

Novel Regulatory Role of BRCA2 in Endothelial Cell Function and Survival Following Genotoxic Stress

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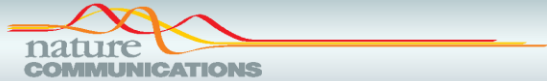


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Background-I

- Mutations in the “tumor suppressors” BRCA1 and BRCA2 are highly penetrant for increased risk of breast and ovarian cancers
- BRCA1 and BRCA2 are key members of the genome surveillance complex, and exert multiple effects on cellular processes involved in DNA damage/repair and cell-cycle regulation
- Homozygous deletion of *BRCA1* or *BRCA2* leads to embryonic lethality and thereby play non-redundant roles
- DNA damage is not only a critical component of cancer syndromes but has also been shown to play an important role in cardiovascular diseases

Background-II



ARTICLE

Received 10 Aug 2011 | Accepted 16 Nov 2011 | Published 20 Dec 2011

DOI: 10.1038/ncomms1601

BRCA1 is an essential regulator of heart function and survival following myocardial infarction

Praphulla C. Shukla^{1,2,*}, Krishna K. Singh^{1,2,*}, Adrian Quan^{1,2}, Mohammed Al-Omran^{2,3}, Hwee Teoh^{1,2}, Fina Lovren^{1,2}, Liu Cao⁴, Ilsa I. Rovira⁵, Yi Pan^{1,2}, Christine Brezden-Masley^{2,6,7}, Bobby Yanagawa^{1,8}, Aanika Gupta⁹, Chu-Xia Deng¹⁰, John G. Coles^{8,11}, Howard Leong-Poi^{2,7,12}, William L. Stanford¹³, Thomas G. Parker^{2,7,12}, Michael D. Schneider¹⁴, Toren Finkel⁵ & Subodh Verma^{1,2,8}

Gene Therapy (2012) 1–11

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www.nature.com/gt



ORIGINAL ARTICLE

BRCA1 gene therapy reduces systemic inflammatory response and multiple organ failure and improves survival in experimental sepsis

H Teoh^{1,2,3,4}, A Quan^{1,3,4}, AK Creighton^{1,4}, KW Annie Bang⁵, KK Singh^{1,3,4}, PC Shukla^{1,3,4}, N Gupta⁶, Y Pan^{1,4}, F Lovren^{1,3,4}, H Leong-Poi^{4,7}, M Al-Omran^{4,8} and S Verma^{1,2,4}

BRCA1 is a Novel Regulator of Endothelial Function and Atherosclerosis. *J Thorac Cardiovasc Surg (Submitted)*

Krishna K. Singh, Praphulla C. Shukla, Adrian Quan, Mohammed Al-Omran, Fina Lovren, Yi Pan, Christine Brezden-Masley, William L. Stanford, Hwee Teoh, Subodh Verma

Background-III

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 9, pp. 6604–6614, February 24, 2012
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BRCA2 Protein Deficiency Exaggerates Doxorubicin-induced Cardiomyocyte Apoptosis and Cardiac Failure^{*,§}

Received for publication, August 10, 2011, and in revised form, November 28, 2011. Published, JBC Papers in Press, December 8, 2011, DOI 10.1074/jbc.M111.292664

Krishna K. Singh^{‡§1,2}, Praphulla C. Shukla^{‡§1,3}, Adrian Quan^{‡§}, Jean-François Desjardins^{§¶}, Fina Lovren^{‡§}, Yi Pan^{‡§}, Vinay Garg^{||}, Sumandeep Gosal^{‡§}, Ankit Garg^{||}, Paul E. Szmitko^{**4}, Michael D. Schneider^{‡‡}, Thomas G. Parker^{§¶**}, William L. Stanford^{§§}, Howard Leong-Poi^{§¶**}, Hwee Teoh^{‡§}, Mohammed Al-Omran^{§¶¶}, and Subodh Verma^{‡§|||§}

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Potential Excess Mortality in *BRCA1/2* Mutation Carriers beyond Breast, Ovarian, Prostate, and Pancreatic Cancers, and Melanoma

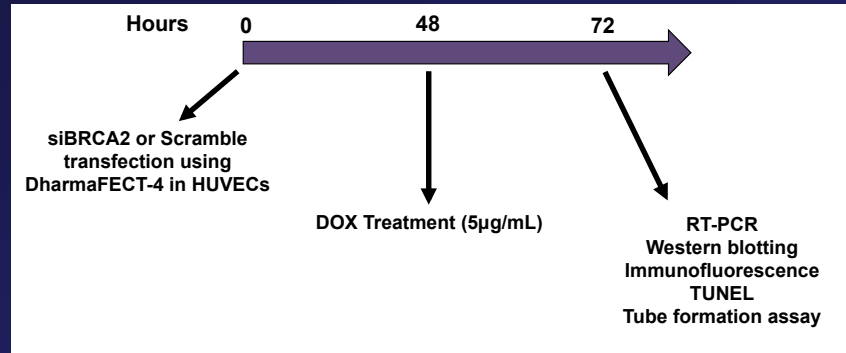
Phuong L. Mai^{1☯*}, Nilanjan Chatterjee^{2☯}, Patricia Hartge³, Margaret Tucker⁴, Lawrence Brody⁵, Jeffery P. Struwing⁵, Sholom Wacholder²

Hypothesis

BRCA2 is an essential regulator of endothelial function and apoptosis following genotoxic stress

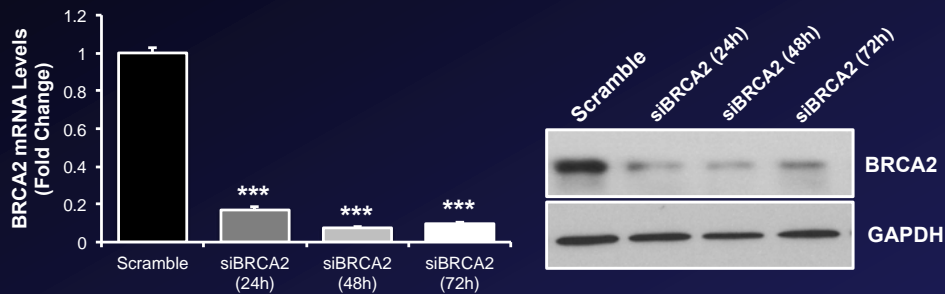
Methods

- *In Vitro* (HUVECs)
 - Loss-of-function (with siBRCA2)
 - Apoptosis
 - Endothelial function (tube formation, proliferation)
 - Mechanistic studies

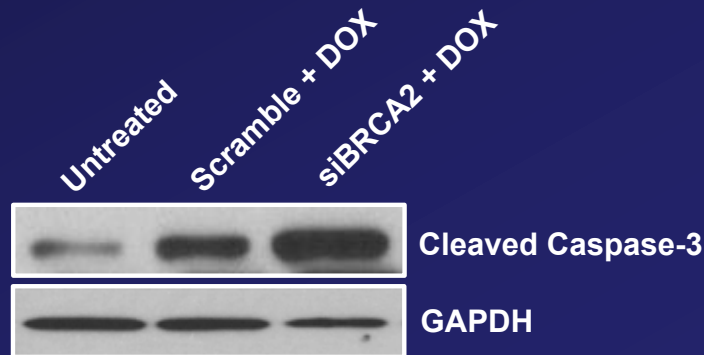
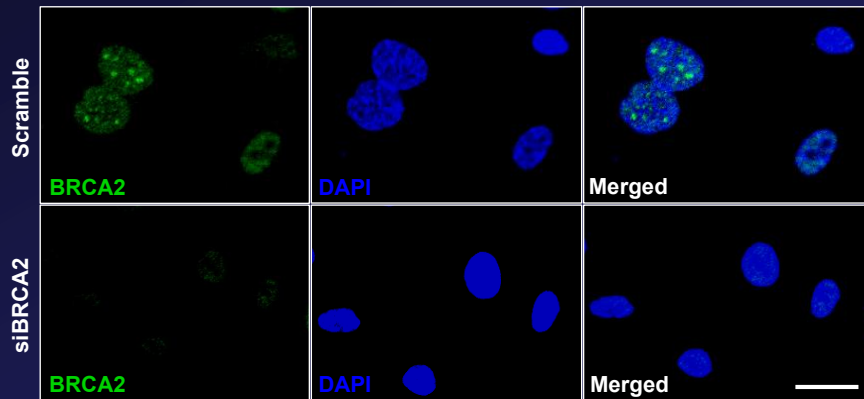
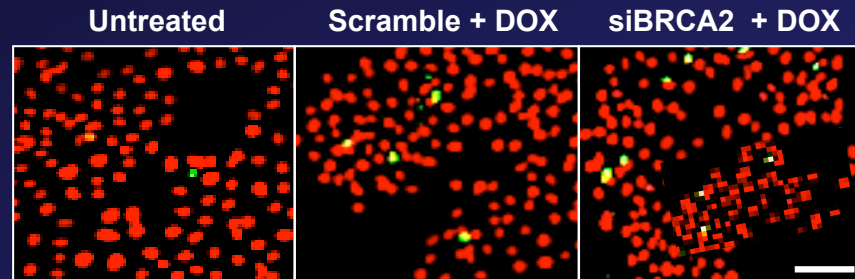


Loss-of-Function: Loss of BRCA2 Exacerbates Endothelial Cell Apoptosis

(A) Confirmation of gene silencing

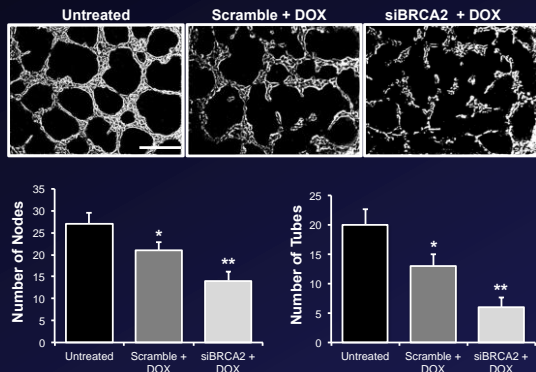


(B) Cell apoptosis

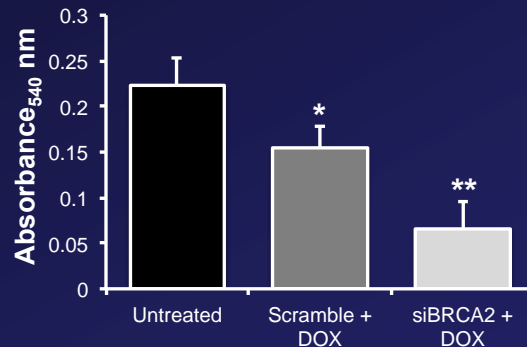


Loss-of-Function: Loss of BRCA2 Exacerbates Endothelial Dysfunction

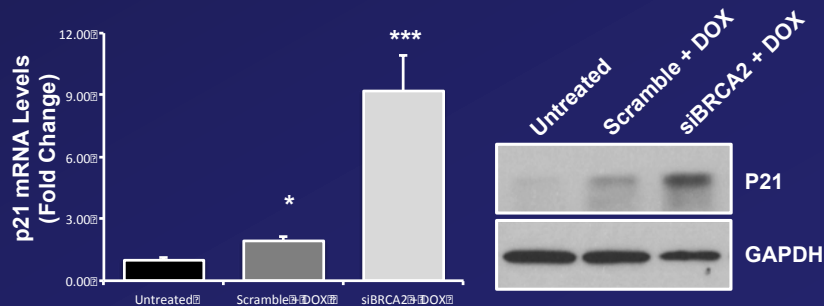
(A) Tube formation & quantification



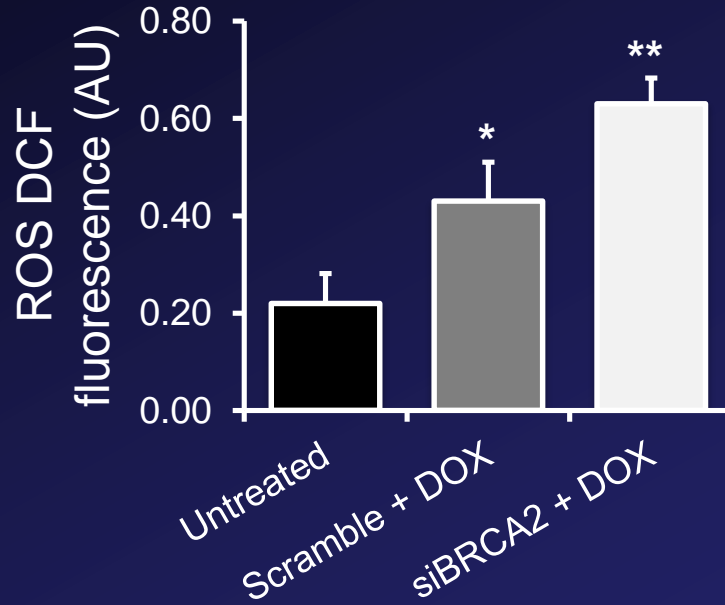
(B) Cell proliferation (MTT)



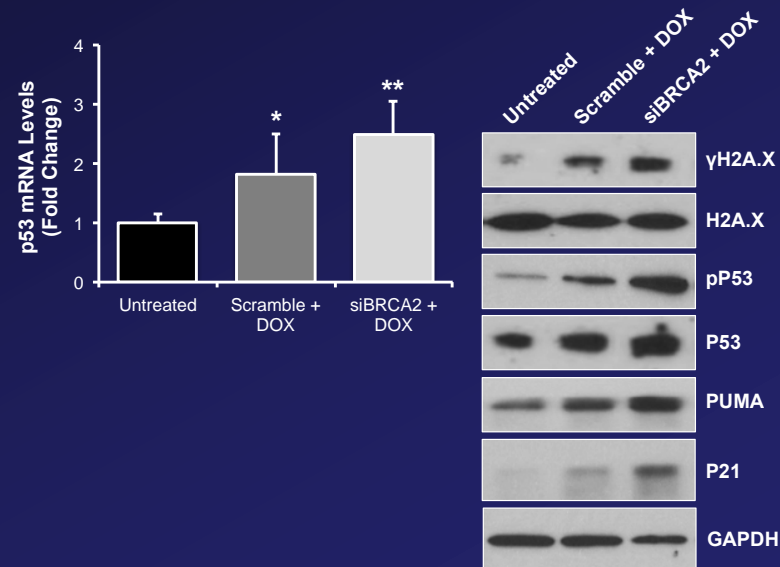
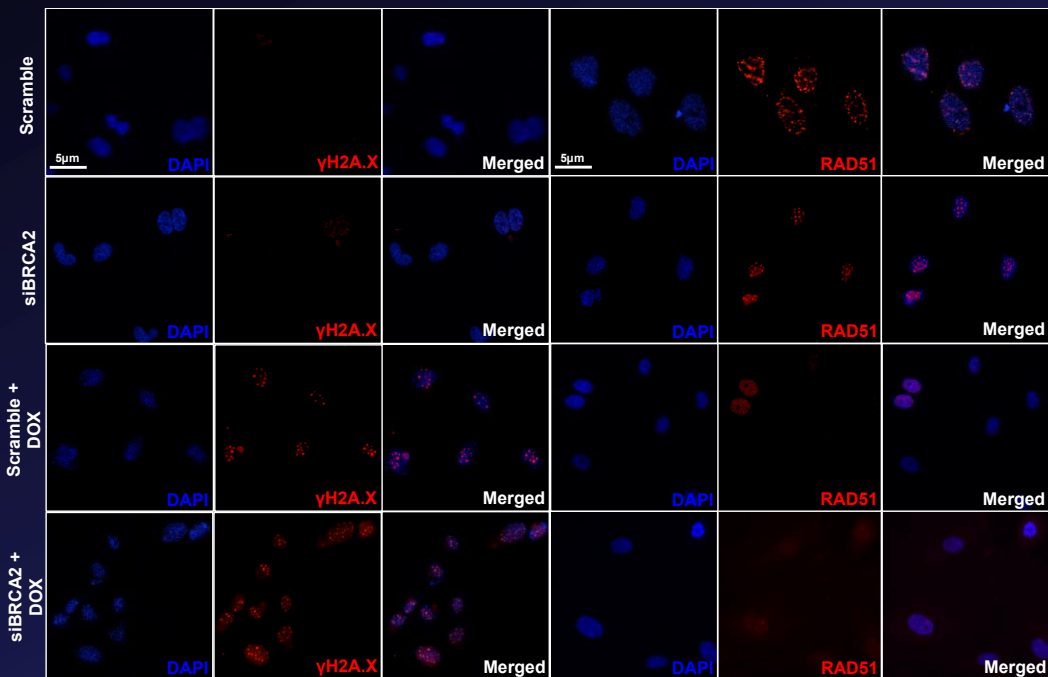
(C) p21 levels



Loss-of-Function: Loss of BRCA2 Exacerbates Endothelial ROS production



Loss-of-Function: Loss of BRCA2 Leads to Accumulation of DNA Damage in Endothelial Cells



Conclusions

- We provide the first evidence for the role of BRCA2 in the vascular disease
- Loss of BRCA2 in the endothelial cells leads to increased DNA damage and P53-mediated apoptosis
- BRCA2 is a novel and essential regulator of endothelial function particularly with genotoxic stress

Translational Implications

BRCA2 mutation carrier cancer patients, receiving anthracycline (DOX)-based chemotherapy, may be at a higher risk of developing vascular disease versus alternative therapy

Acknowledgements

Dr. Subodh Verma

Dr. Howard Leong-Poi

Dr. Mohammed Al-Omran

Verma & Leong-Poi Lab

Thank you