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NDRG2, a New Estrogen-targeted Gene

Yan Li

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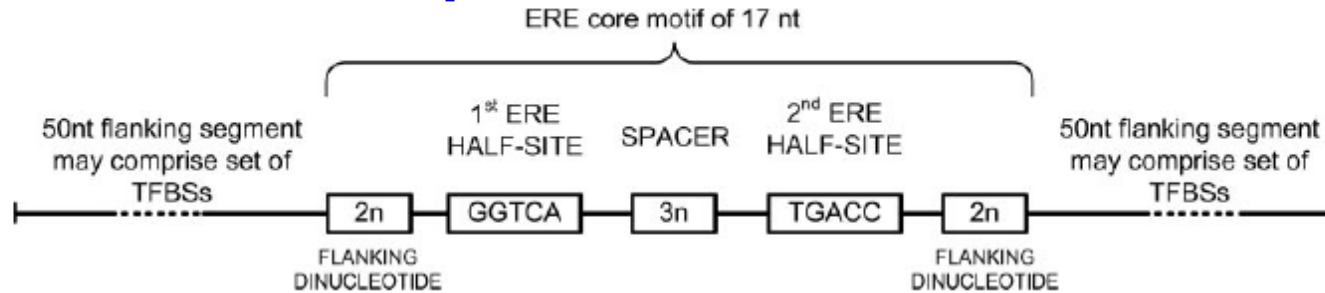


NDRG2

N-Myc Down-stream Regulated Gene 2

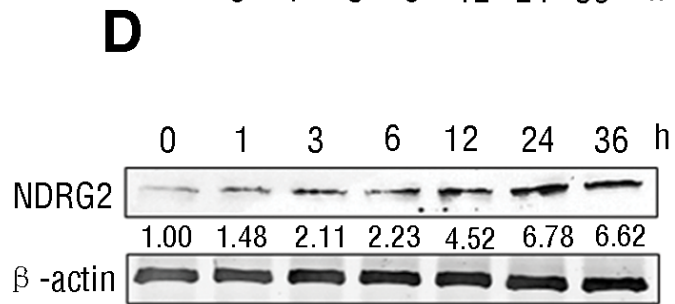
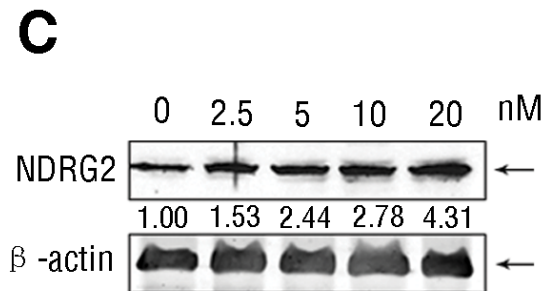
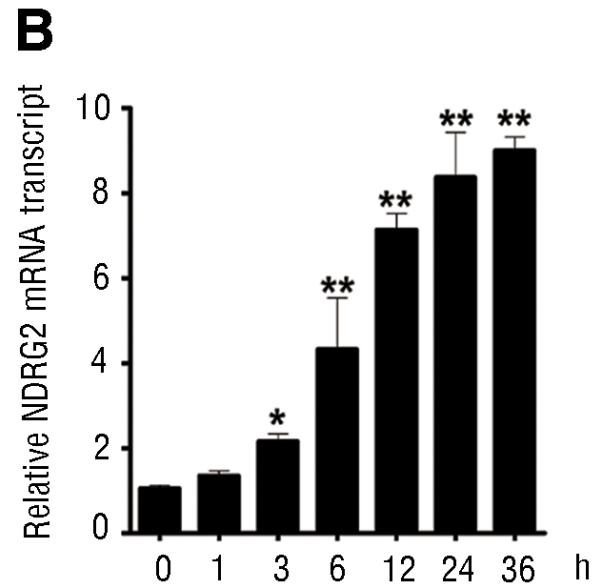
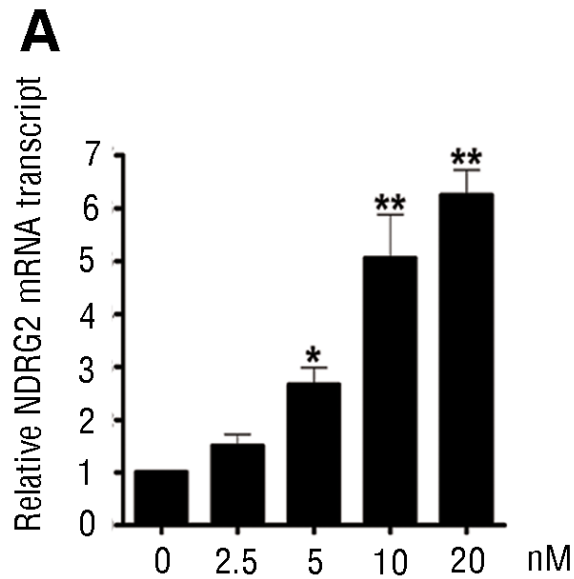
GenBank: AF159092

a putative ERE (estrogen response element) in the promoter of *NDRG2*



GAGCTGCCCTGACATGGAAGAACCATATCTTAGGGGAGAACCAGCCTTACTTCTGCCTGCAGCAGGCTGGGTGGGACCC
 CAAGGTCTAGGAAGCCAATGGATGTCAGTGGAAATTTCCATCTCCTGCCCTGCCCTGCGCCCTGCGTAGGCCCTTATC
 AGGTTCCCTCTGGTCAATCCTGACCCAGAGACGAATTTAGATGCTGGAACCTTCAGGTCCTTCCCTCCCCACTCCAAGT
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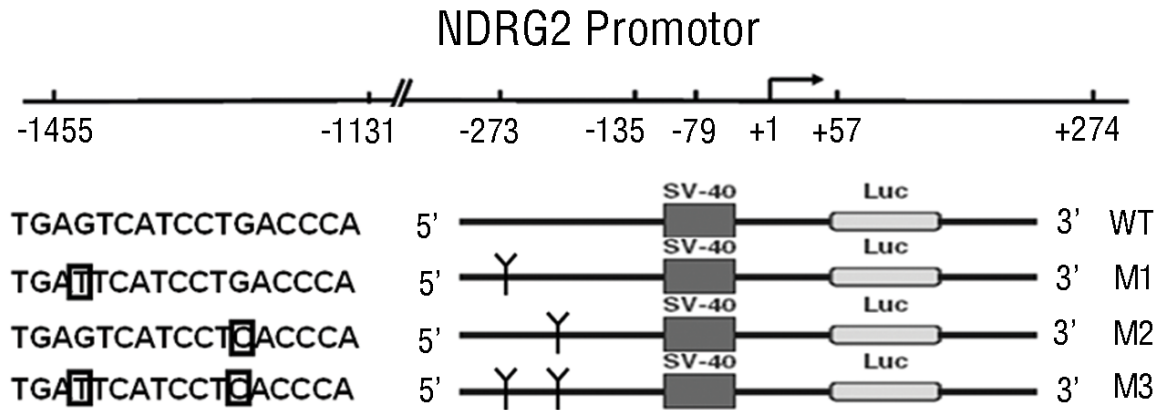
Estrogen Up-regulates Expression of NDRG2



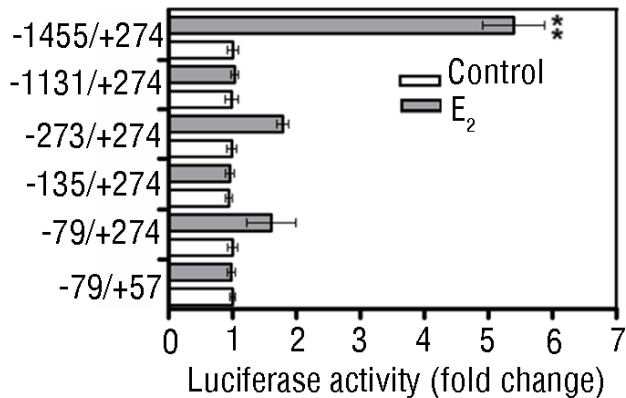
HeLa

Estrogen up-regulates expression of NDRG2 by binding to the putative ERE in *NDRG2* promoter

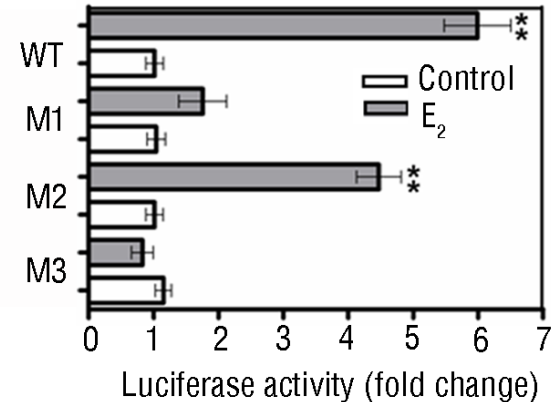
E



F

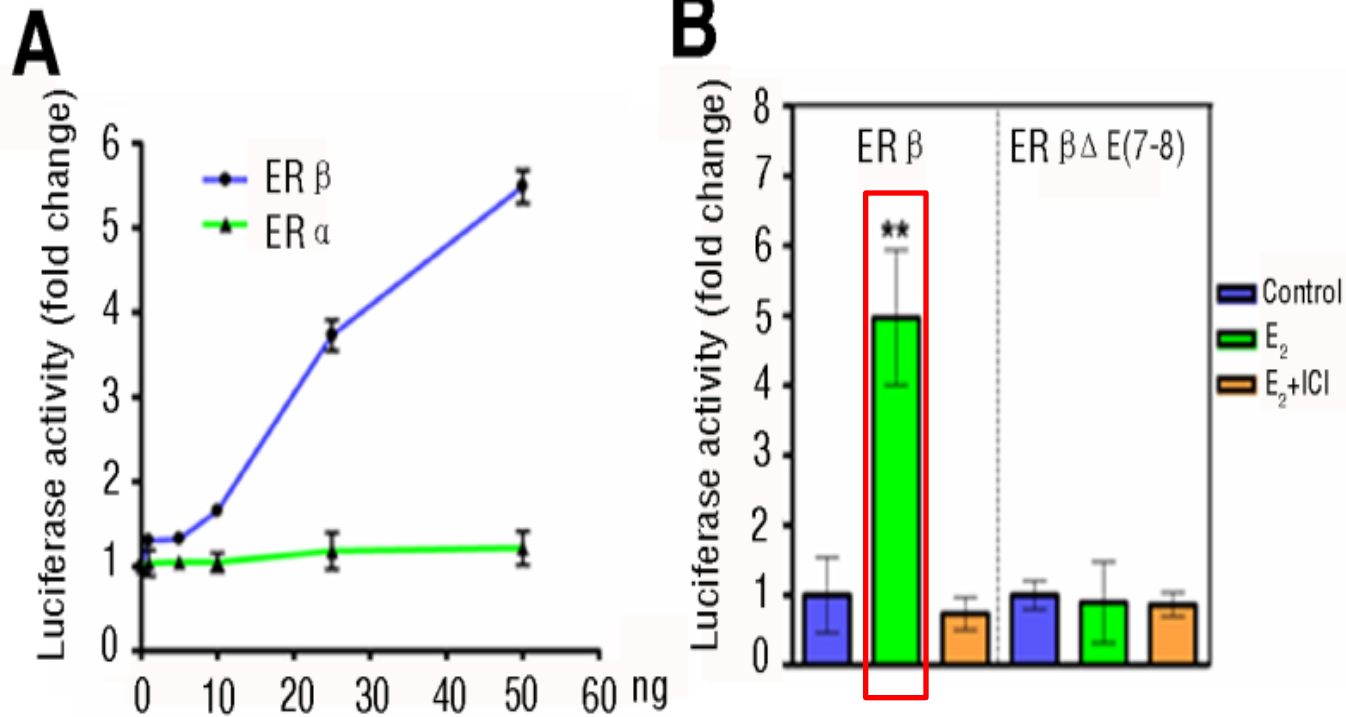


G



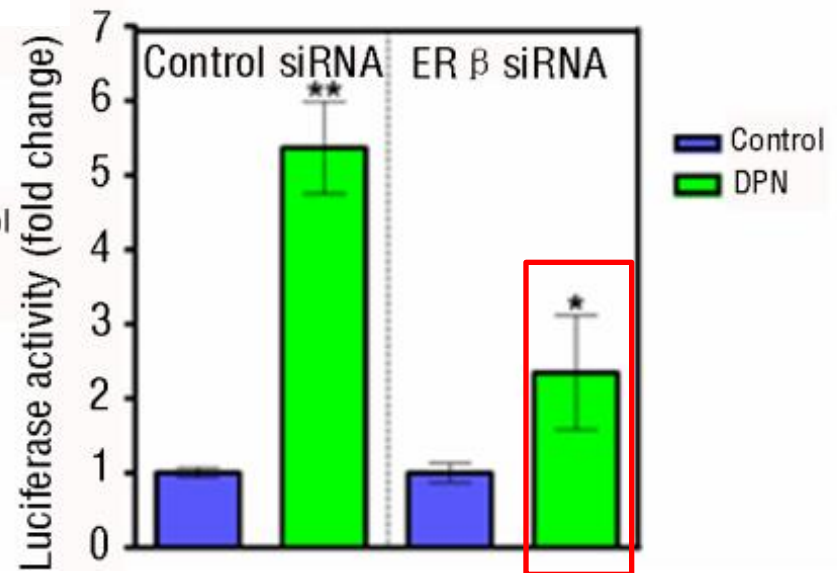
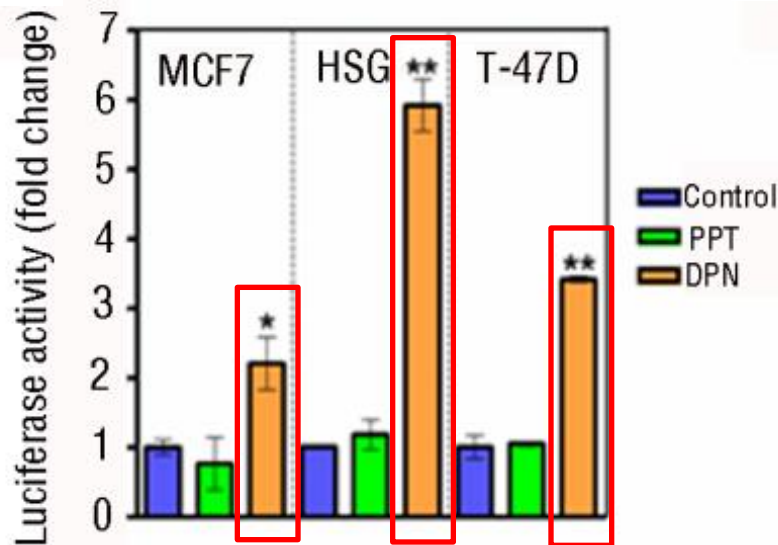
HeLa

ER β mediates the estrogen-induced NDRG2 transcriptional activation by binding to the ERE of *NDRG2* promoter



HEK293

ER β mediates the estrogen-induced NDRG2 transcriptional activation by binding to the ERE of *NDRG2* promoter

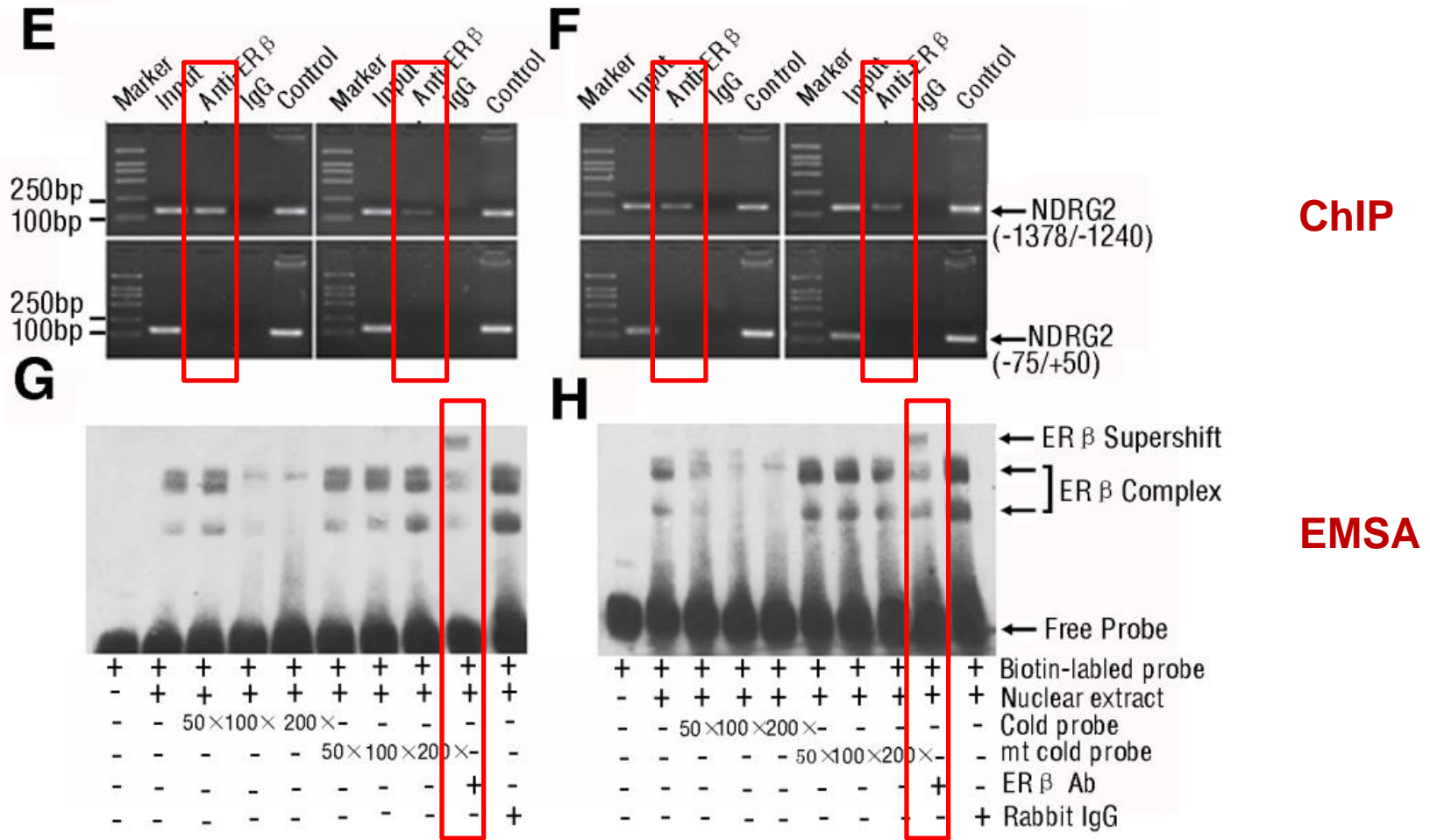


HSG

ER β mediates the estrogen-induced NDRG2 transcriptional activation by binding to the ERE of *NDRG2* promoter

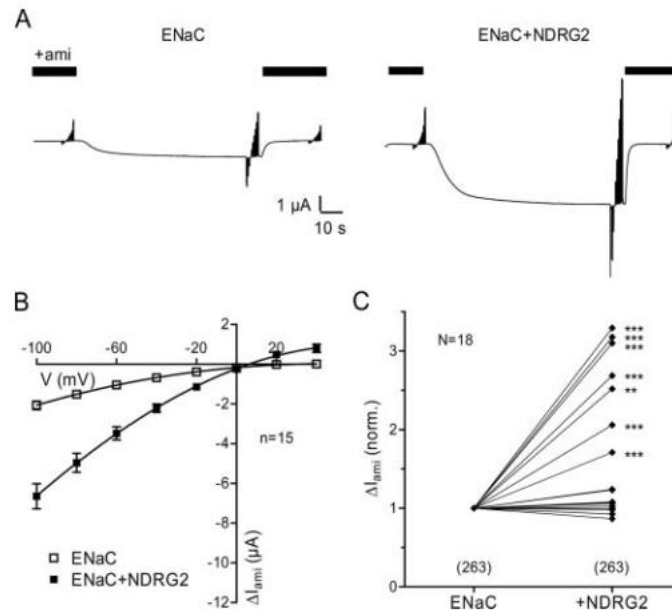
HSG

T-47D



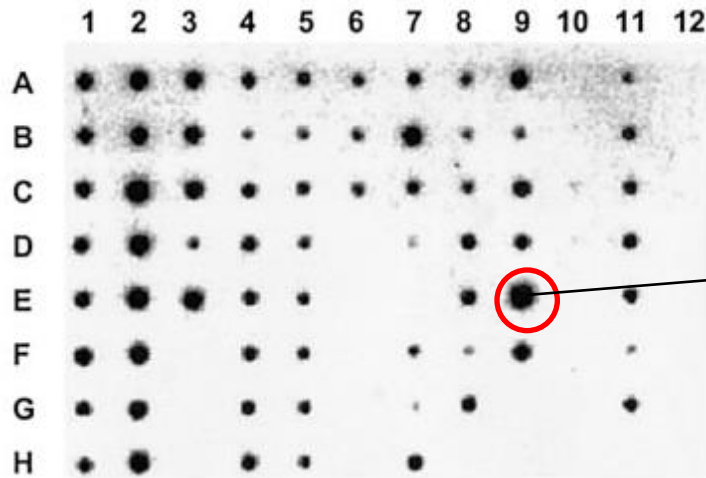
The functions of NDRG2

- 1. Proliferation and differentiation
- 2. Cell stress response
- 3. **Na⁺ transport**



ENaC: epithelial amiloride-sensitive sodium channel

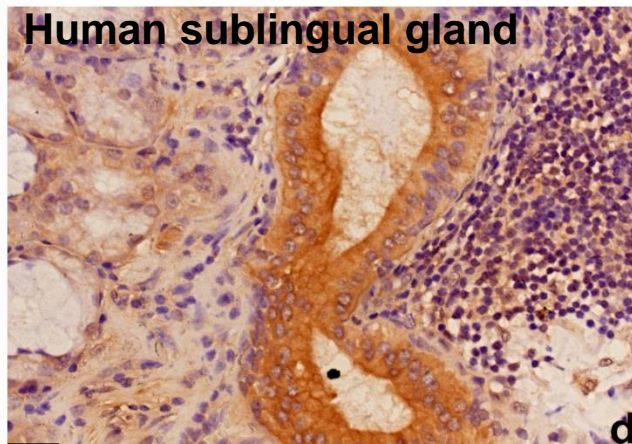
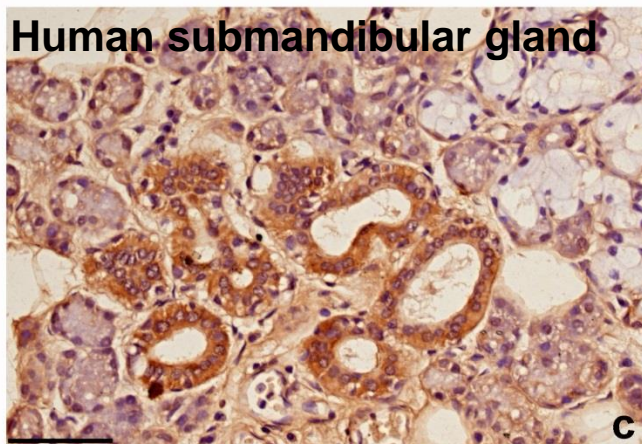
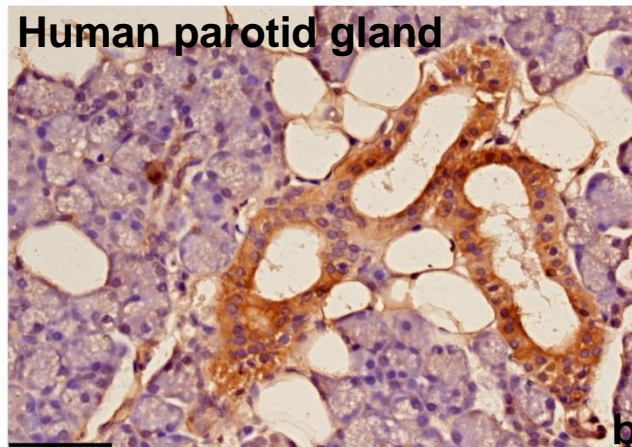
Analysis of NDRG2 distribution (Tissue RNA dot hybridization)



whole brain	cerebellum, left	substantia nigra	heart	oesophagus	colon, transverse	kidney	lung	liver	leukemia, HL-60	fetal brain	yeast total RNA
cerebral cortex	cerebellum, right	nucleus accumbens	aorta	stomach	colon, descending	skeletal muscle	placenta	pancreas	Hela S3	fetal heart	yeast tRNA
frontal lobe	corpus callosum	thalamus	atrium, left	duodenum	rectum	spleen	bladder	adrenal gland	leukemia, K-562	fetal kidney	<i>E. coli</i> rRNA
parietal lobe	amygdala	pituitary gland	atrium, right	jejunum		thymus	uterus	thyroid gland	leukemia, MOLT-4	fetal liver	<i>E. coli</i> DNA
occipital lobe	caudate nucleus	spinal cord	ventricle, left	ileum		peripheral blood leukocyte	prostate	salivary gland	Burkitt's lymphoma, Raji	fetal spleen	poly r(A)
temporal lobe	hippocampus		ventricle, right	ileocecum		lymph node	testis	mammary gland	Burkitt's lymphoma, Daudi	fetal thymus	human C β -1 DNA
paracentral gyrus of cerebral cortex	medulla oblongata		inter-ventricular septum	appendix		bone marrow	ovary		colorectal adenocarcinoma, SW480	fetal lung	human DNA 100 ng
pons	putamen		apex of the heart	colon, ascending		trachea			lung carcinoma, A549		human DNA 500 ng

Deng *et al.* *Int. J. Cancer.* 106, 342–347 (2003)

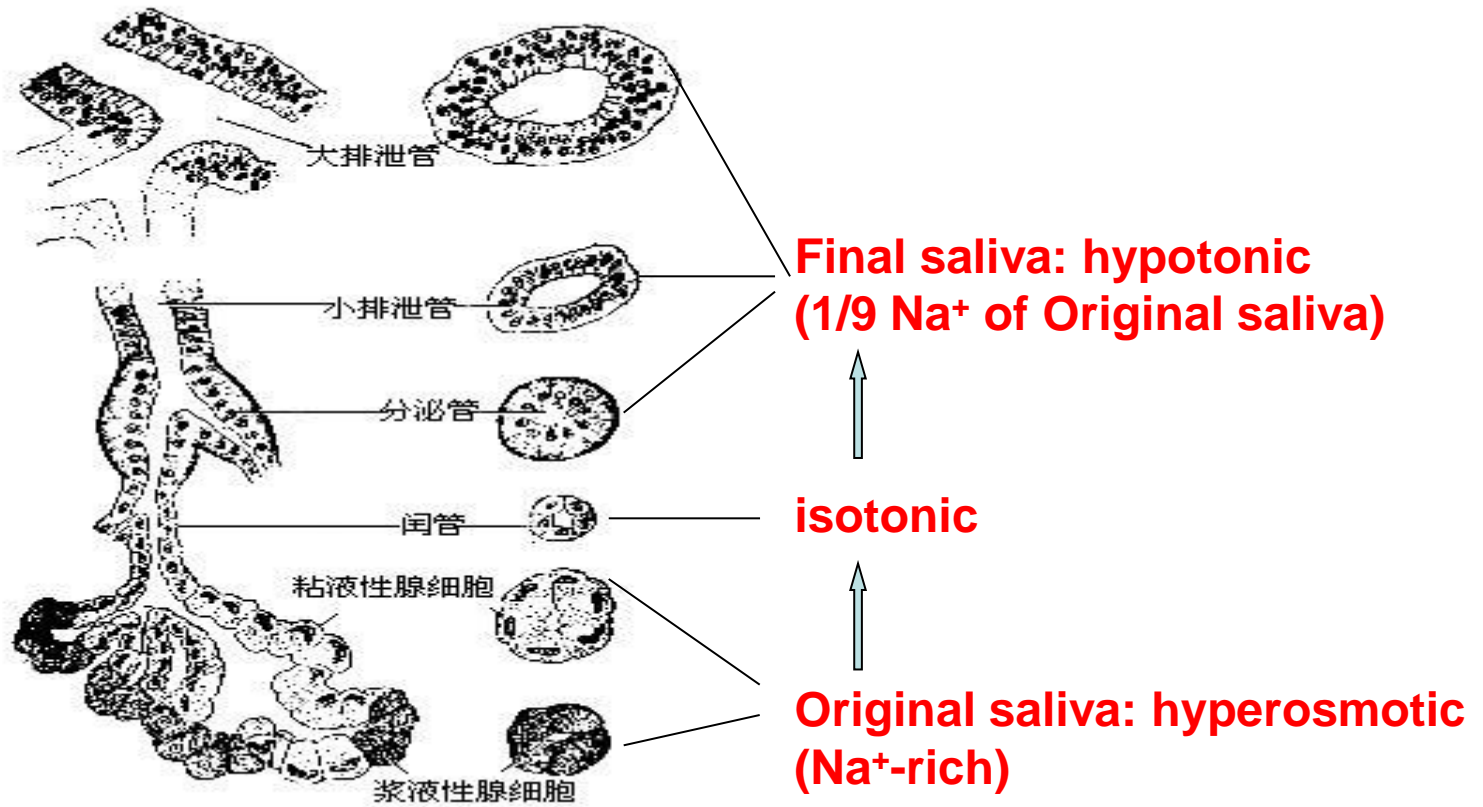
Immunohistochemistry analysis of NDRG2 expression in human and rat salivary glands



Bar = 50 μ m

The structure of the salivary glands and saliva secretion

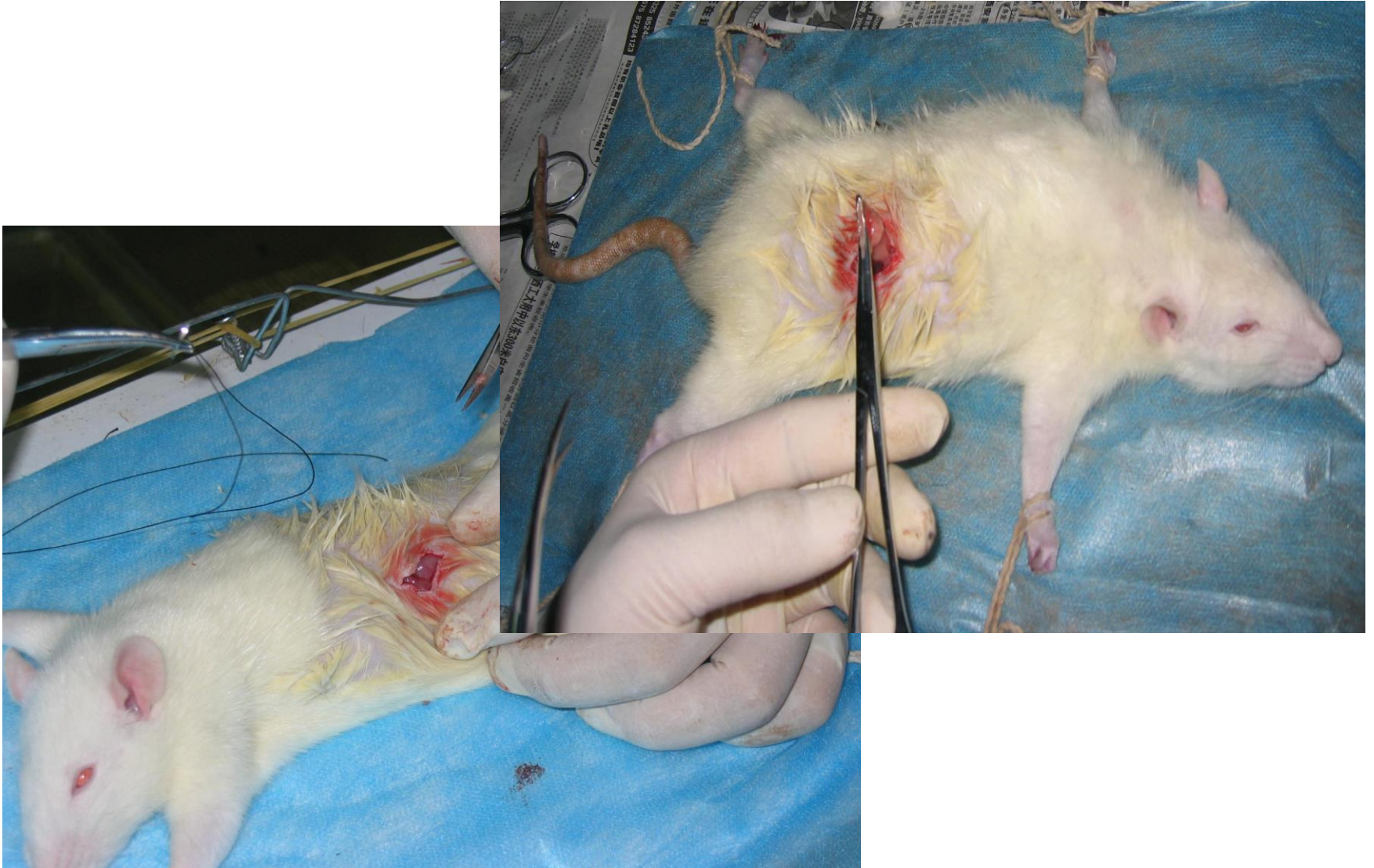
Acini cells + Ductal cells



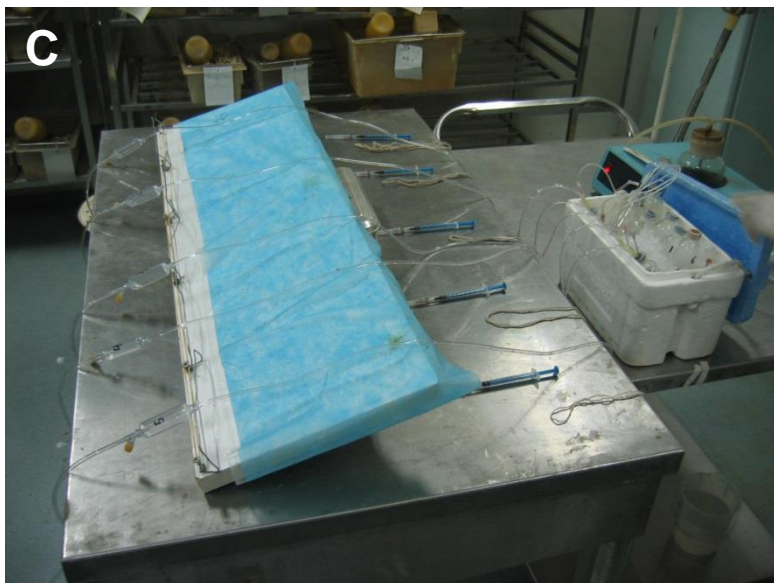
**The major oral symptoms of menopause are
xerostomia (oral dryness)**



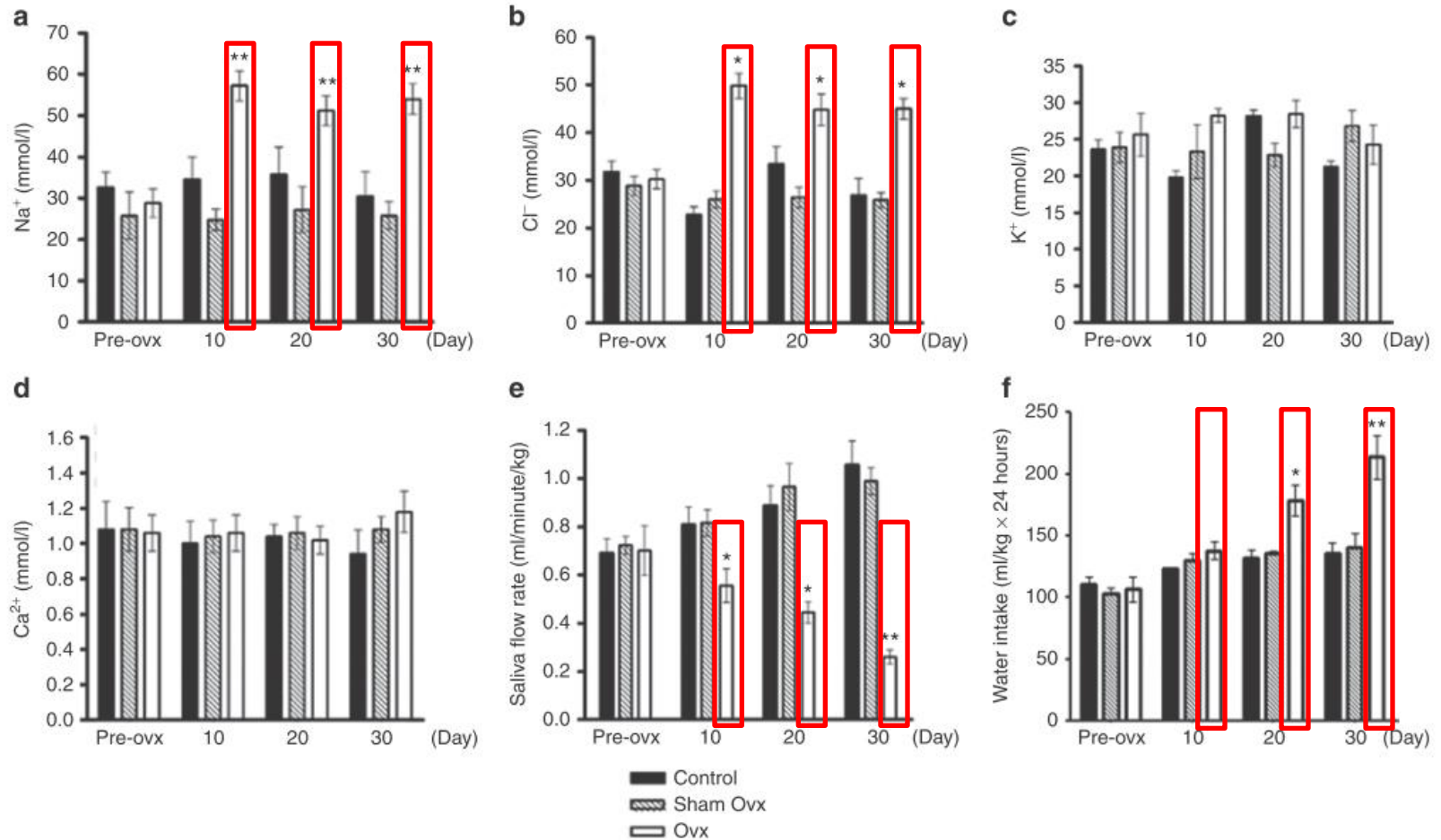
Ovariectomy mimics menopause



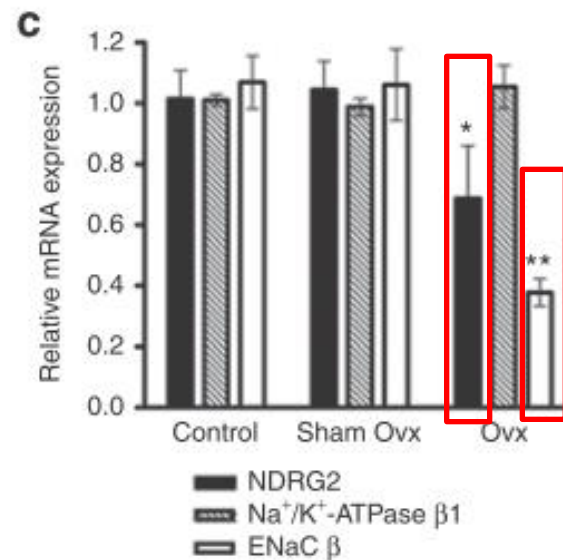
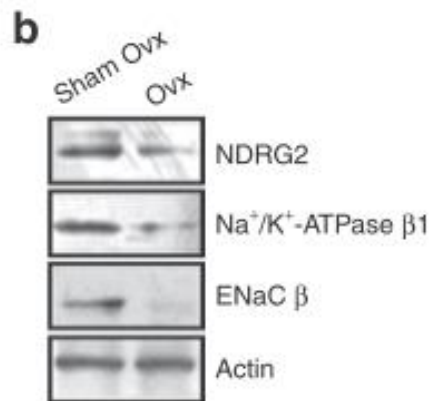
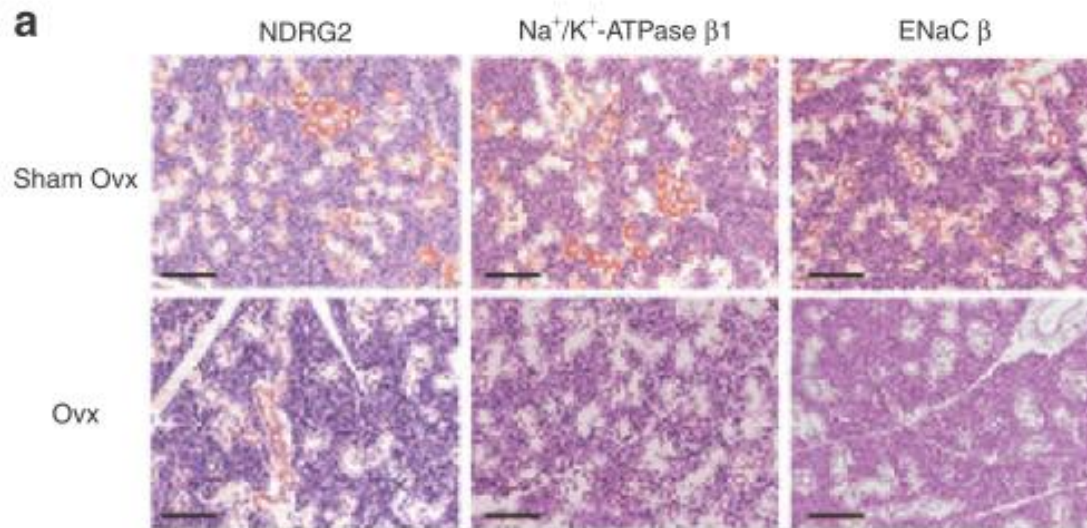
Saliva collection



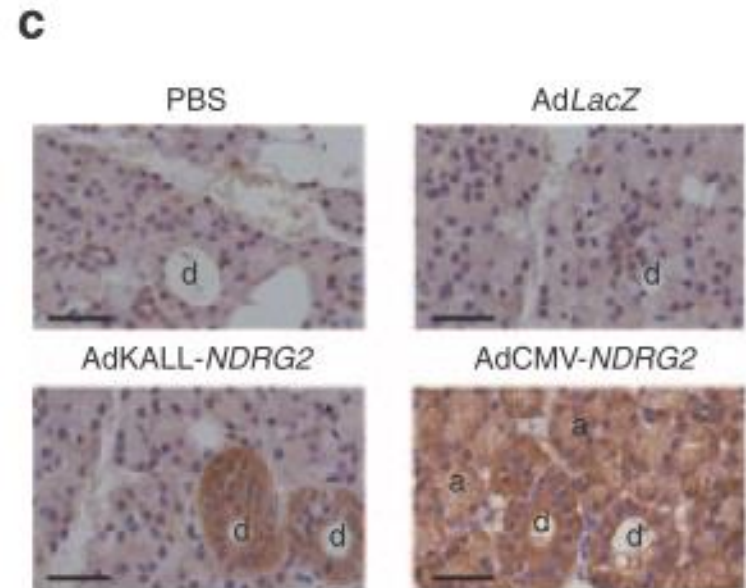
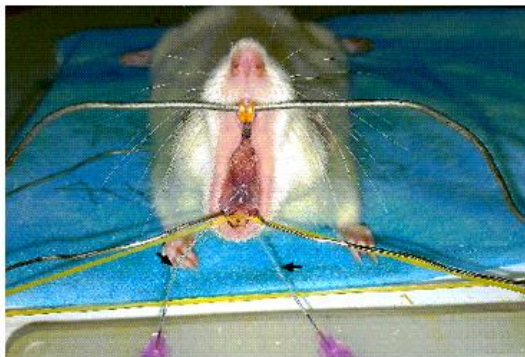
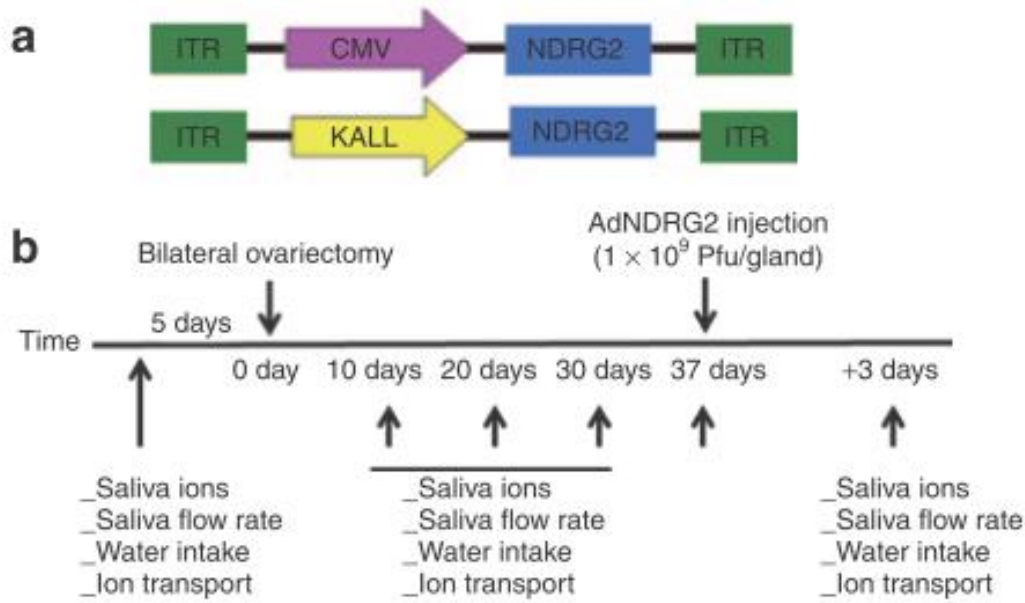
Sialaden hypofunction induced in salivary gland cells by ovariectomy (Ovx)



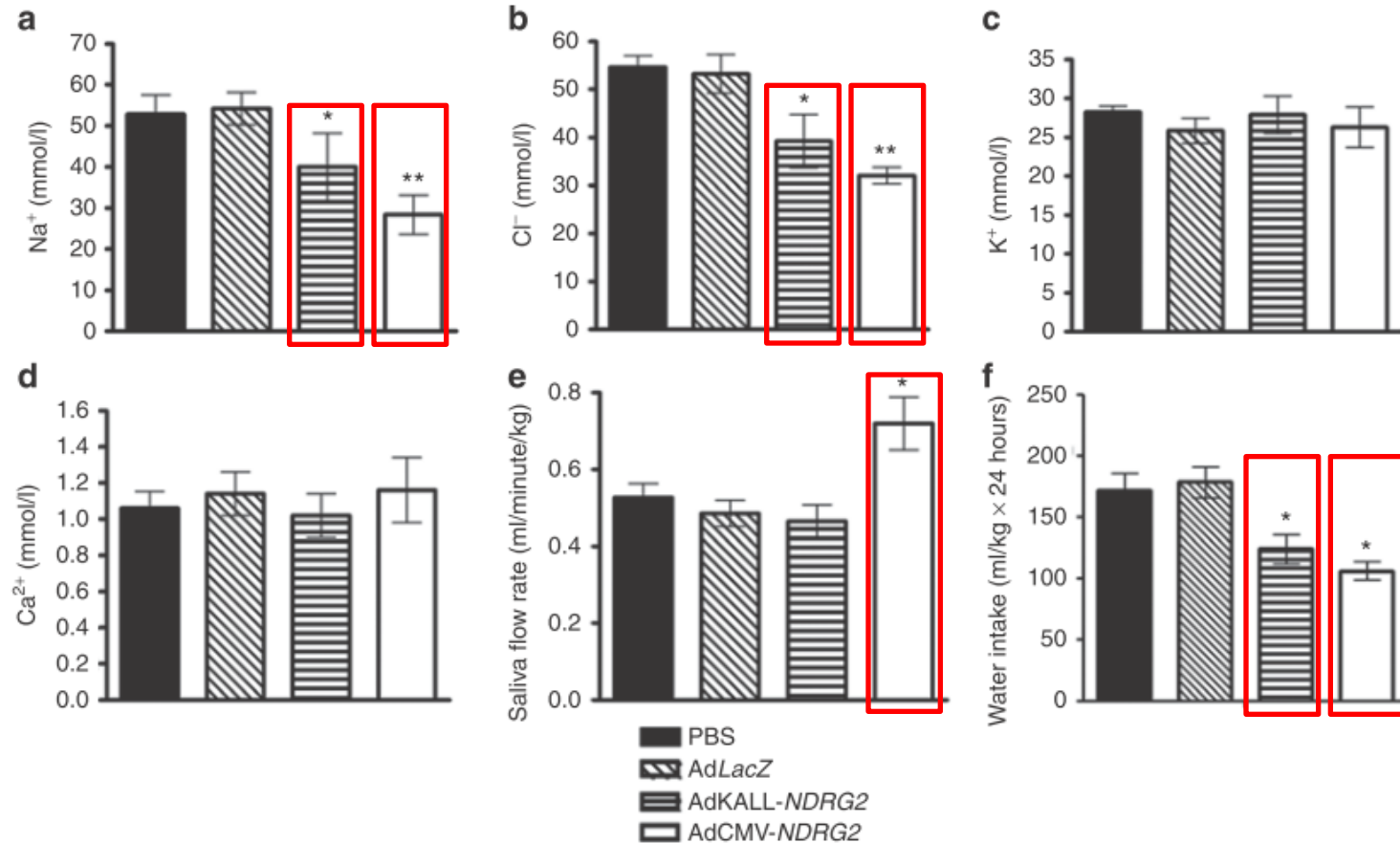
Estrogen deprivation is associated with Na⁺ transporters in the submandibular gland of Ovx-rats



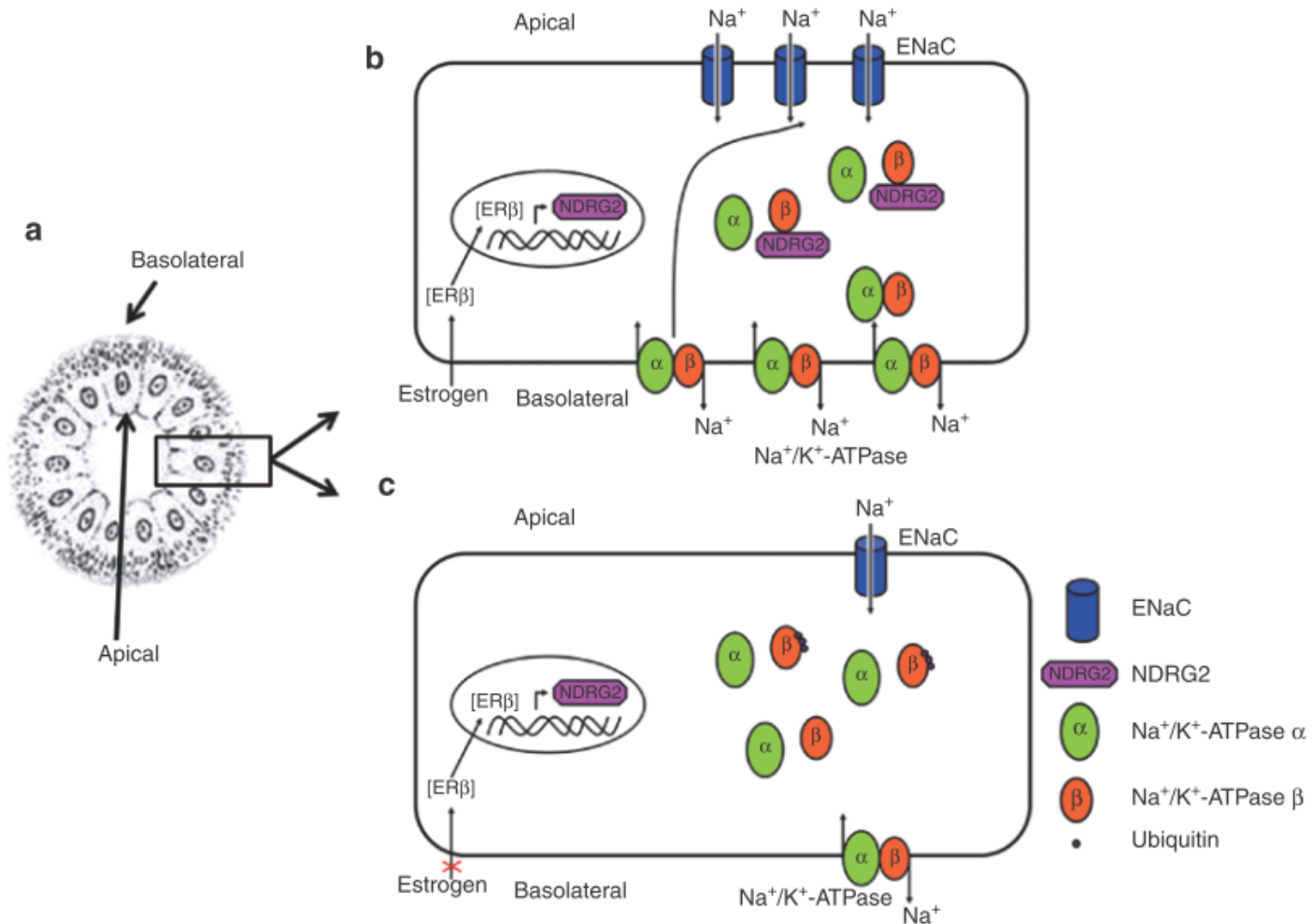
Ad-NDRG2 retrograde ductal administration mediated efficient gene delivery in the rat submandibular gland



Adenovirus-mediated submandibular gland delivery of NDRG2 improved sialaden hypofunction in Ovx-rats



Model for the mechanism of NDRG2 participation in estrogen-mediated Na^+ reabsorption in salivary gland ductal cells



Acknowledgments



Shaoqing Li
Jiandong Yang
Changhao Liu

Jian Zhang
Minggao Zhao
Wugang Hou

Changyu Zheng
Jan-Åke Gustafsson

NIH, Bethesda, MD, USA
Karolinska Institutet, Sweden

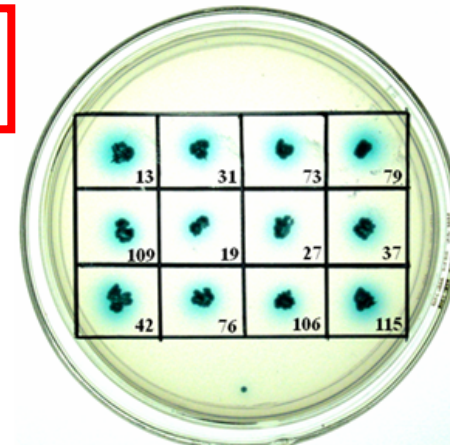
National Natural Science Foundation of China Grants 81100764, 81230043, 81202139, and 81371446

The molecules can interact with NDRG2 (yeast two-hybrid)

A

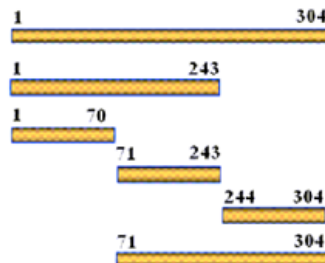
克隆编号	基因名称	插入片段大小 (bp)
13	Na ⁺ /K ⁺ ATPase β1 polypeptide (ATP1B1)	462
73		288
109		183
31	cannabinoid receptor interacting protein 1 (CNRIP1)	414
79		408
19	SH3-domain GRB2-like interacting protein 1 (SGIP1)	297
27	unc-84 homolog B (UNC84B)	270
37	Poly (rC) binding protein 1 (PCBP1)	897
42	calpain 7 (CAPN7)	543
76	procollagen C-endopeptidase enhancer (PCOLCE)	444
106	lipoprotein lipase (LPL)	372
115	chitinase domain containing 1 (CHID1)	990

B



C

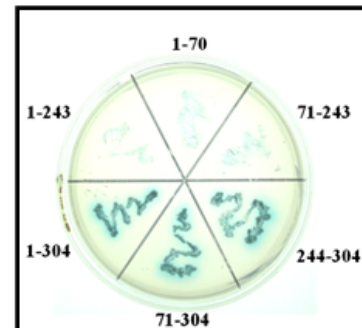
Na⁺/K⁺-ATPase β1 constructs



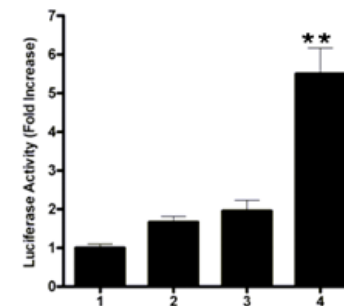
NDRG2 binding

+
-
-
-
+
+

D



E



Na⁺/K⁺-ATPase β1

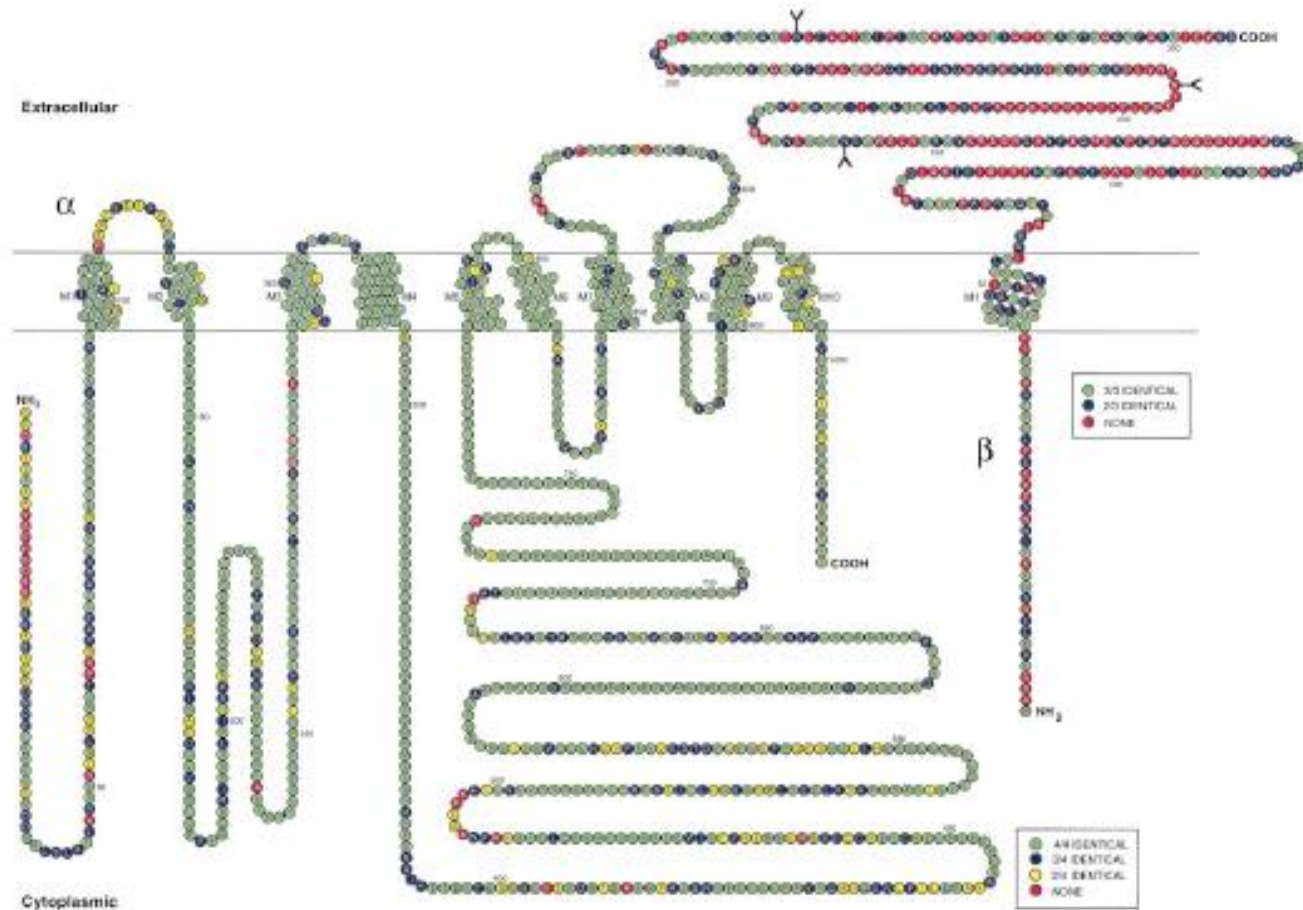
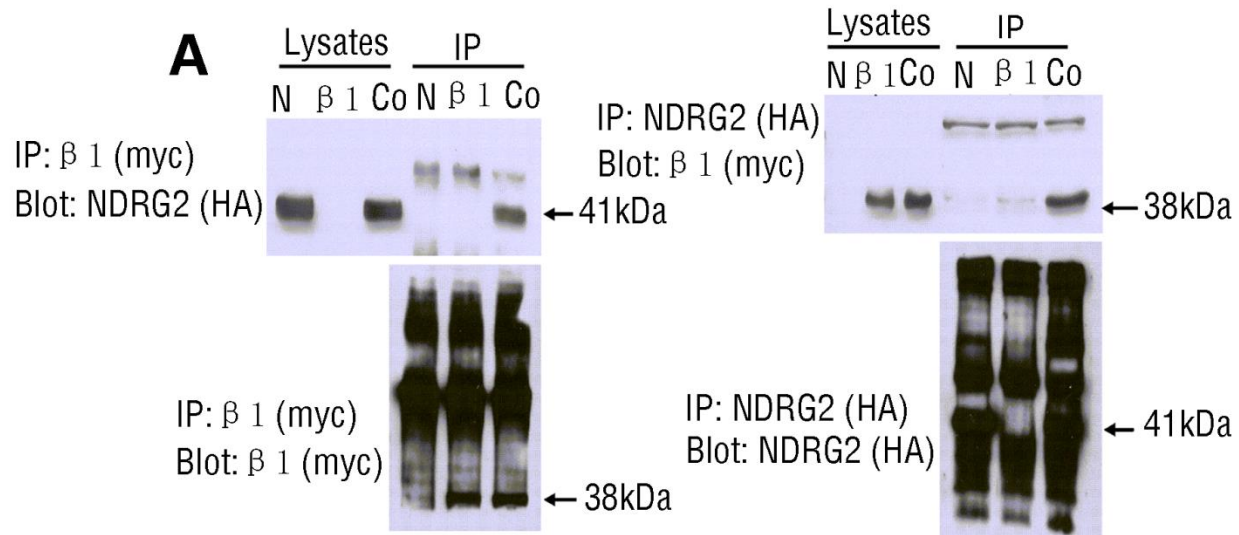
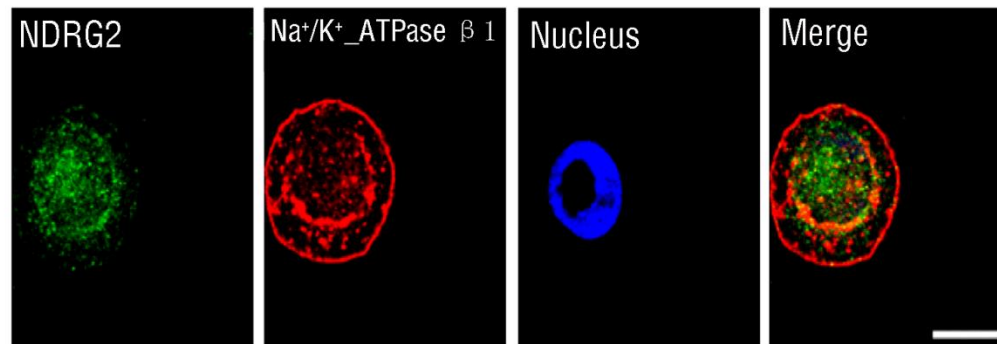


Fig. 1. Scheme of the membrane topology of the α - and β -isoforms of the Na⁺/K⁺-ATPase. Sequences of rat α 1- and β 1 isoforms are shown. Residues are colored to indicate the amino acid homology among the different α -isoforms (α 1, α 2, α 3, and α 4) or β -isoforms (β 1, β 2, and β 3).

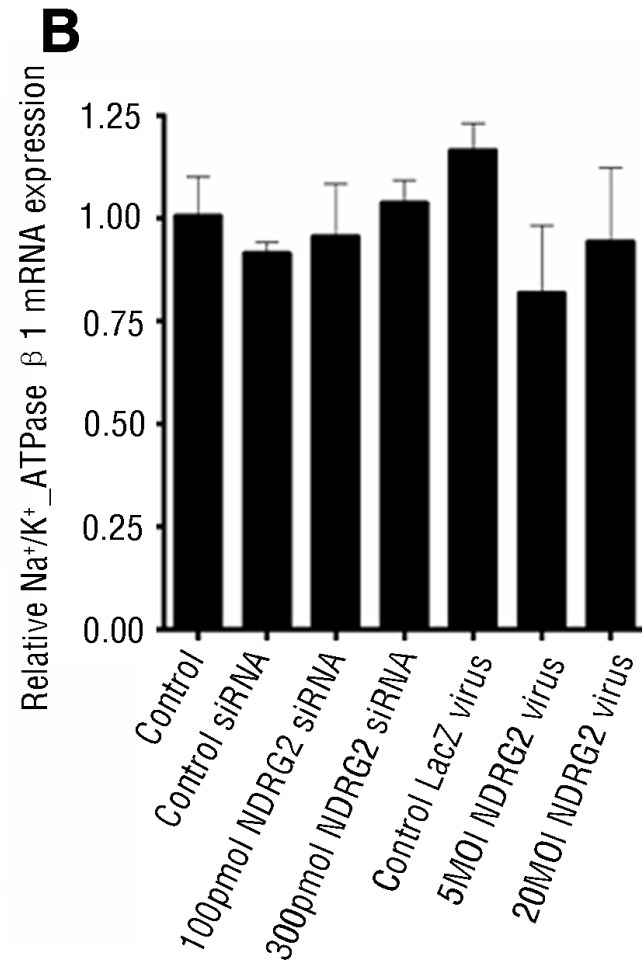
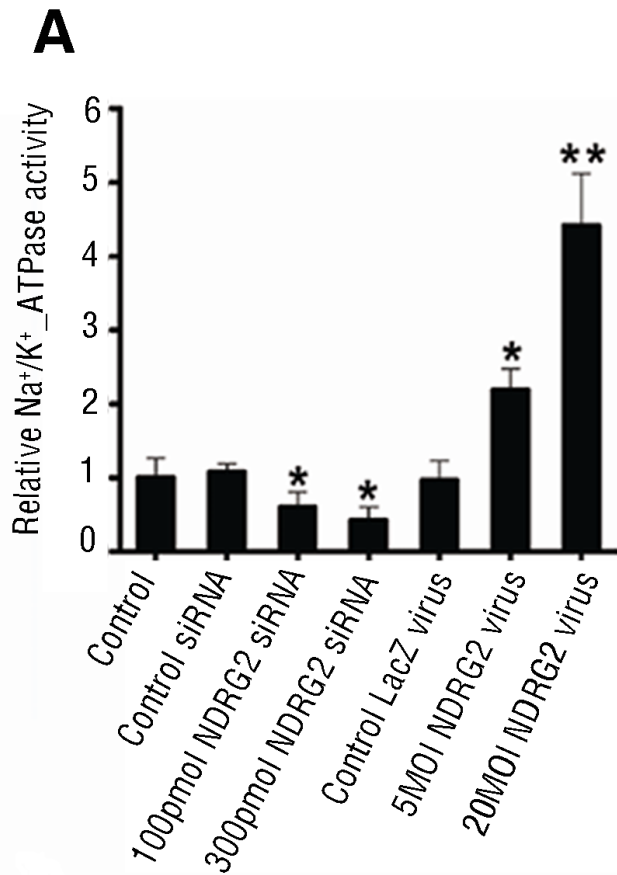
NDRG2 and Na⁺/K⁺-ATPase β 1 Interact



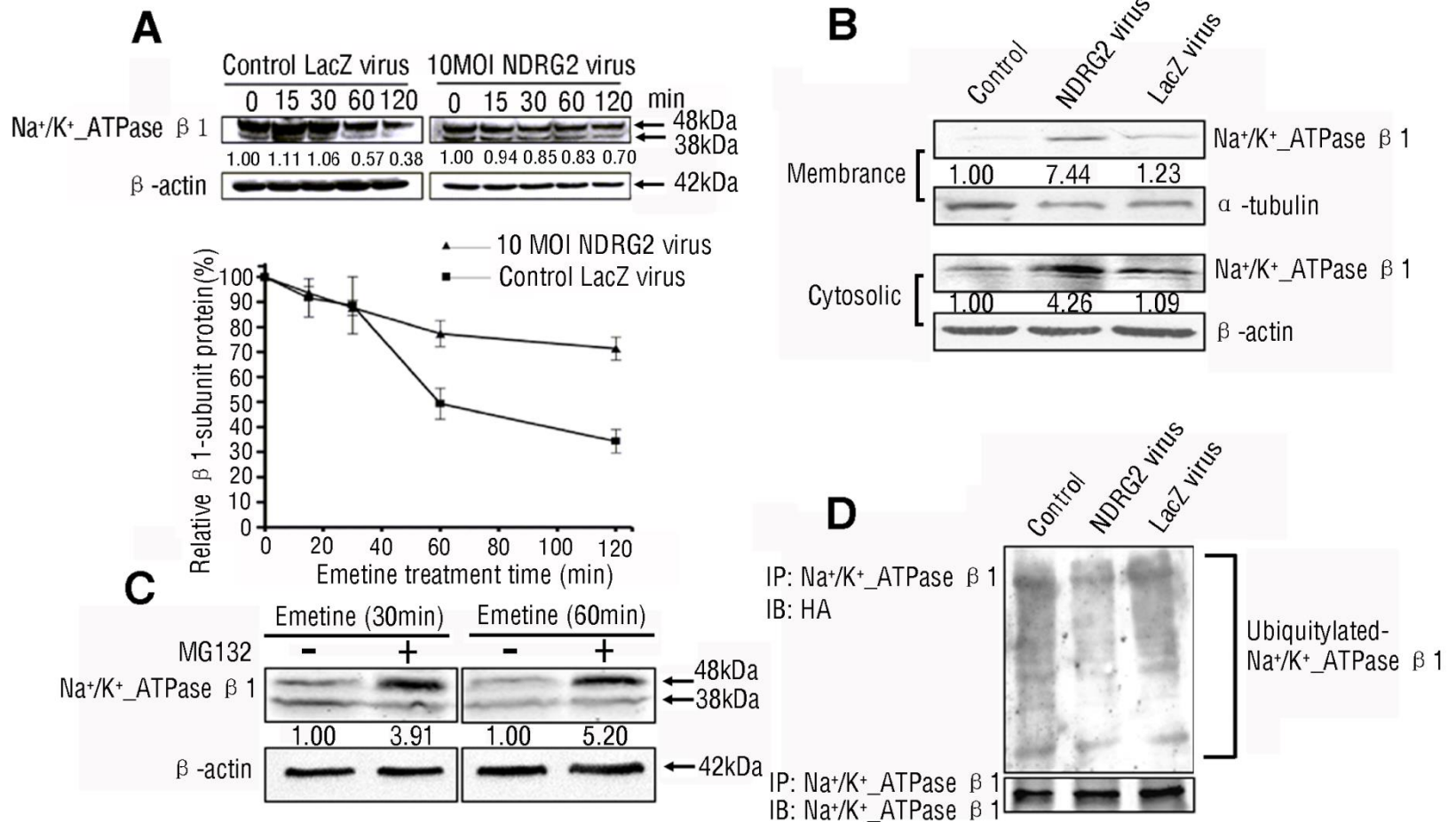
B



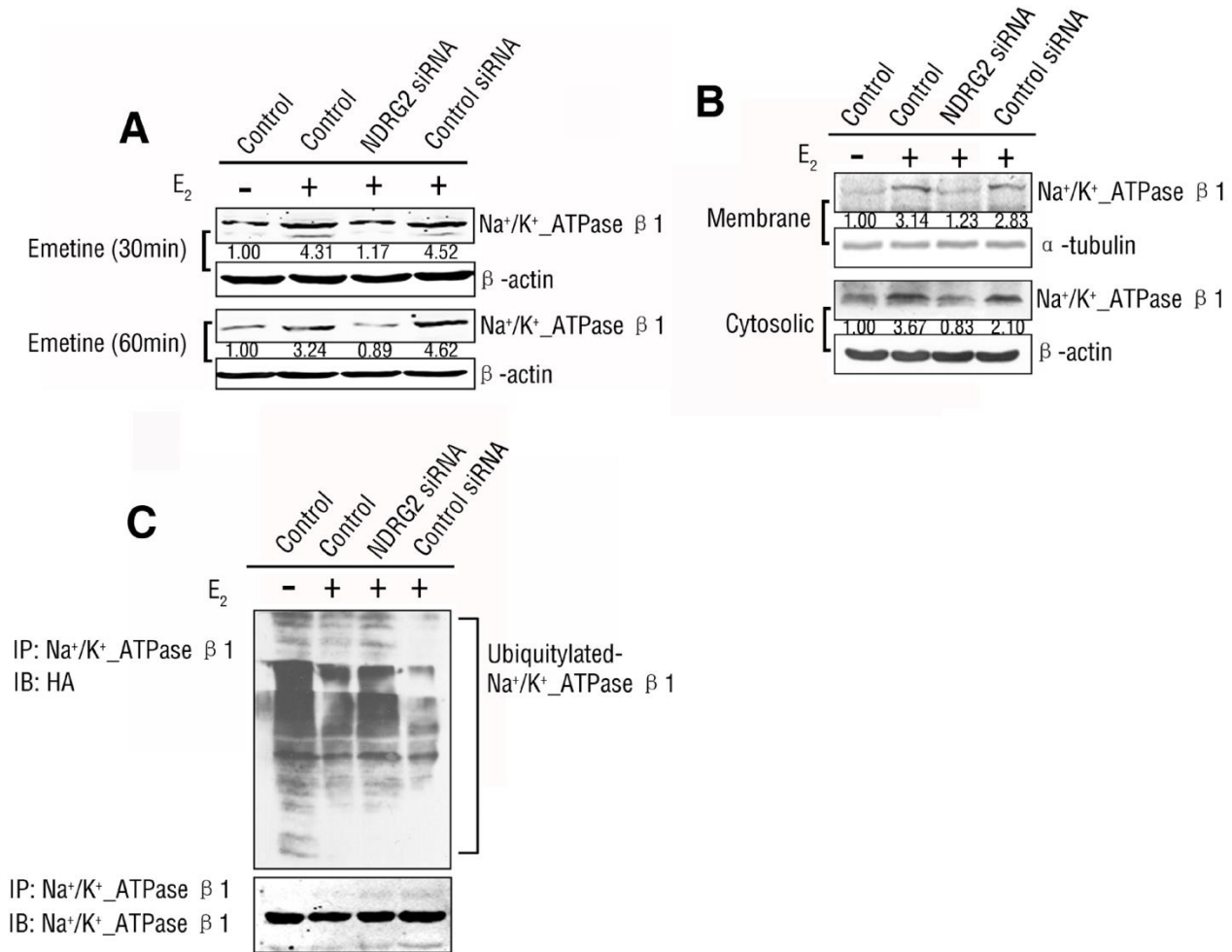
NDRG2 Upregulates Na⁺/K⁺-ATPase Activity



NDRG2 Inhibits the Ubiquitination of $\beta 1$ -subunit



NDRG2 is involved in estrogen-mediated Na⁺/K⁺-ATPase regulation



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