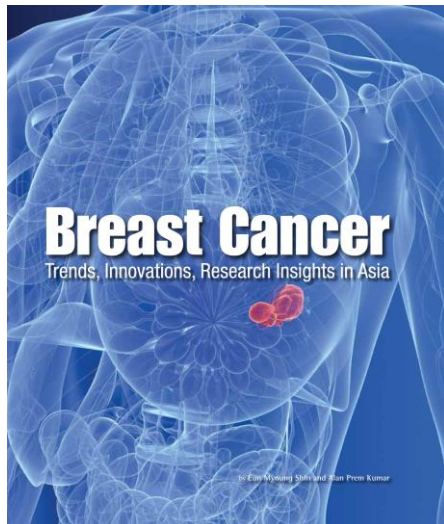


DEAD-BOX RNA HELICASE DDX20 ENHANCES YAP SUMOYLATION FOR YAP-TEAD DEPENDENCE AND STATIN SENSITIVITY IN TRIPLE NEGATIVE BREAST CANCER



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- A/P Marius Sudol
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- Dr Ruby Huang
- Dr Melissa Fullwood



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Triple Negative Breast Cancers (TNBC)

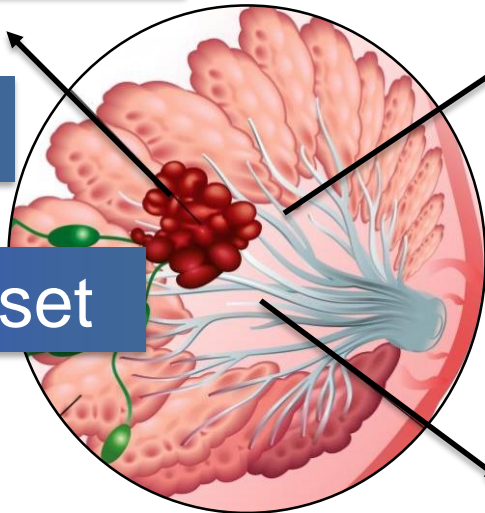
10-20%

HER2 -

Progesterone Receptor -

poor prognosis

early age of onset



Estrogen Receptor -

Chemotherapy



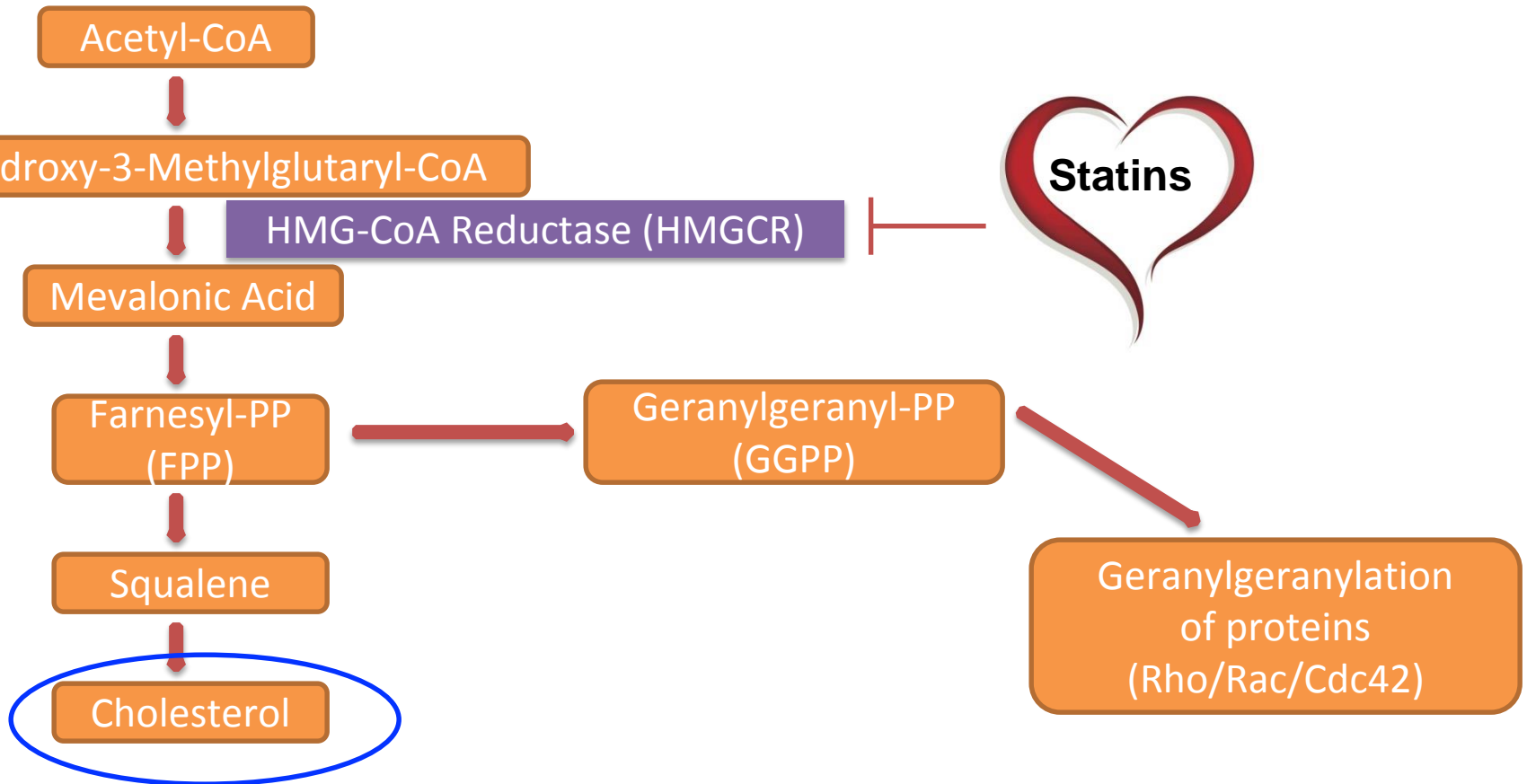
Hormone Therapy



Targeted Therapy



Mevalonate Pathway & Statins



The anti-cancer effects of statins

Simvastatin induces derepression of **PTEN** expression via **NFkappaB** to inhibit **breast cancer** cell growth.

Ghosh-Choudhury N et al., Cell Signal, 2011

Statin-induced inhibition of **breast cancer** proliferation and invasion involves attenuation of iron transport: intermediacy of nitric oxide and antioxidant defence mechanisms.

Kanuqula et al., FEBS J, 2011

Statin induces inhibition of triple negative **breast cancer** (

Yeon Hee Park et al., BBRC, 2013

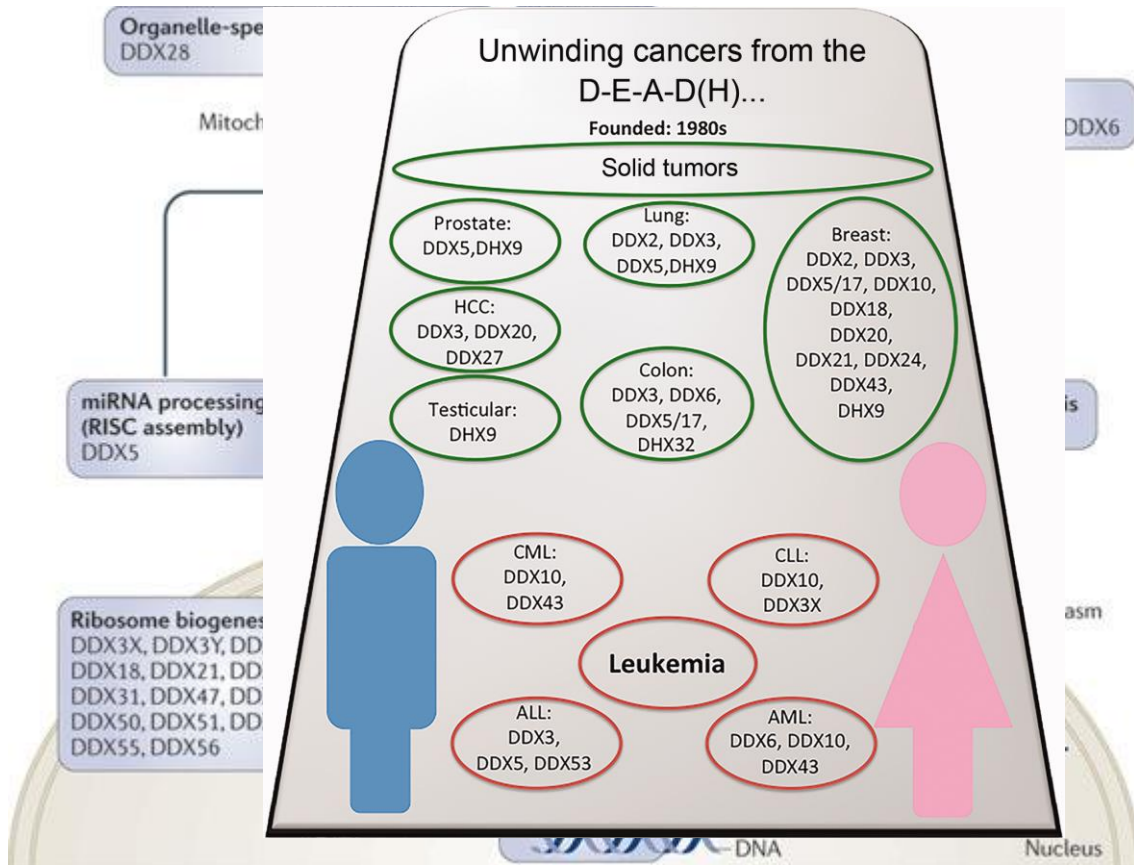
Biomarker



PI3K

DDX20/DP103

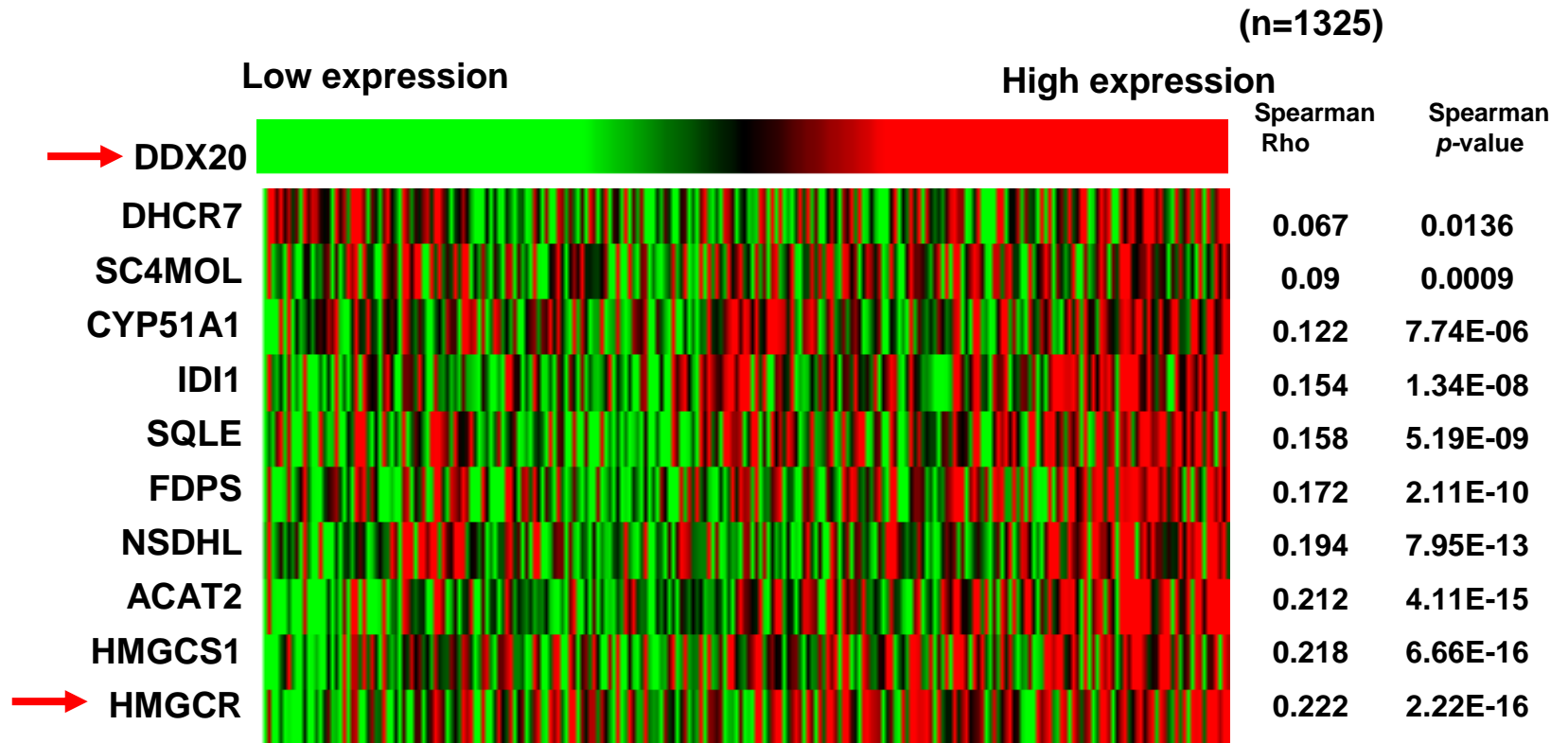
D-E-A-D box family RNA helicase.



Linder P et al., Nat Rev Mol Cell Biol. 2011

Cai W et al., J Natl Cancer Inst. 2017

Positive correlation between DDX20 expression and mevalonate pathway genes

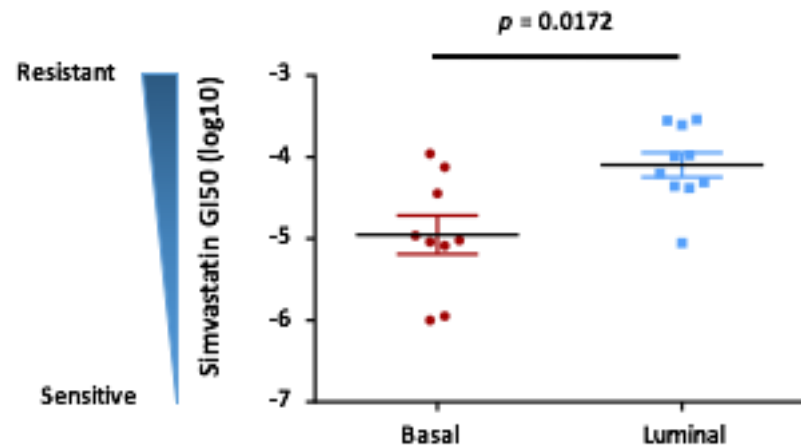
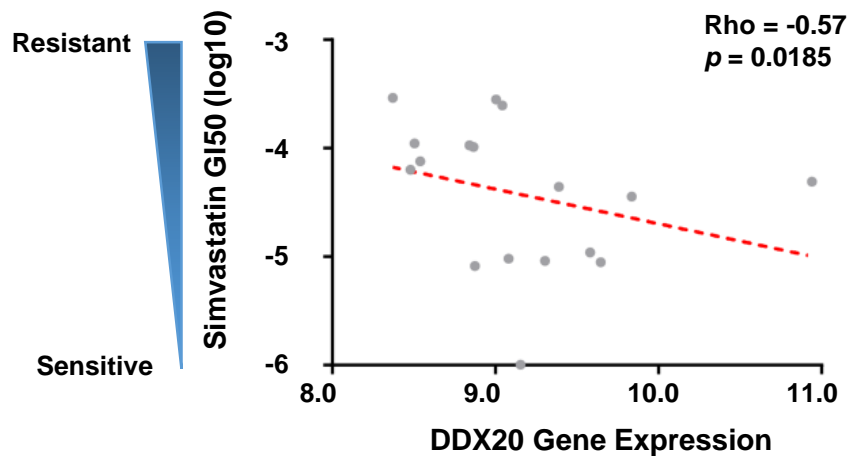




Question 1: Can DDX20 be used as a biomarker for statin sensitivity?



DDX20 expression positively correlates with statin sensitivity

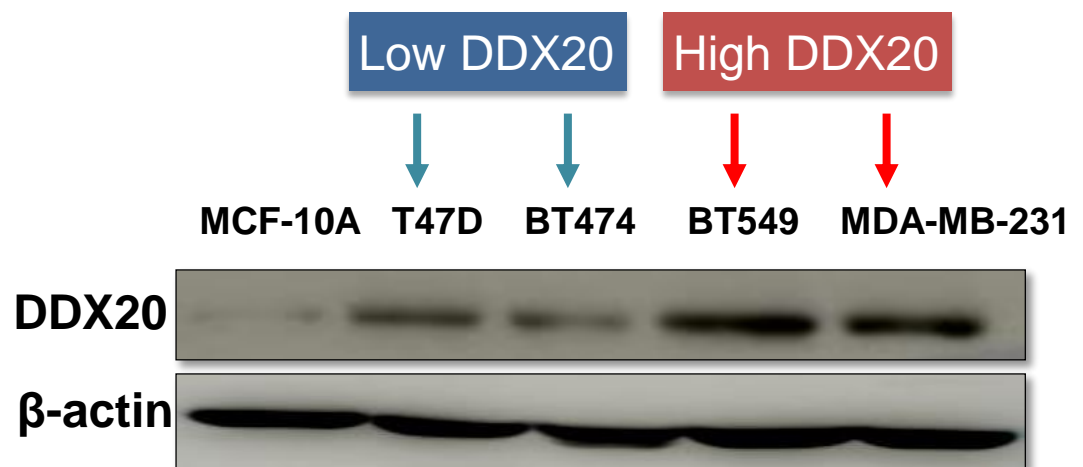
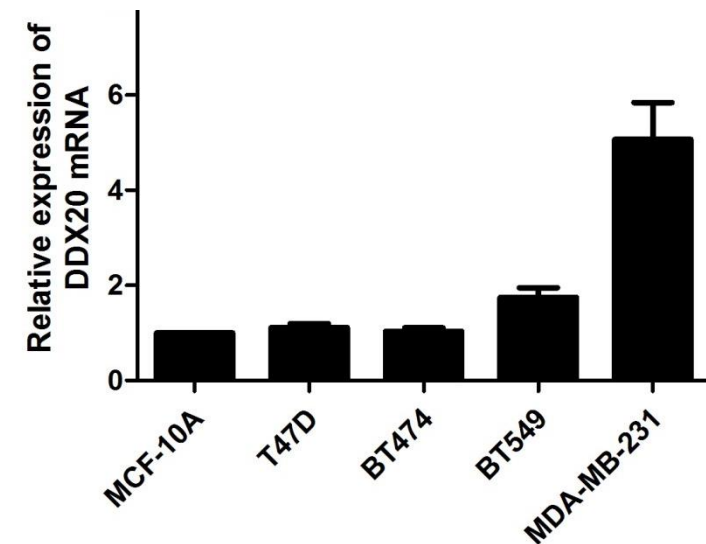




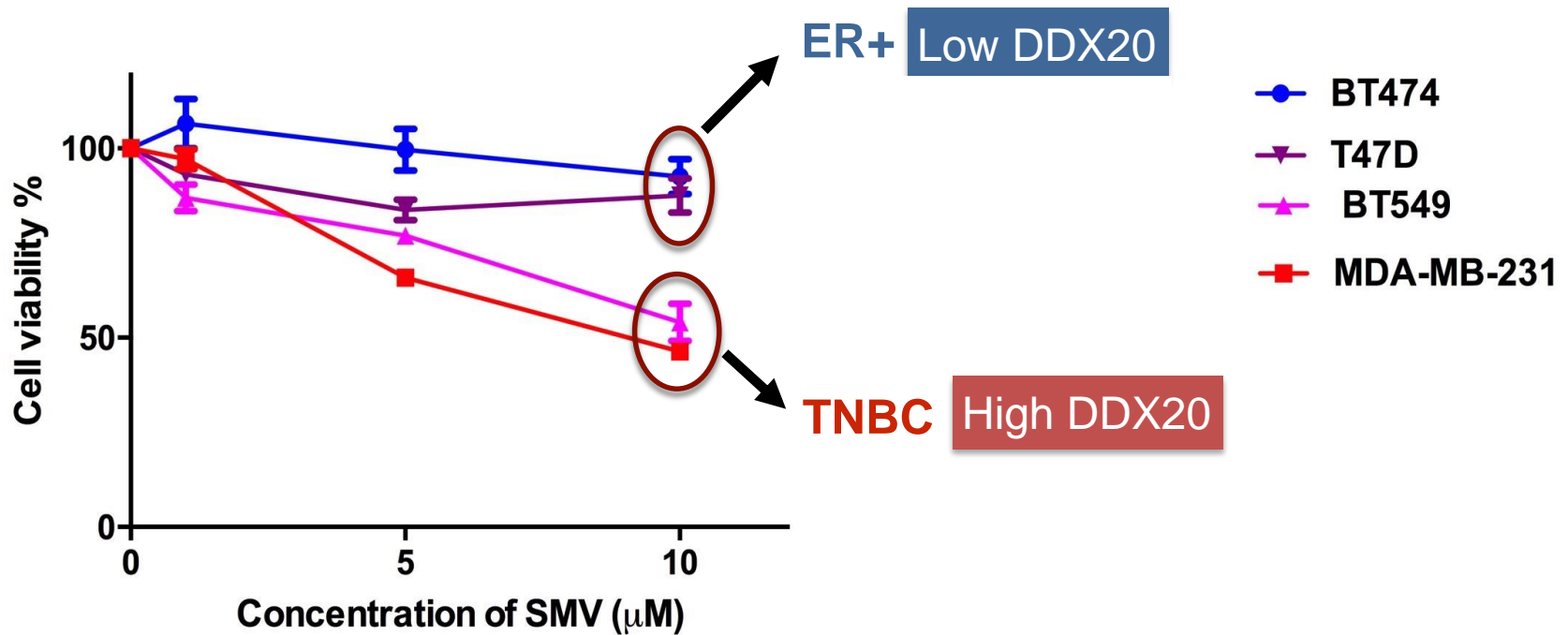
DDX20 is highly expressed in triple negative breast cancer cells



	ER	PR	HER2
MCF-10A			
BT474	+	+	+
T47D	+	+	-
BT549	-	-	-
MDA-MB-231	-	-	-



TNBCs are more sensitive to simvastatin than ER+



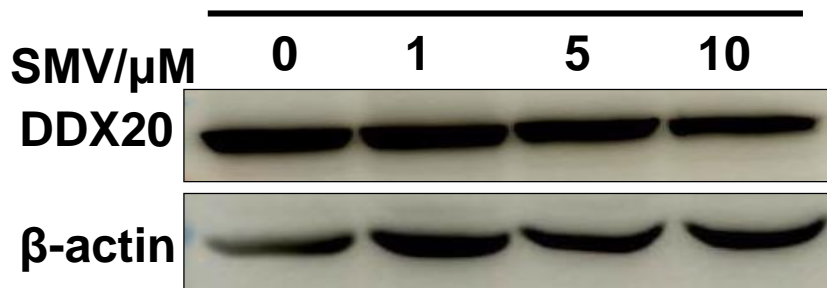


Question 2: How does statin treatment affect DDX20 expression?

TNBCs are more sensitive to simvastatin than ER+

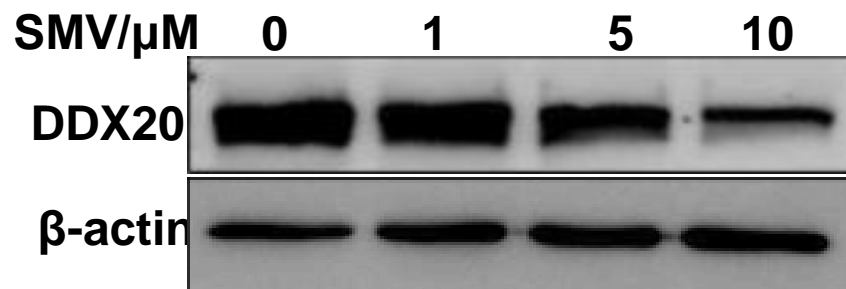
Luminal

BT474



Basal

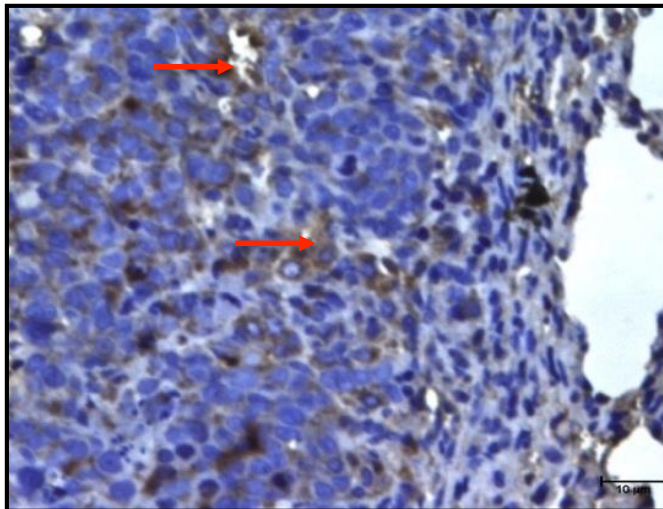
MDA-MB-231



Simvastatin decreases DDX20 expression in mice

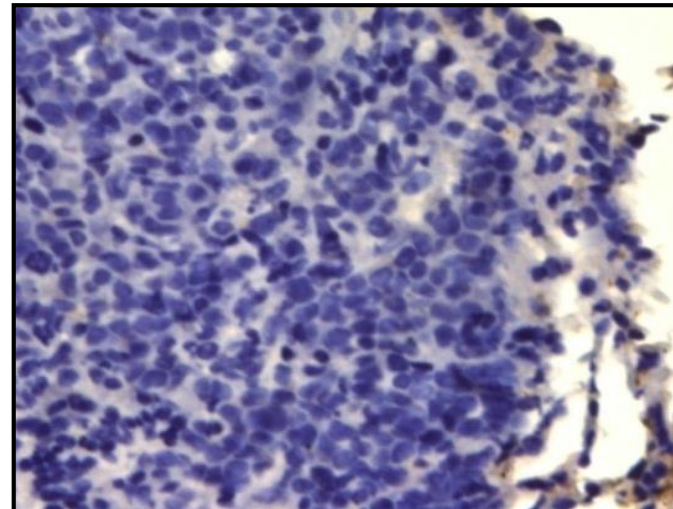


Control



200 X

Simvastatin

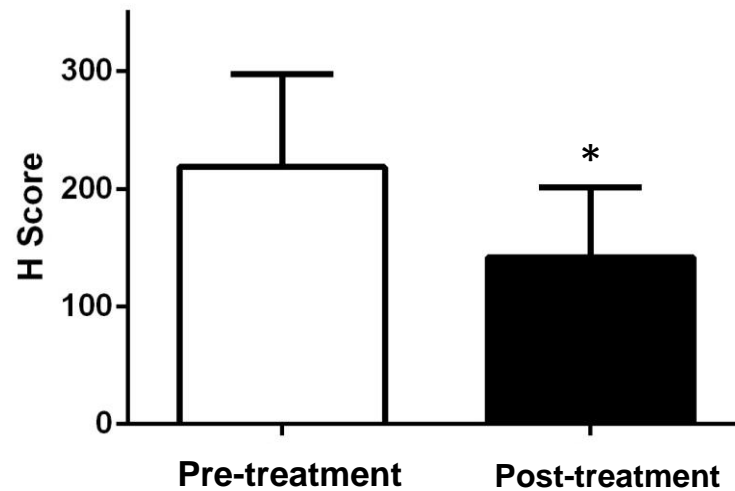
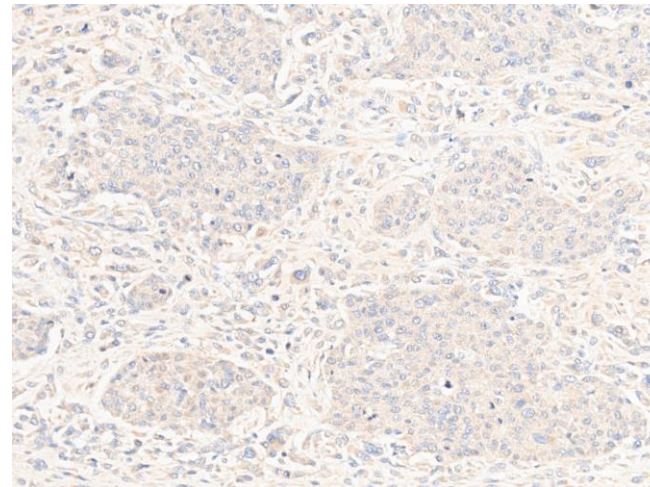
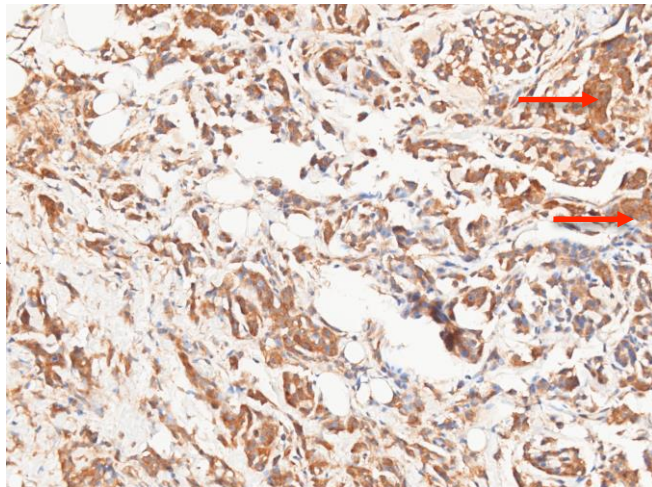


Simvastatin decreases DDX20 in Breast Cancer Patients

Pre-treatment

Post-treatment
(with simvastatin)

200 X

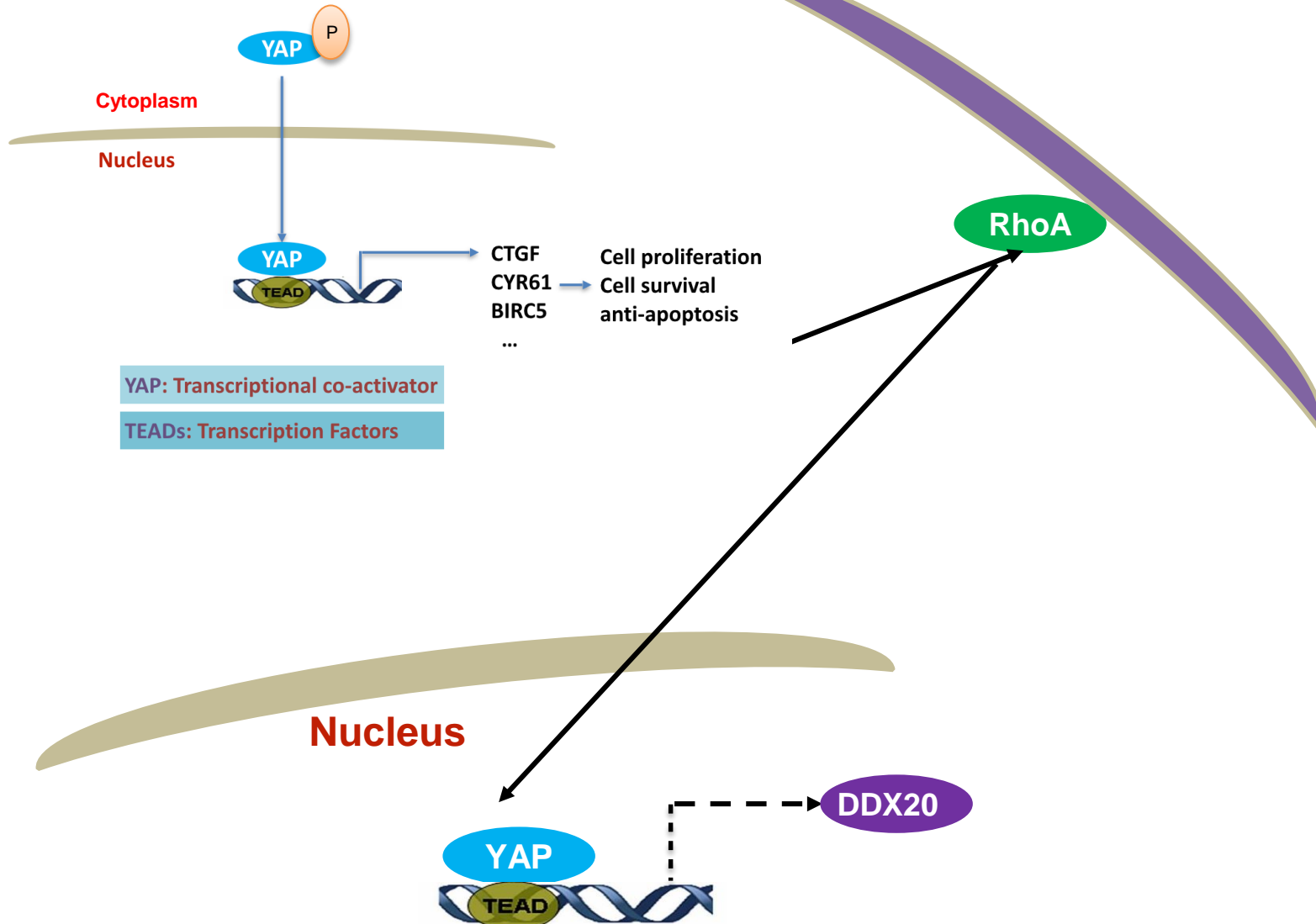


* denotes $p < 0.05$

Statins inhibit YAP via GGPP-RhoA

Metabolic control of YAP and TAZ by the mevalonate pathway.

Sorrentino G et al. , Nat Cell Biol, 2014

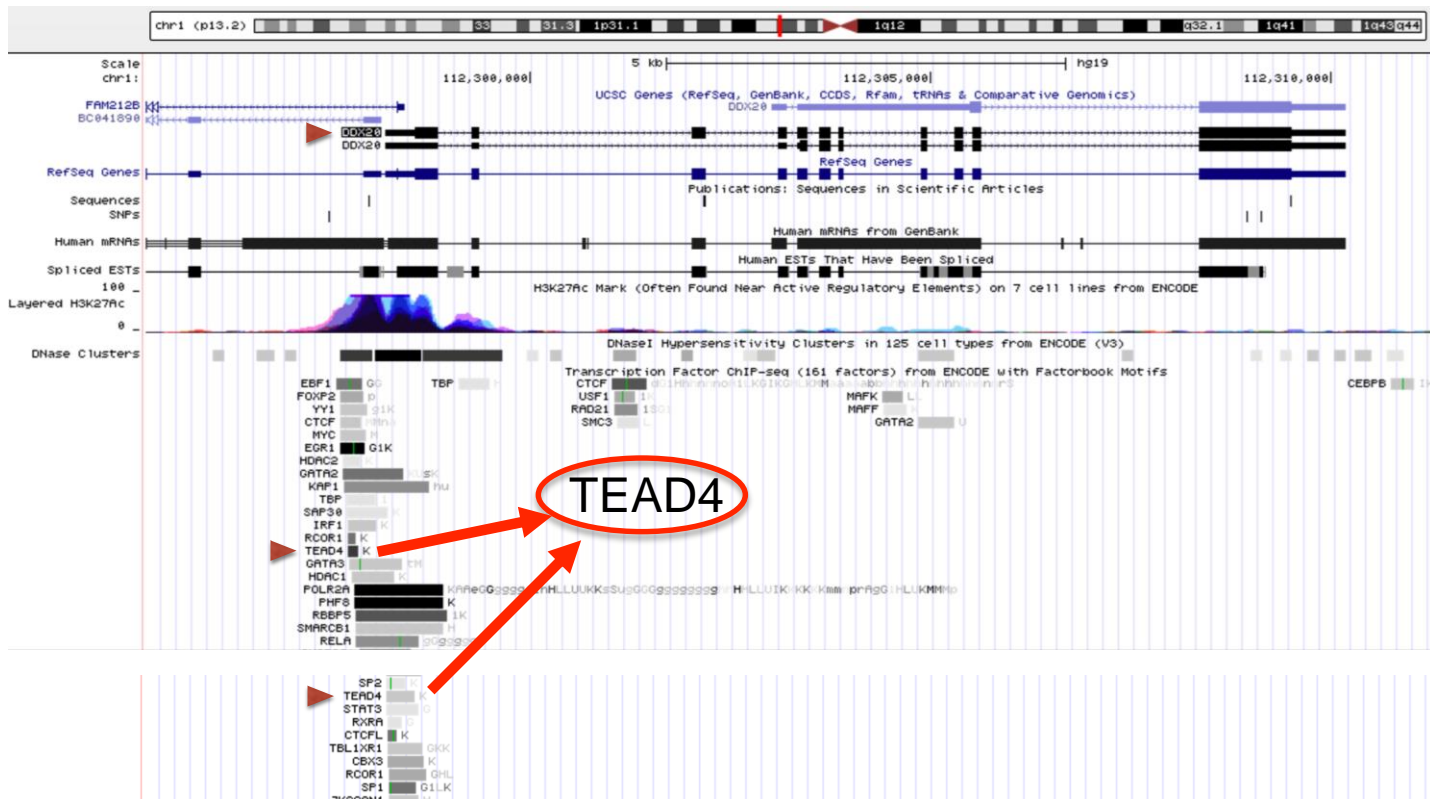




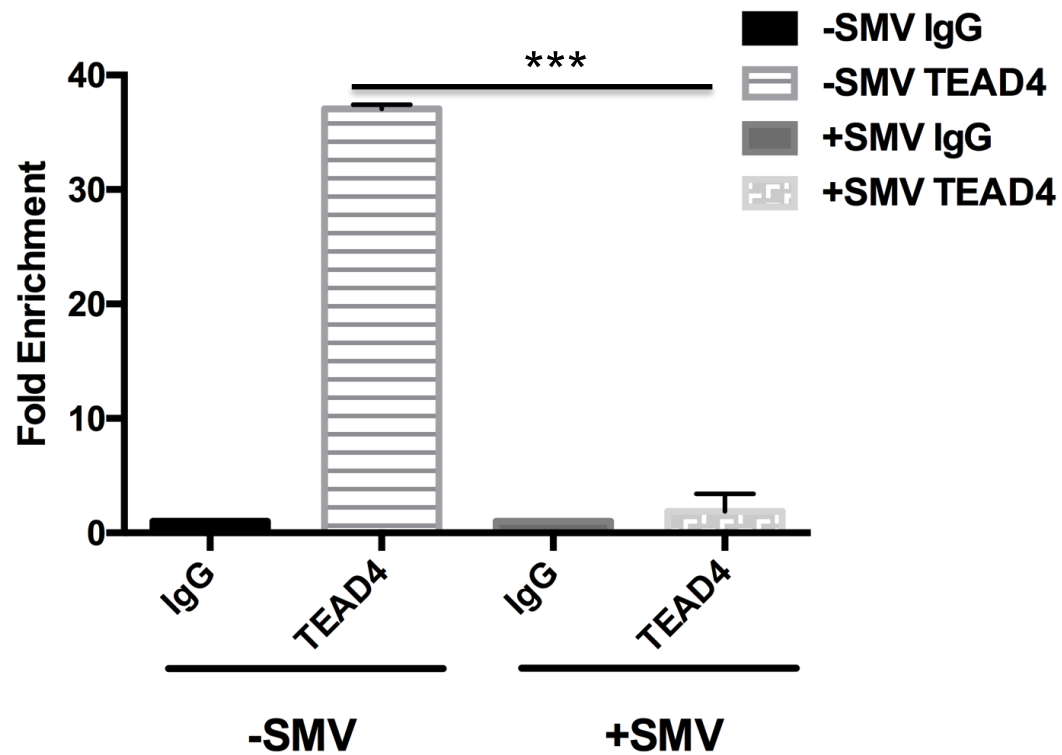
Question 4: Does YAP/TEAD regulate DDX20 transcription?

TEAD4 binds to DDX20 promoter

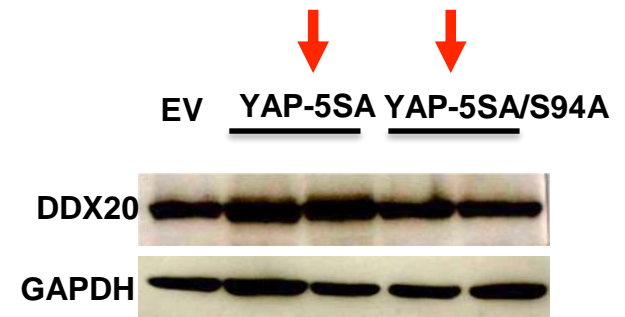
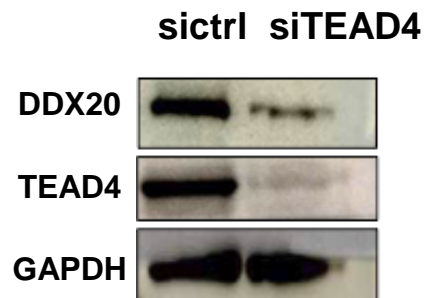
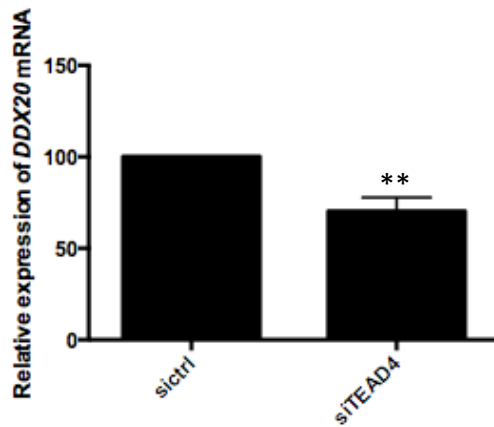
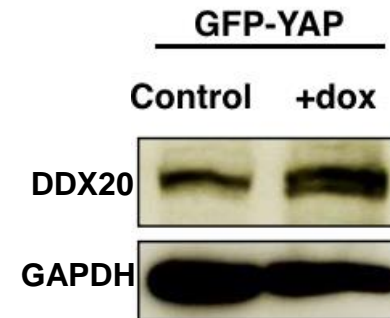
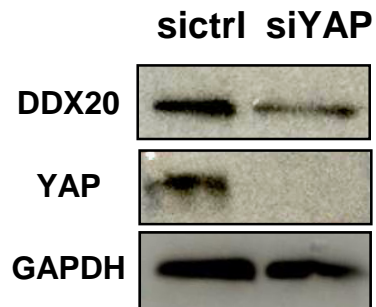
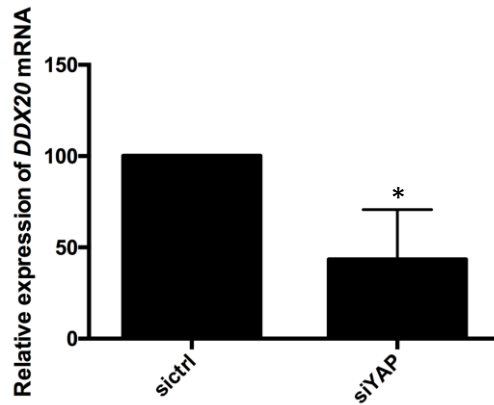
ENCODE



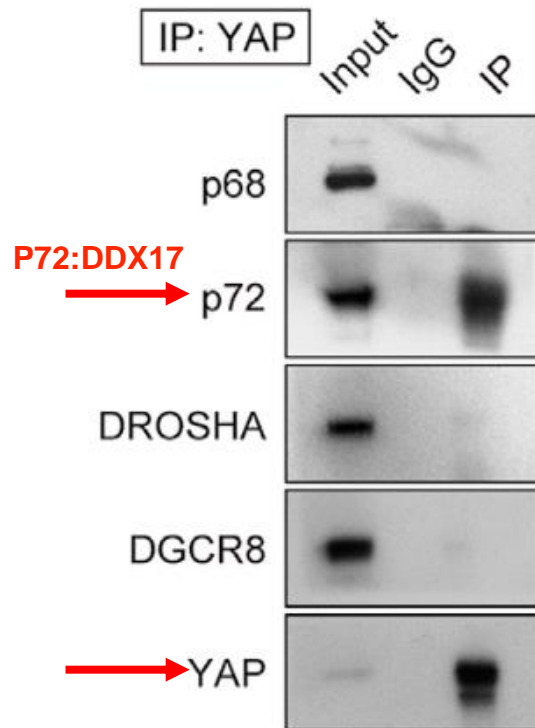
Simvastatin disrupts TEAD4 binding to DDX20 promoter



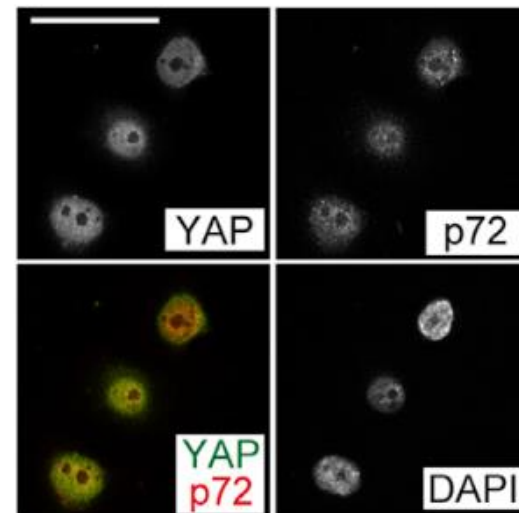
TEAD4/YAP regulates DDX20



DDX17 interacts with YAP



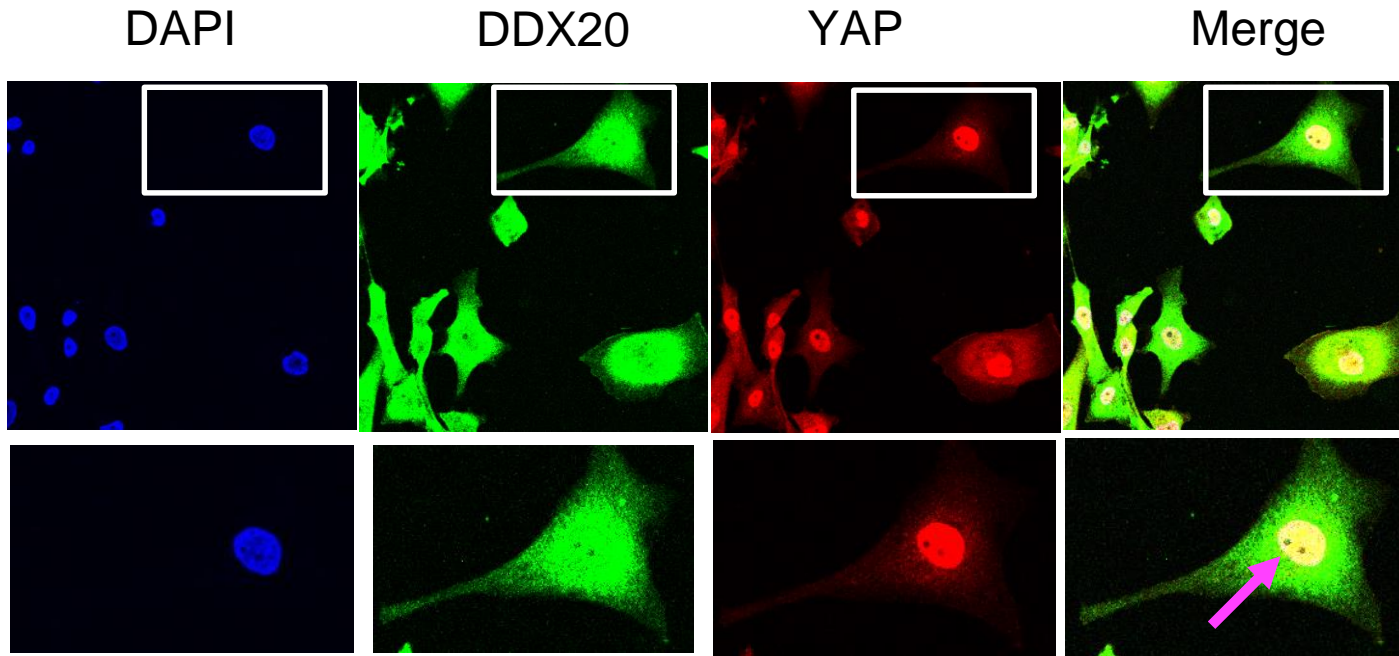
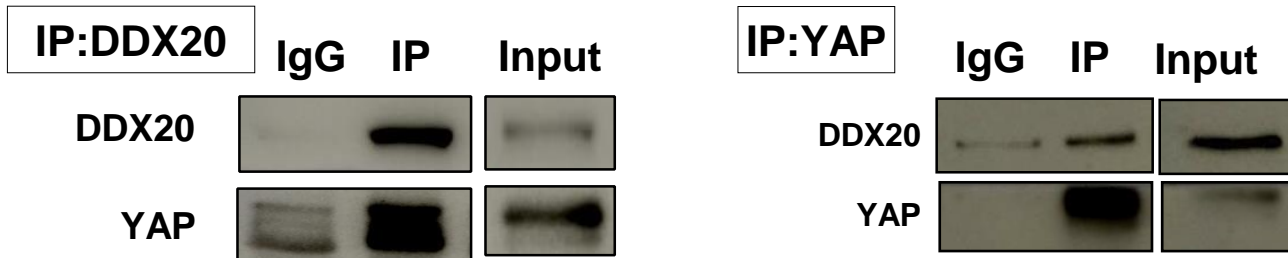
Colocalization of YAP and p72 at low cell density



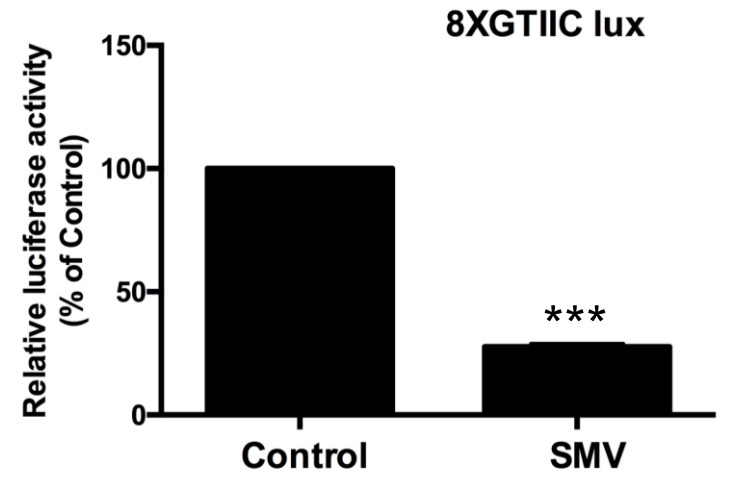
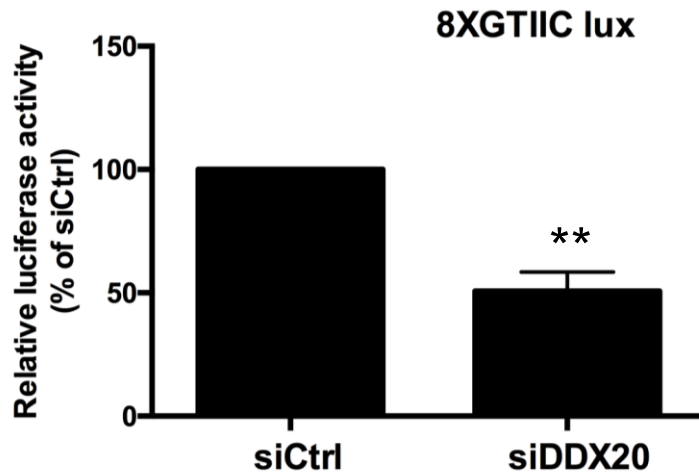


**Question 5: Does DDX20 interact with YAP
and regulate it?**

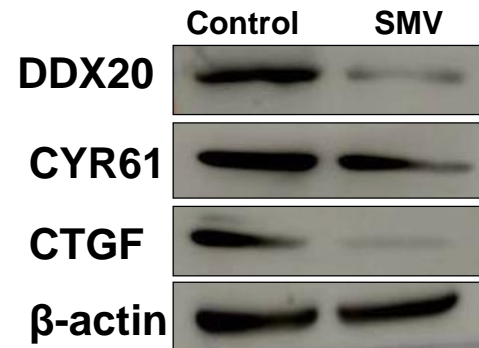
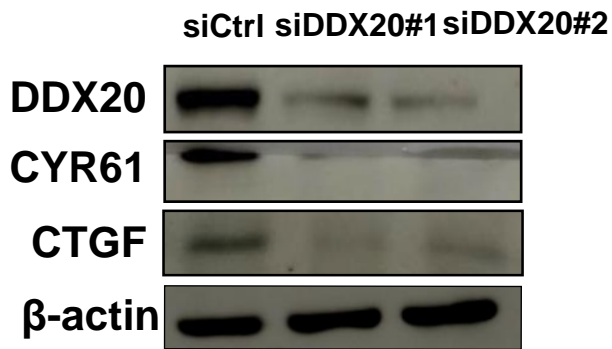
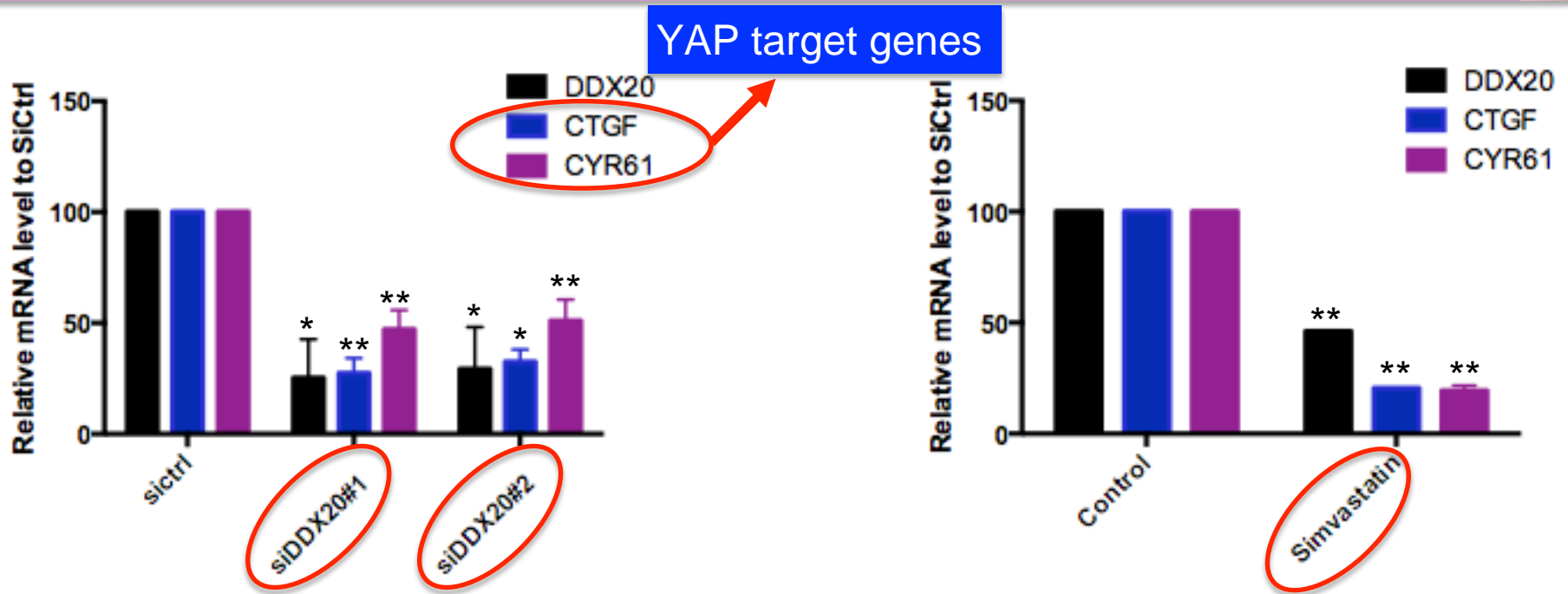
DDX20 interacts with YAP



DDX20 positively regulates TEAD/YAP activity

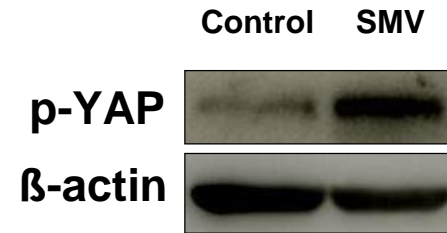
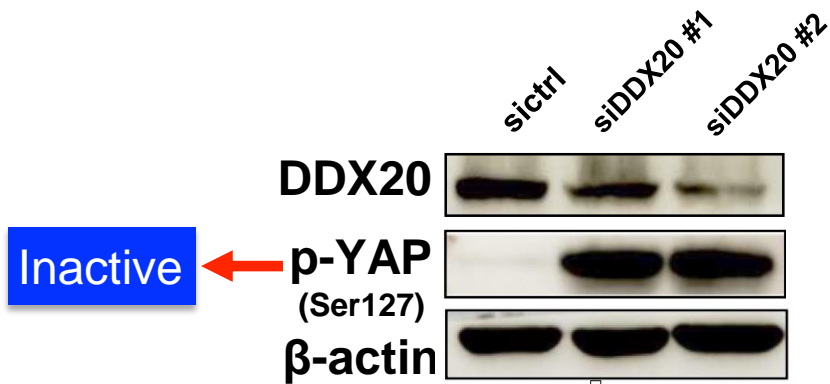


DDX20 positively regulates YAP target genes



* : p<0.05
** : p<0.01

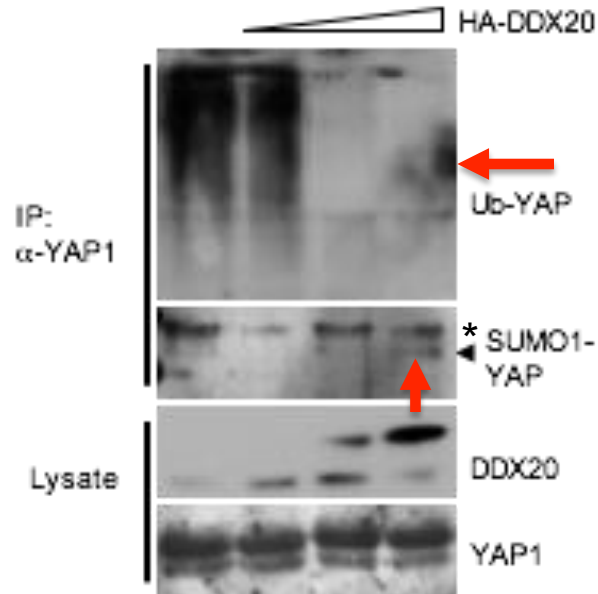
DDX20 positively regulates YAP



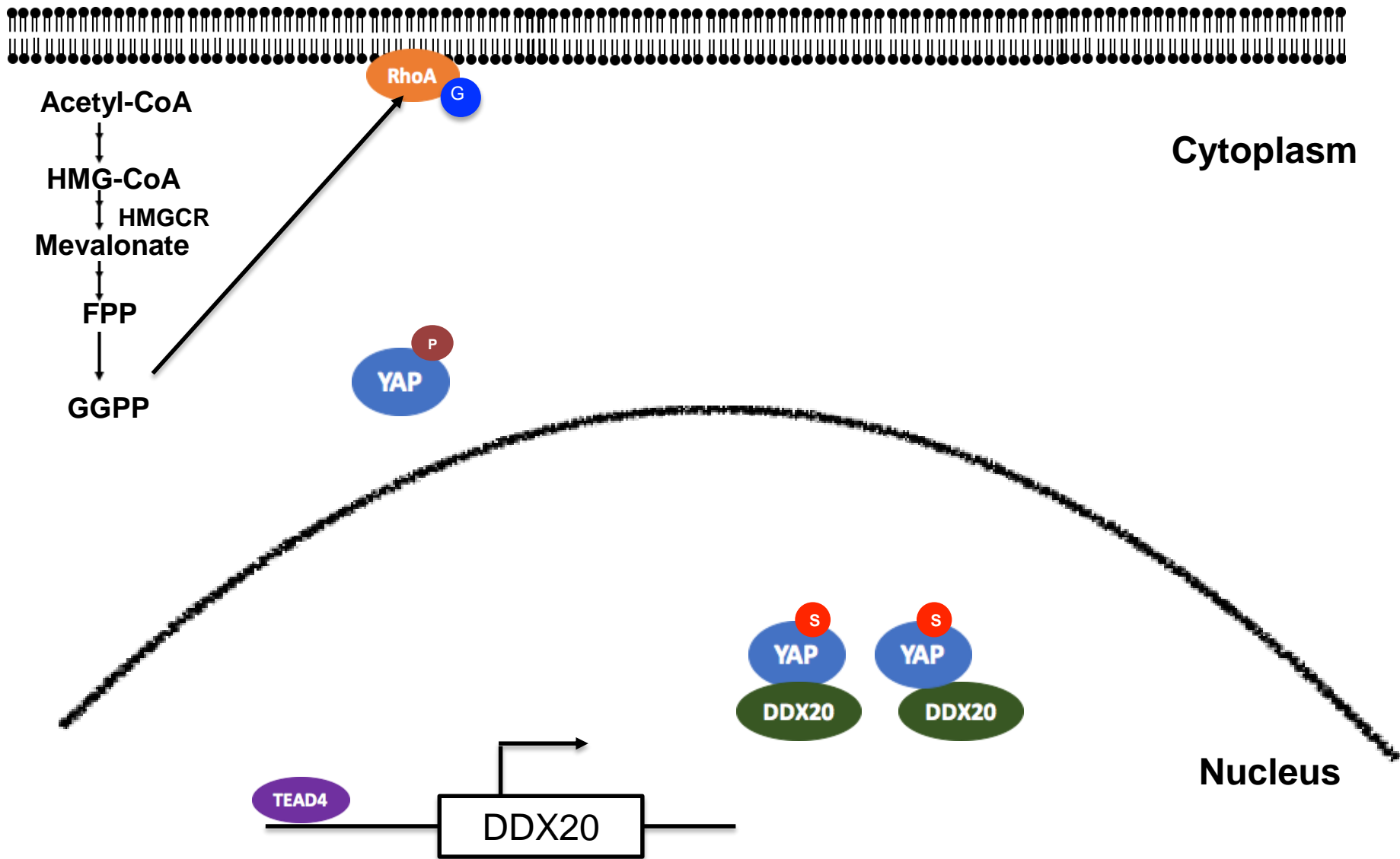


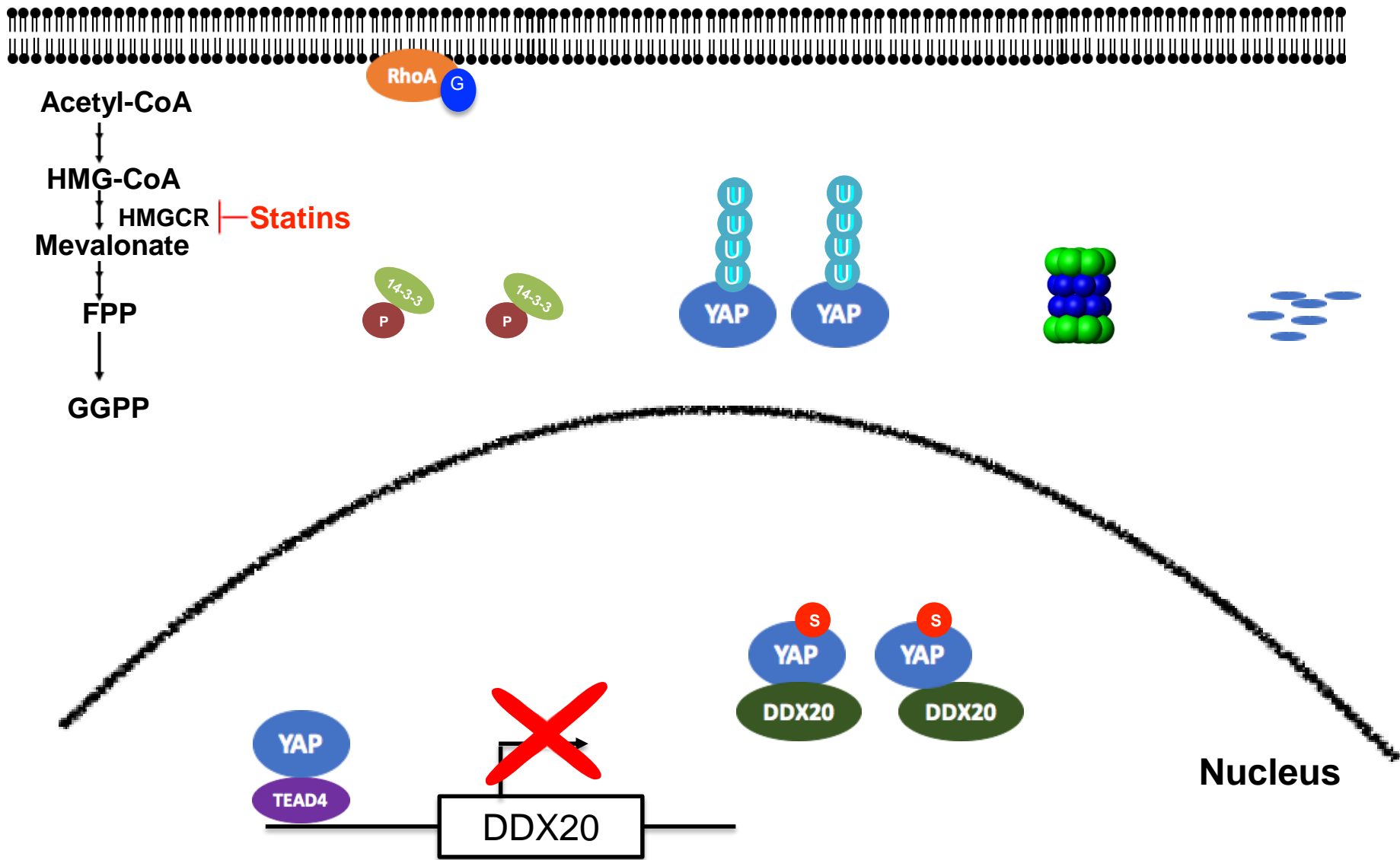
Question 6: What is the mechanism behind YAP regulation by DDX20?

DDX20 regulates SUMOylation of YAP



*: non-specific bands







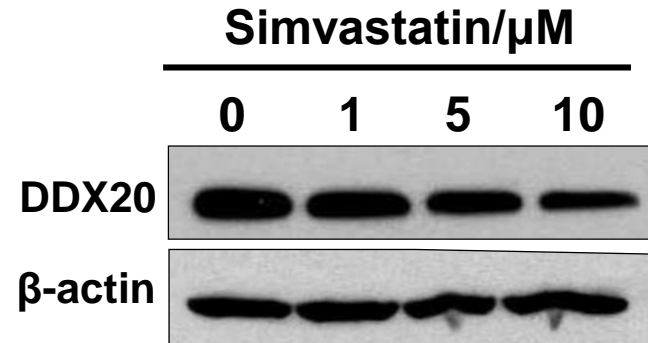
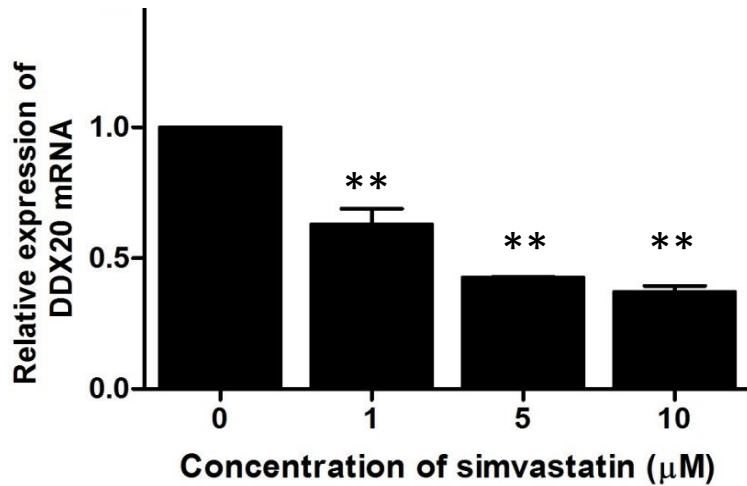
Thank You



Simvastatin downregulates DDX20 in TNBC cells in a dose-dependent manner



MDA-MB-231



BT549

