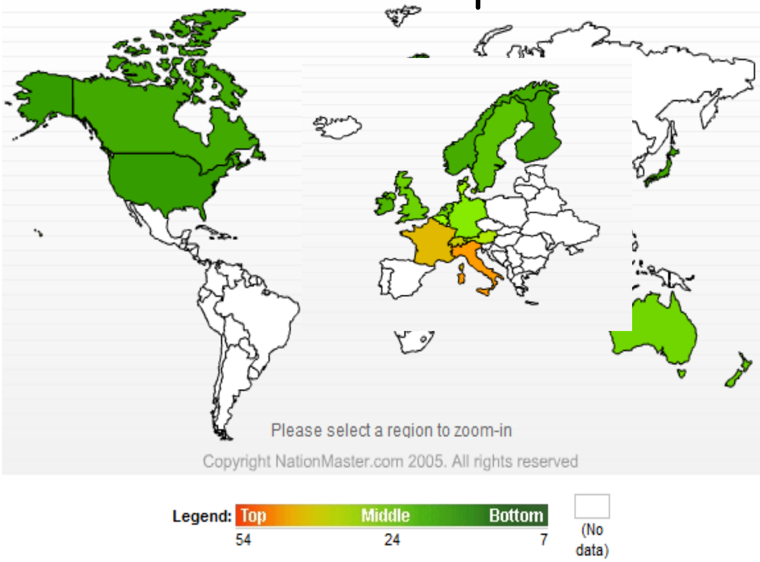
French Paradox

- the observation that French people show low coronary heart disease (CHD) death rates despite high intake of dietary cholesterol and saturated fat.

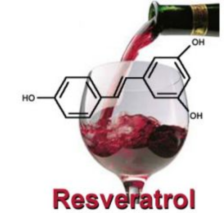
	French	US
Fat	171g/d	157g/d
Fat from animal	108g/d	72g/d
Incidence of Coronary heart disease	83/100,000	115/100,000

Reported by FAO(Food and Agriculture Organization of the United Nations) at 2002

Wine consumption



Global Market Information Database



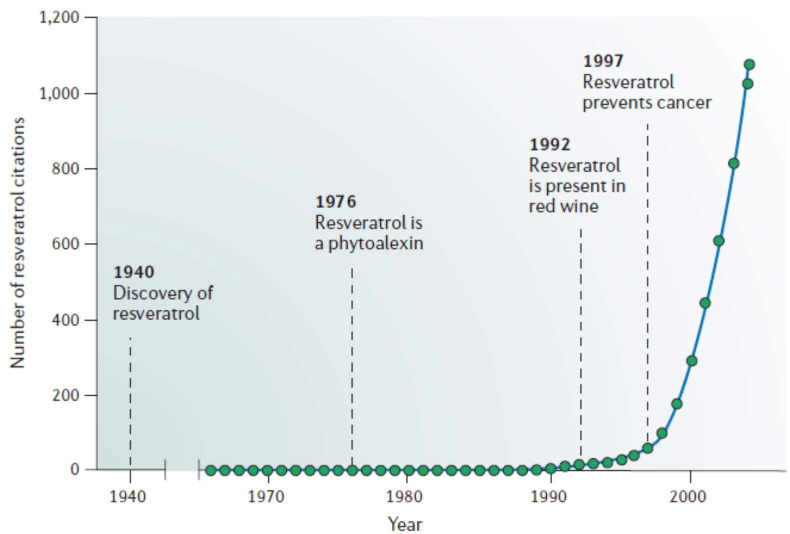
AMERICAN JOURNAL of ENOLOGY AND VITICULTURE

Article

Concentration of the Phytoalexin Resveratrol in Wine

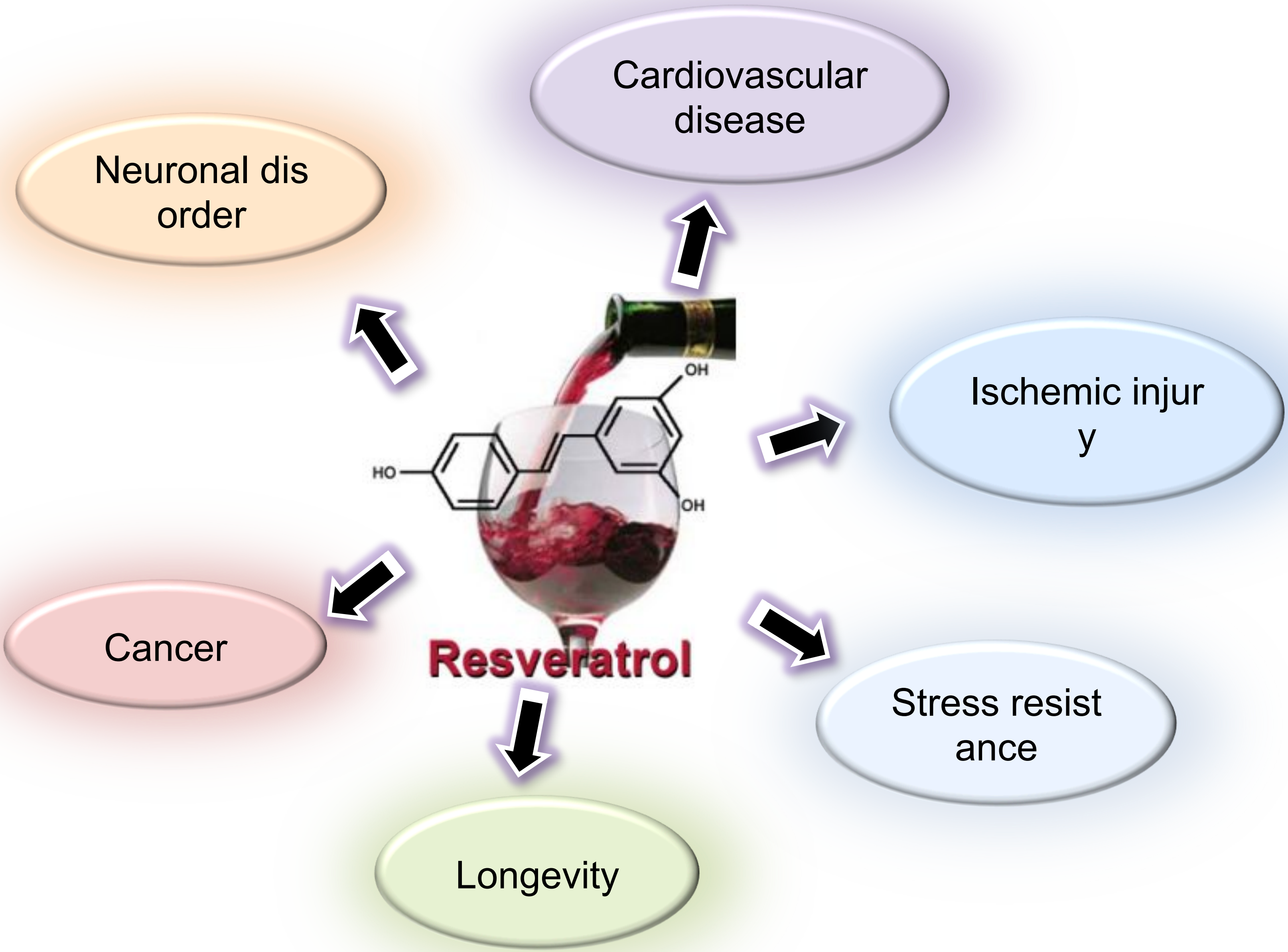
E. H. Siemann and L. L. Creasy

Am. J. Enol. Vitic 1992 vol. 43 no. 1 49-52



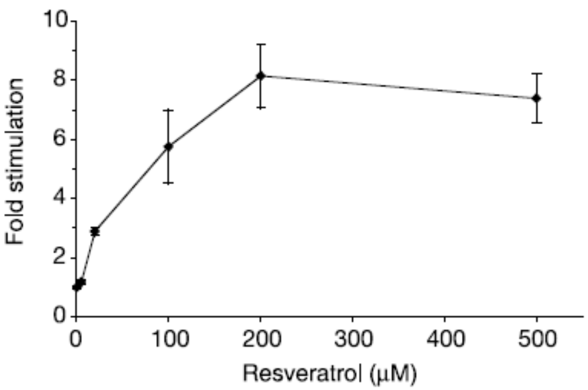
Nature review of drug discovery, 2006

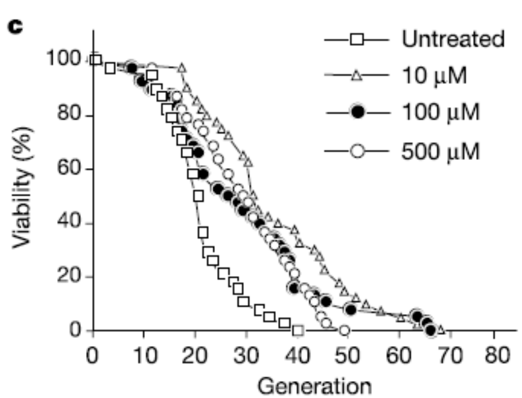
Biological activities of Resveratrol



Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan

Konrad T. Howitz[1], Kevin J. Bitterman[2], Haim Y. Cohen[2], Dudley W. Lamming[2], Siva Lavu[2], Jason G. Wood[2], Robert E. Zipkin[1], Phuong Chung[1], Anne Kisielewski[1], Li-Li Zhang[1], Brandy Scherer[1] & David A. Sinclair[2]



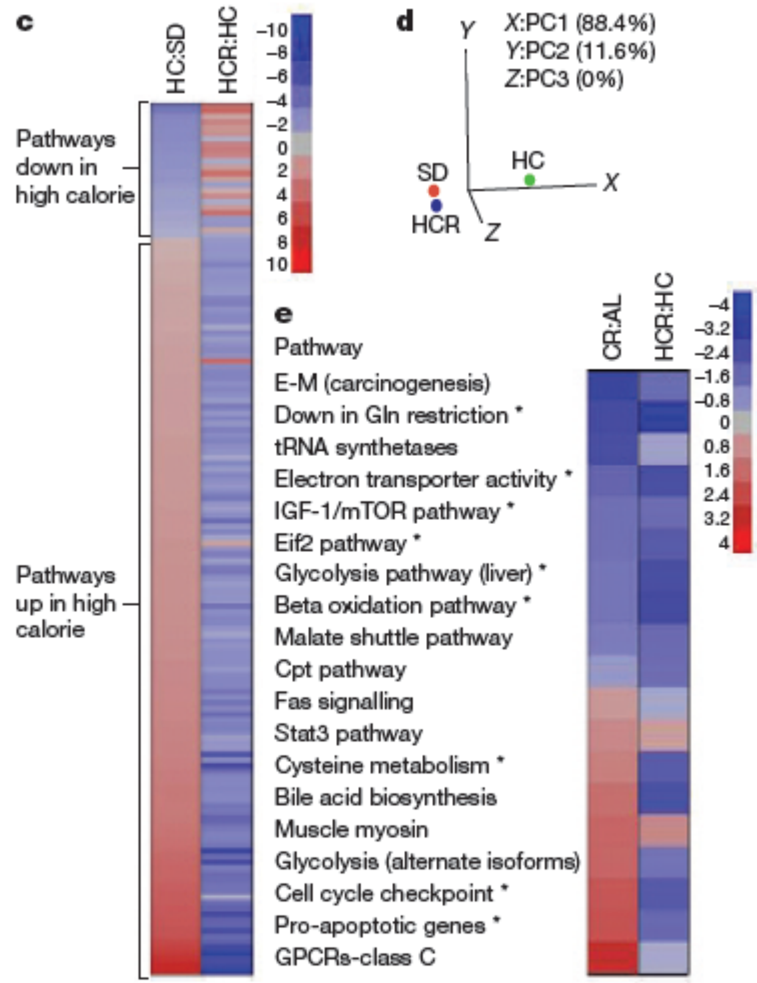


NATURE, 2003

Vol 444|16 November 2006|doi:10.1038/nature05354

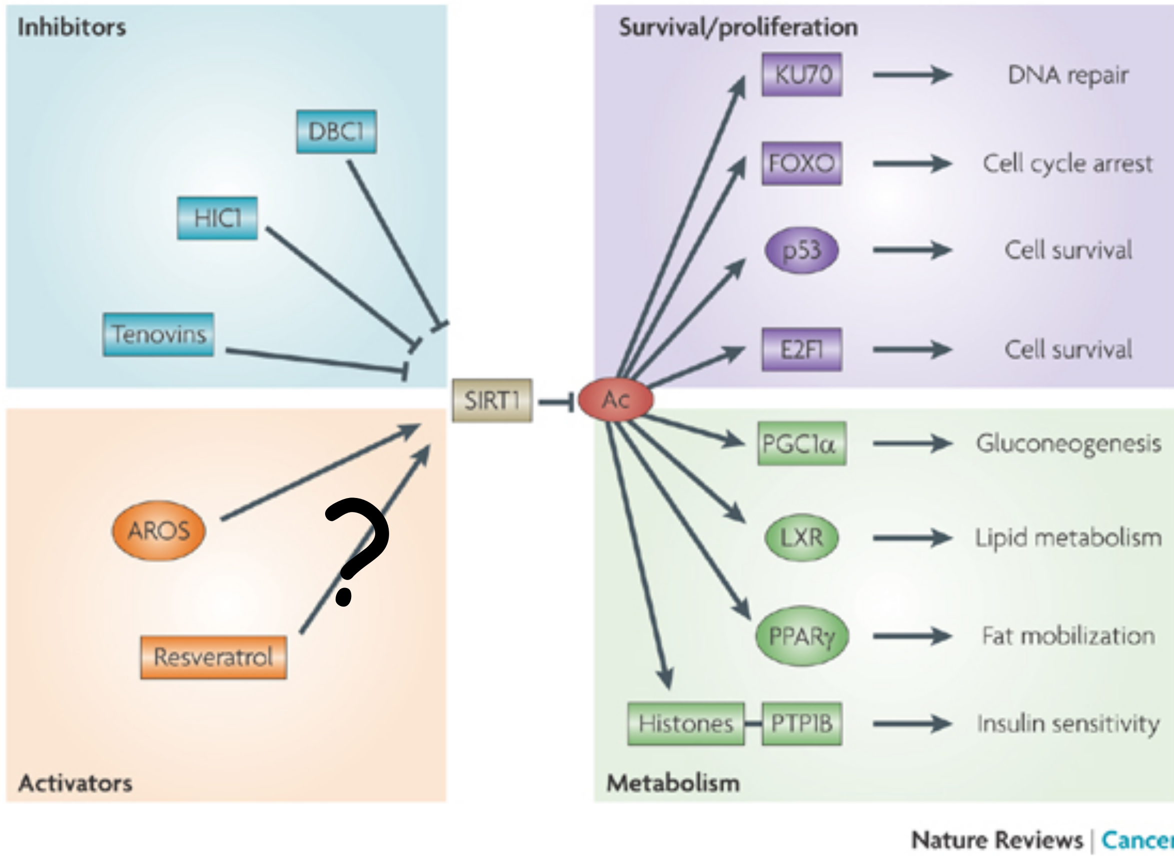
ARTICLES

Resveratrol improves health and survival of mice on a high-calorie diet



E, 2006

Major question of this study

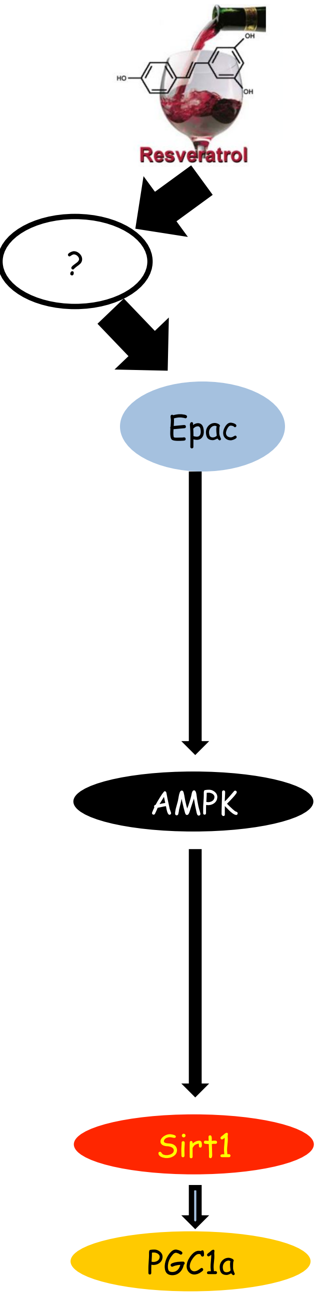


-Resveratrol can't activate Sirt1 to deaetylate native substrate in vitro. (J. Biol. Chem, 2010)

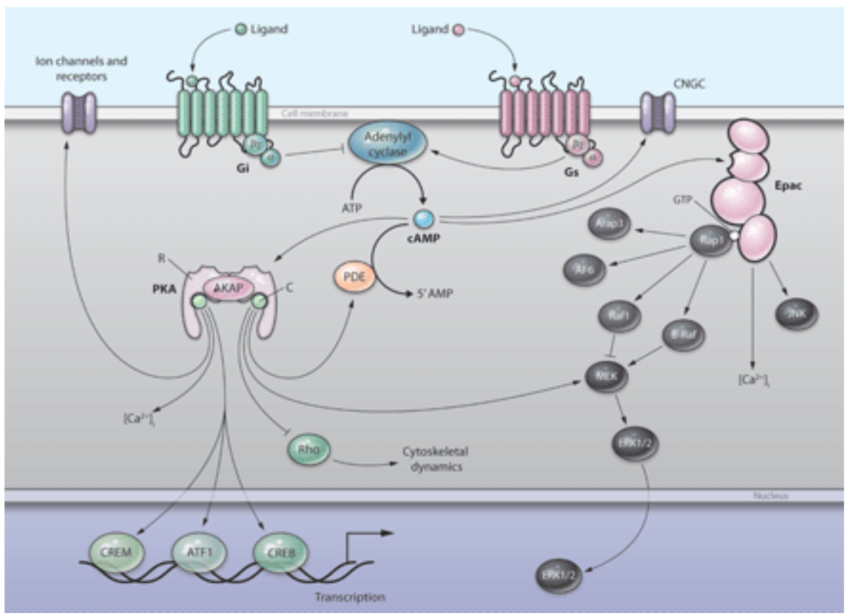
-AMPK deficient mice are resistant to the metabolic effects of resveratrol. (Diabetes, 2010)

→ What's the direct target of resveratrol for sirt1-PGC1a mediated metabolic effects?

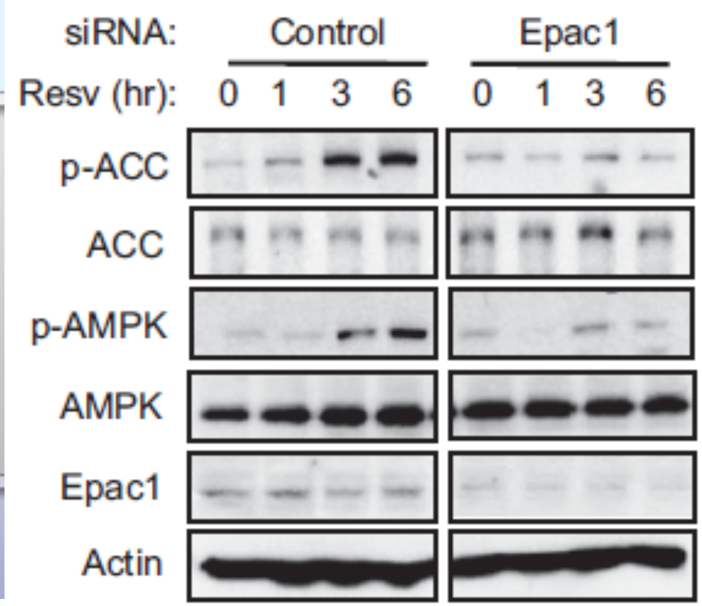
- Resveratrol Activates AMPK in an Epac1-Dependent Manner



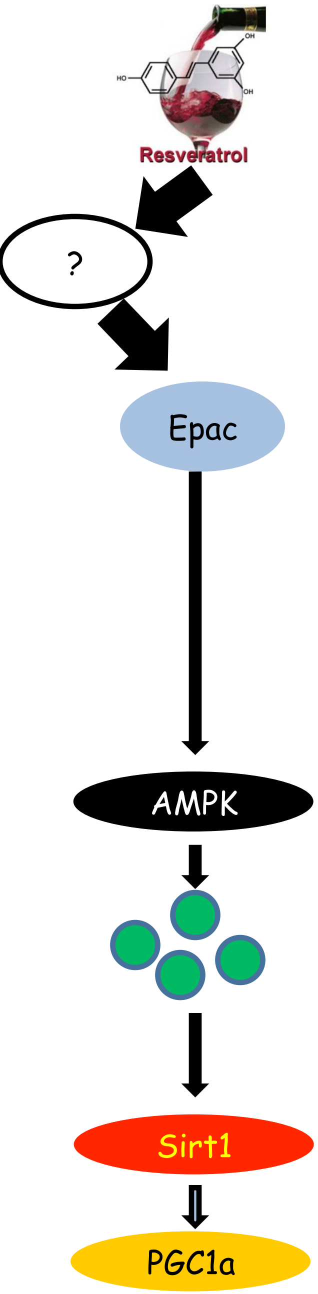
Treatment of Resveratrol,
-Increased cAMP level in vitro & in vivo
-Inhibitor for Adenyl cylase blocked phosphorylation of AMPK



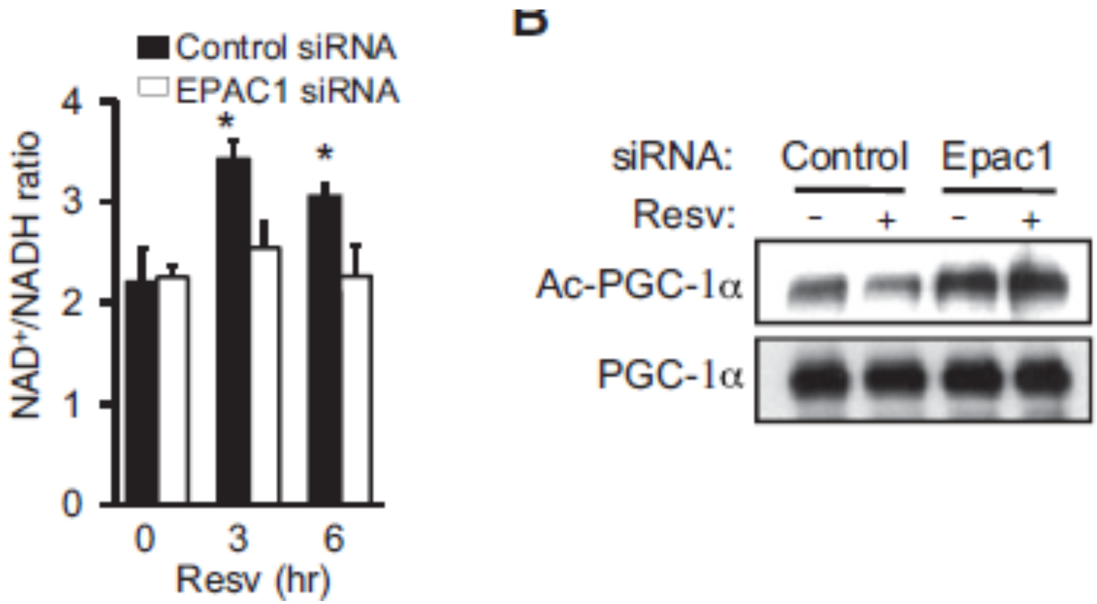
A. J. Murray, Sci. Signal. (2008)



- Resveratrol Increases NAD+ Levels and Sirt1 Activity via Epac1

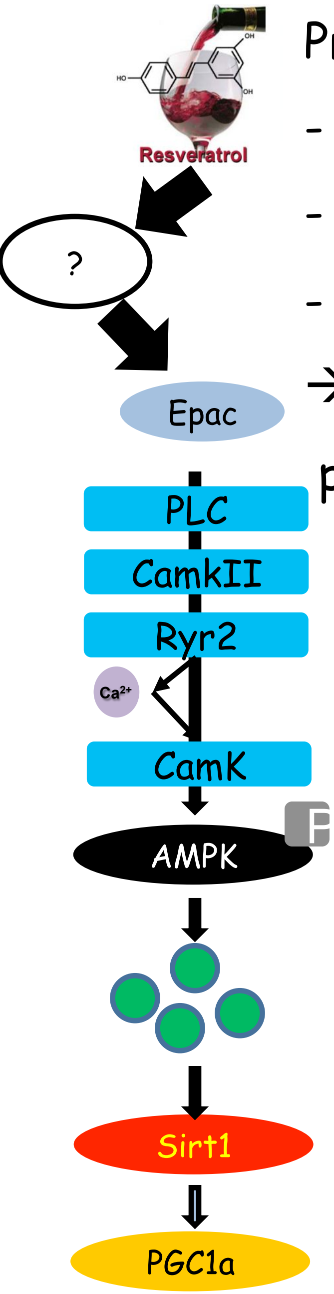


Previously, AMPK have shown to increases NAD+ and Sirt1 activity
→ What's the roles of Epac1/Resv for increase of NAD+?



-Other Sirt1 dependent metabolic effects were also shown by treatment of 007 (Mitochondrial biogenesis, Fat oxidation, ROS production)

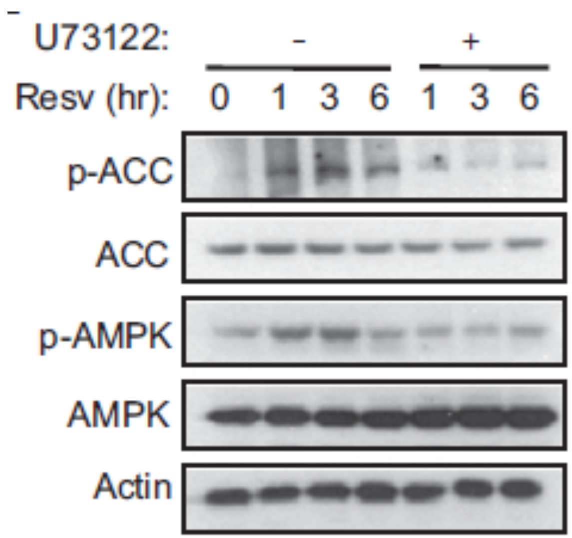
- Resv activates the CamKKb-AMPK via PLC-Ryr2 pathway

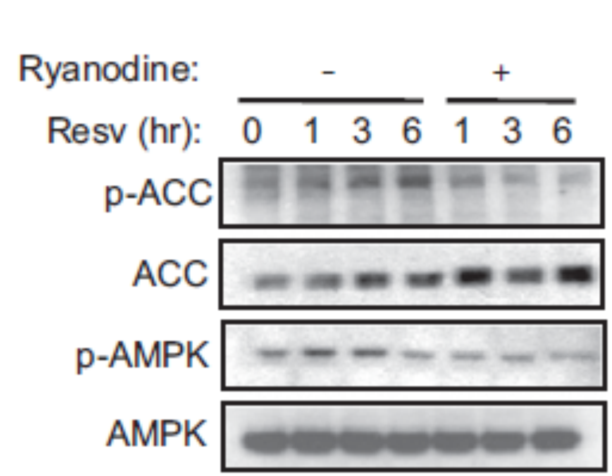


Previously,

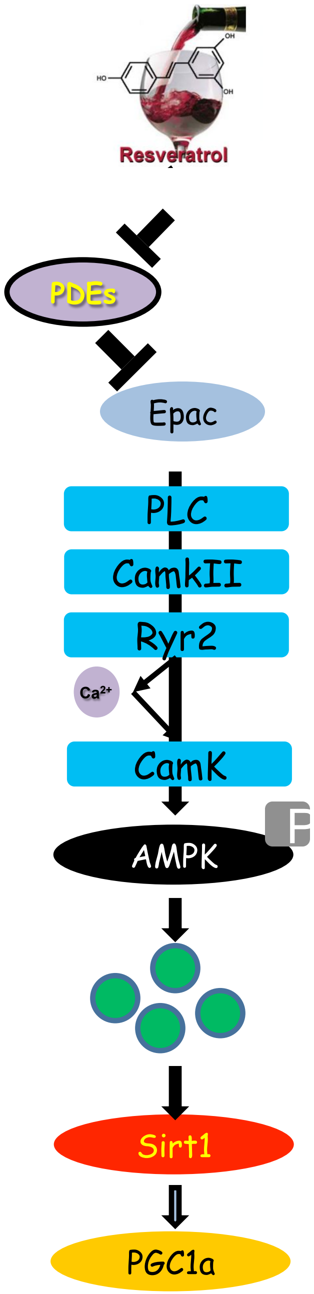
- AMPK activation require phosphorylation by LKB1 or CamKKβ
- Resveratrol increased cytosolic Ca^{2+}
- Epac1 increased cytosolic Ca^{2+} in PLC dependent manner via CamKII

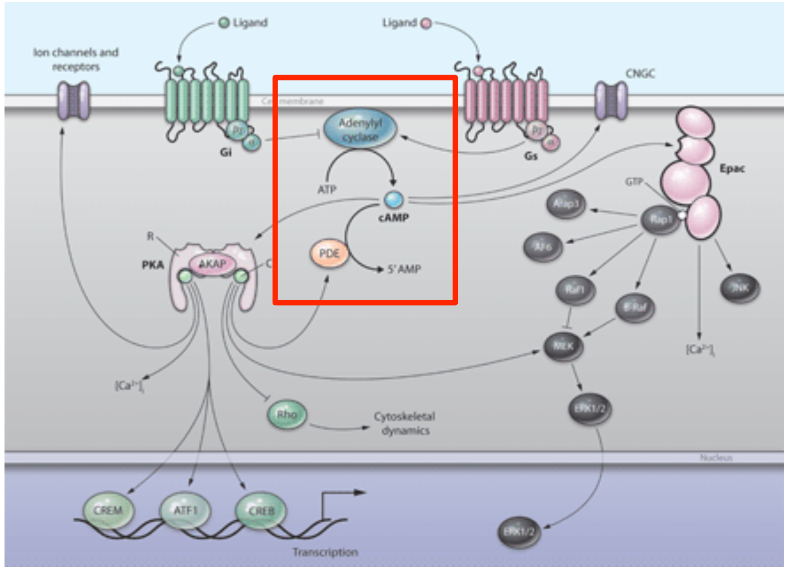
→ What's the roles of Resv/Epac1 for the activation of CamKKb/AMPK pathway?





- Resveratrol is nonselective phosphodiesterase inhibitor



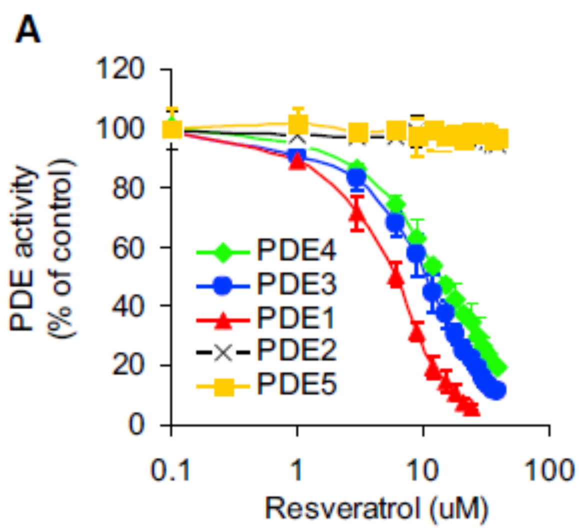


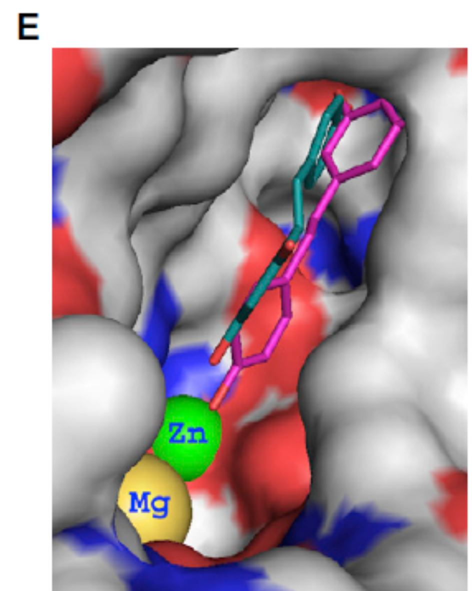
A. J. Murray, Sci. Signal. (2008)

cAMP level
-Adenyl Cylase: ATP → cAMP
-PDE: cAMP → AMP

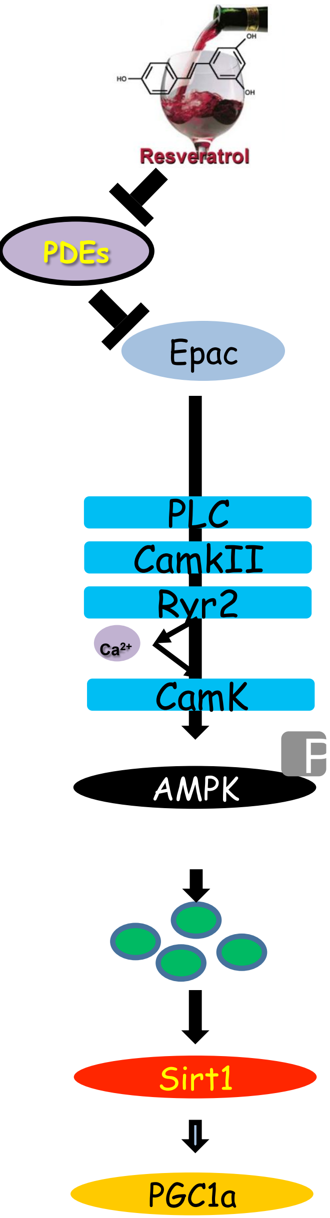
-No effect of Resv on AC activity

-11 types of PDEs
① PDE4/7/8: cAMP
② PDE5/6/9: cGMP
③ PDE1/2/3/10/11: cAMP&cGMP

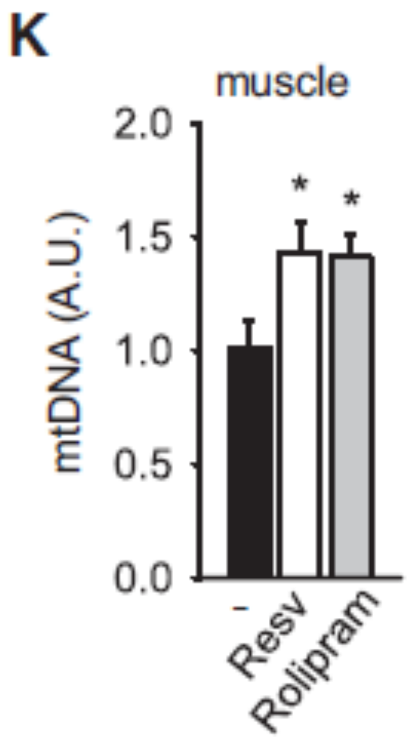


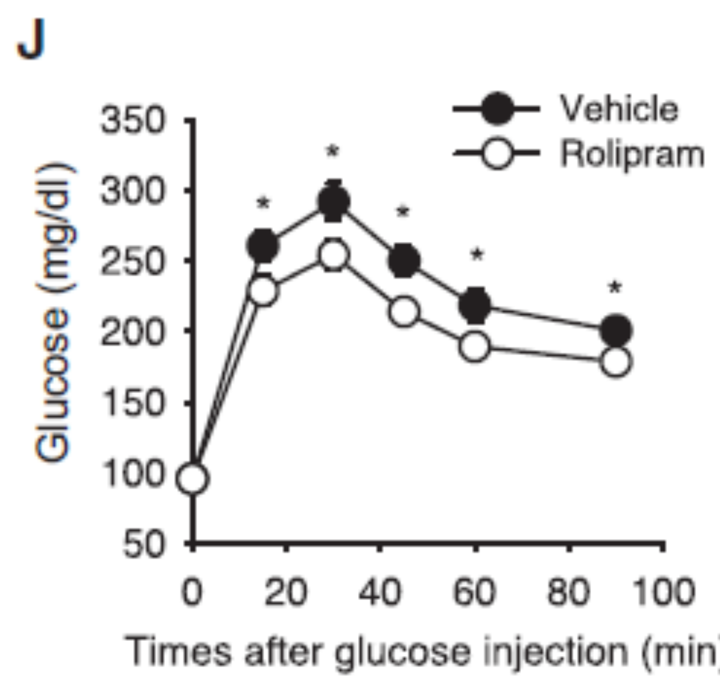


- Resv increase mitochondrial biogenesis and protect diet-induced obesity & glucose tolerance in a PDE dependent manner

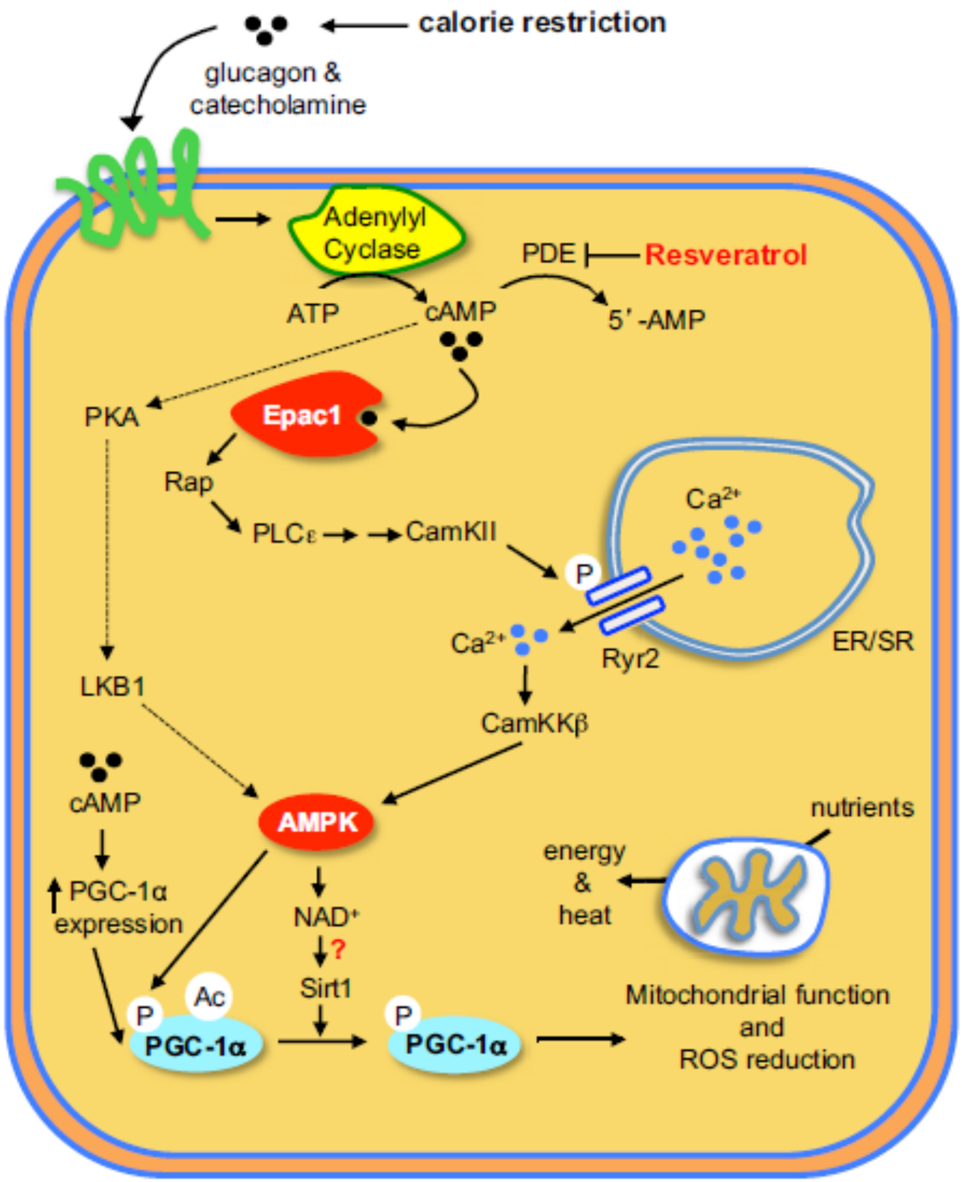


If Resv effects is mediated by inhibition of PDEs,
can the inhibition of PDEs mimic metabolic effects of Resv?
→ Mitochondrial Biogenesis and glucose tolerance





Proposed Model of How Resveratrol Mimics CR



Further questions?

① Does Resveratrol selectively activate CR related pathway or also acti vate other cAMP dependent pathways?

② What's the effects of Resveratrol or Rolipram for Treg?
- cAMP?
- Treg stability?

③ What's the roles of Sirt1 in non-T compartment?
- $Sirt1^{-/-}$: Abnormal T responses
- $CD4^{cre}/Sirt1^{flox}$: Normal T responses

④ What's the effect of Resveratrol or Rolipram for the development an d function of Fat Treg?

⑤ How much do we need to drink wine?

→ Daily intake of 375 ml, or about two glasses of wine, → ~27 μg per kg (body wei ght) each day.
→ At higher doses, the detrimental effects of alcohol are likely to mask any healt h benefits.


"Just love your brother and drink a good glass of red wine every day!"
Antonio Todde (World's oldest man)

Table 1 | **Dietary sources of resveratrol**

Source	*trans*-Resveratrol concentration	Comments	Refs
Dietary			
Red wines	0.1–14.3 mg l^{-1}	*cis*-Resveratrol, *trans*-piceid and *cis*-piceid also present, typically at slightly lower concentrations	181,207–213
White wines	<0.1–2.1 mg l^{-1}	Generally resveratrol found at concentrations of <0.1 mg l^{-1}, exceptions include Swiss, Portuguese and German Riesling wines, *cis*-resveratrol, *trans*-piceid and *cis*-piceid also present	181,201,207, 209,210
Ports and sherries	Generally <0.1 mg l^{-1}		207
Grapes*	0.16–3.54 µg g^{-1}	Contents are similar for wine or table grapes, and black or white grapes. *trans*-Piceid is predominant at concentrations of 1.5–7.3 µg g^{-1}	211,214–216
Dry grape skins	24.06 µg g^{-1} (average)	*trans*-Piceid and *cis*-piceid found at concentrations of 42.19 µg g^{-1} and 92.33 µg g^{-1}, respectively	217
Red grape juices	0.50 mg l^{-1} (average)	*trans*-Piceid, *cis*-piceid and *cis*-resveratrol found at concentrations of 3.38 mg l^{-1}, 0.79 mg l^{-1} and 0.06 mg l^{-1}, respectively	218
White grape juices	0.05 mg l^{-1} (average)	*trans*-Piceid and *cis*-piceid found at concentrations of 0.18 mg l^{-1} and 0.26 mg l^{-1}, respectively	218
Cranberry raw juice	~0.2 mg l^{-1}	*cis*-Resveratrol also found at a concentration of ~0.03 mg l^{-1}	219
Blueberries	Up to ~32 ng g^{-1}		220
Bilberries	Up to ~16 ng g^{-1}		220
Other *Vaccinium* berries	7–5,900 ng g^{-1} (dry sample)	Highest concentrations in lingonberries	216
Peanuts	0.02–1.92 µg g^{-1}		221,222
Roasted peanuts	0.055 µg g^{-1}		223
Boiled peanuts	5.1 µg g^{-1}		211,223
Peanut butters	0.3–0.4 µg g^{-1} (average)	*trans*-Piceid also found at a concentration of 0.13 µg g^{-1}	211,223,224
100% Natural peanut butters	0.65 µg g^{-1} (average)	*trans*-Piceid also found at a concentration of 0.14 µg g^{-1}	224
Pistachios	0.09–1.67 µg g^{-1}		222
Groundnuts (*Arachis hypogaea*)	ND		225
Rhubarb	ND		226
Hops	0.5–1 µg g^{-1}	*trans*-Piceid and *cis*-piceid found at concentrations of 2–9 µg g^{-1} and 0.9–6 µg g^{-1}, respectively	227,228
Itadori (*Polygonum cuspidatum*) tea	0.68 mg l^{-1}	*trans*-Piceid also found at a concentration of 9.1 mg l^{-1}	211
Herbal			
Veratrum (Lily)	ND		1
Cassia quinquangulata	ND		5
Gnetum klossii	ND		229
Polygonum cuspidatum	0.524 mg g^{-1}	*trans*-Piceid also found at a concentration of 1.65 mg g^{-1}	211,230
Rhubarb (*Rheum rhaponticum*) dry root	3.9 mg g^{-1}		230
Yucca schidigera bark	ND		231

Nature Review of Drug Discovery, 2006