FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS

Project Title: Research project on anti-tumor therapy based on the molecular analyses of epigenetically coordinated endothelial cell activation	
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1. Background of research

Current an aging society in Japan, three major mortalities is becoming tumor, stroke, and cardiovascular dys-function. Important issues for cancer treatment are the therapy ways against tumor recurrence and metastasis. To that end, we need to uncover the molecular mechanisms for vascular activation into a cancer micro-environment. Moreover, it is increasing cases for atherosclerosis diseases based on hyper-lipidemia and chronic-inflammation. A remarkable feature of these vascular disorders in the focal nature of their distribution. One clue to vascular bed specific pathology is a delineate of the epigenetic regulations into the endothelium.

2. Research objectives

We have recently shown that Down Syndrome related genes, Down Syndrome Critical Region (DSCR)-1 and Early Growth Response (Egr)-3 was the highest induced at the pathological vascular activation status, such as in tumor or in severe inflammation, sepsis. In this project, we would further elucidate the molecular mechanisms in these genes expression, (patho)-physiological function by using these conditional transgenic or knockout mice, and the following epigenetic dynamics occurred in the primary cultured endothelial cells.

3. Research characteristics (incl. originality and creativity)

From the epidemiological studies, Down Syndrome population appears to have dramatically reduced incidence of most solid tumors. In the large study involving 17,800 Down Syndrome individuals, the mortality of cancers were less than 10% of expected. Moreover, previously reported that Down Syndrome patient have a much lower incidence of angiogenesis related disease, such as diabetic retinopathy and atherosclerosis. Therefore, it is emergent study to understand the detailed mechanisms why DSCR-1 potentiates protective effect for vascular diseases.

4. Anticipated effects and future applications of research

Epigenetic analysis using the advanced fine technology would create the frontier multi-disciplined scientific field involved with technology, pharmacology, and medical biology. These research promotion would provide us a great hint for therapeutic targets with reducing side effect risks, against solid tumor and vasculopathic diseases.

Emergent study for Vascular Biology

Tumor

Angiogenesis

Vascular endothelium

Block for angiogenesis

Therapy for cancers

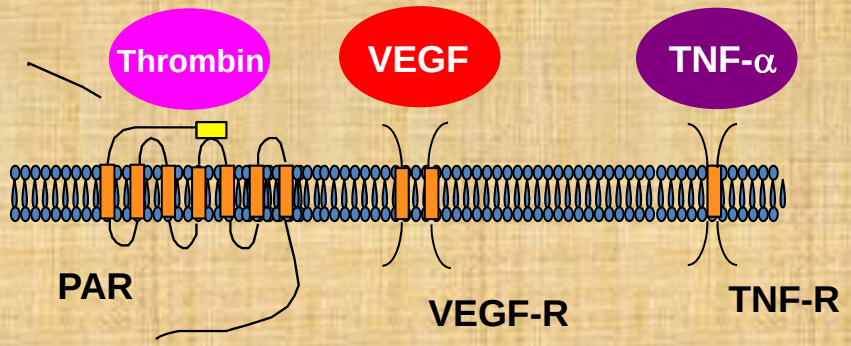
Three major mortalities

1. Cancer
2. Stroke
3. Heart attack

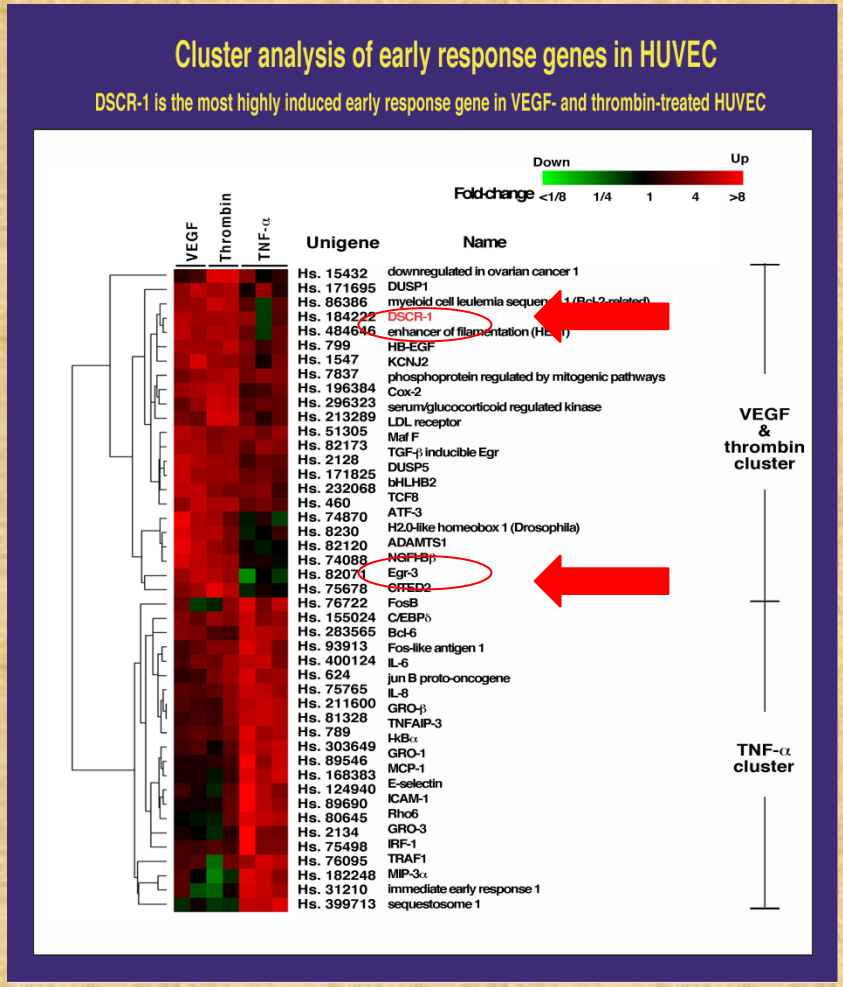
Block for vascular inflammation

Therapy for Arthrosclerosis and thrombosis

Endothelial cells



Endothelial cell activation is mediated in large part, by changes in gene transcription. To determine downstream transcriptional programs, we carried out a global survey in primary cultured endothelial cells using DNA microarrays and ChIP-seqs



Vol 441|1 June 2006|doi:10.1038/nature04678 nature

Both 1.5-fold upregulations of DSCR1 and DYRK1A would lead the dysfunction of NFAT activities, which cause the onset of Down Syndrome pathology.

ARTICLES

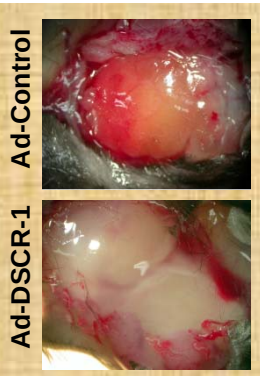
NFAT dysregulation by increased dosage of *DSCR1* and *DYRK1A* on chromosome 21

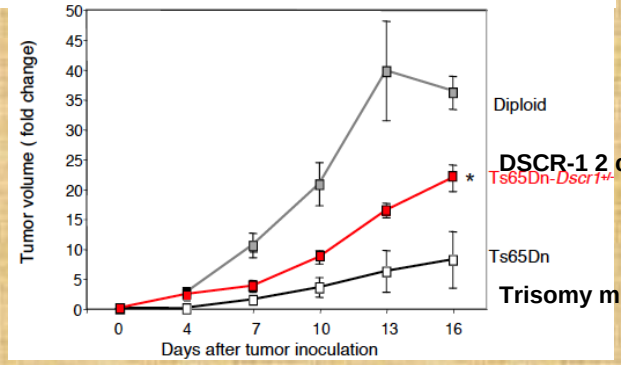
doi:10.1038/nature08062 nature

Baek, Minami, Ryeom, et.al. *Nature* 2009

LETTERS

Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1

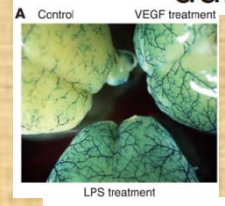




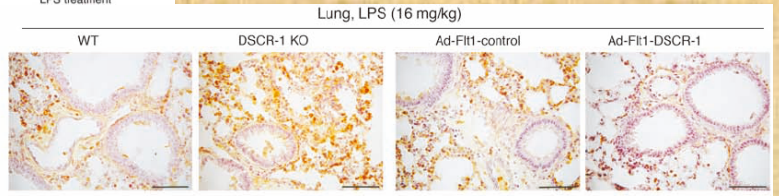
Minami, et.al. *J.Clin.Invest.* 2009

Research article

The Down syndrome critical region gene 1 short variant promoters direct vascular bed–specific gene expression during inflammation in mice



DSCR-1s was induced in pathologically activated Endothelium and functioned with anti-inflammatory Molecule. Null mutation of the DSCR-1s increased mortalities with severe inflammation, when sepsis shock.



Research Style

Collaboration

Integrative research on cancer microenvir onment network

ES to EC differentiation Kyoto University

Collaboration

Research direct, and analyze NFAT/DSCR-1 function : Minami

Analyze Egr-3 function, and epigenome study : Suehiro

Analyze GATA function and ES differentiation: Kanki

Epigenome analysis in Cancer: Osawa

Production of the high spec antibody

Plus research assistant

Epigenome analysis Solexa Sequencer Affymetrix array

Proteomics analysis LC-MS-MS-orbitrap LC-TOFMS

Bio-informatics

U.Penn Ryeom Lab

Share DSCR-1 Knockout mice

Harvard University Aird Lab

Collaboration with vascular research

Informed the results