Discovery of TIEG/KLF10 in Osteoblast Cells

Identification of a novel TGF-β-regulated gene encoding a putative zinc finger protein in human osteoblasts

Malayannan Subramaniam*, Steven A. Harris, Merry Jo Oursler, Kay Rasmussen, B. Lawrence Riggs† and Thomas C. Spelsberg

Department of Biochemistry and Molecular Biology and 1Endocrine Research Laboratory, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, USA
Impact of TIEG-Related Projects at Mayo Clinic

- Have secured over 7 million dollars in funding from NIH and Mayo Clinic

- Scientific discoveries detailed in **244 manuscripts** to date
Impact of TIEG-Related Projects at Mayo Clinic

- 10 young investigator awards at international meetings
- 1 training grant for promising scientist
- 5 patent applications
Biological Functions of TIEG/KLF10

Enhanced Bone Formation

M. Subramaniam et al., NAR, 1995
TIEG and Osteoporosis

Candidate Gene Analysis of Femoral Neck Trabecular and Cortical Volumetric Bone Mineral Density in Older Men

Laura M Yerges,1 Lambertus Klei,2 Jane A Cauley,1 Kathryn Roeder,3 Candace M Kammerer,4 Kristine E Ensrud,2 Cara S Nestlerode,1 Cora Lewis,6 Thomas F Lang,7 Elizabeth Barrett-Connor,8 Susan P Moffett,1 Andrew R Hoffman,9 Robert E Ferrell,4 Eric S Orwell,10 and Joseph M Zmuda1,4 for the Osteoporotic Fractures in Men (MrOS) Study Group

Gene expression profile of the bone microenvironment in human fragility fracture bone

B. Hopwood a,+, A. Tsykin b, D.M. Findlay c,+, N.L. Fazzalari a,+,*
TIEG and Cancer

Tissue, Cell Type, and Breast Cancer Stage-Specific Expression of a TGF-β Inducible Early Transcription Factor Gene


TIEG and Cancer

Differential gene expression of TGFβ inducible early gene (TIEG), Smad7, Smad2 and Bard1 in normal and malignant breast tissue

Monica M. Reinholz, Ming-Wen An, Steven A. Johnsen, Malayannan Subramaniam, Vera J. Suman, James N. Ingle, Patrick C. Roche, and Thomas C. Spelsberg

ORIGINAL ARTICLE

KLF10 loss in the pancreas provokes activation of SDF-1 and induces distant metastases of pancreatic ductal adenocarcinoma in the KrasG12D p53flox/flox model

TIEG and Cardiomyopathies

Published in final edited form as:

**TGFβ Inducible Early Gene-1 (TIEG1) and Cardiac Hypertrophy: Discovery and Characterization of a Novel Signaling Pathway**

Nalini M. Rajamannan¹*, Malayannan Subramaniam², Theodore P. Abraham³, Vlad C. Vasile⁴, Michael J. Ackerman⁴,⁵, David G. Monroe⁶, Teng-Leong Chew⁷, and Thomas C. Spelsberg²

Published in final edited form as:

**TGFβ-Inducible Early Gene-1 (TIEG1) Mutations in Hypertrophic Cardiomyopathy**

J. Martijn Bos, MD, PhD¹, Malayannan Subramaniam, PhD², John R. Hawse, PhD², I. Christiaans, MD, PhD³,⁴, Nalini M Rajamannan, MD⁵, Joseph J. Maleszewski, MD⁶, William D. Edwards, MD⁷, Arthur A.M. Wilde, MD, PhD⁸, Thomas C. Spelsberg, PhD², and Michael J. Ackerman, MD, PhD¹,⁷,⁸
Published in final edited form as:


**The E3 ubiquitin ligase Itch regulates expression of transcription factor Foxp3 and airway inflammation by enhancing the function of transcription factor TIEG1**

K Venuprasad, Haining Huang, Yousuke Harada, Chris Elly, Malayannan Subramaniam, Thomas Spelsberg, Jin Su, and Yun-Cai Liu

1 Division of Cell Biology, La Jolla Institute for Allergy and Immunology, La Jolla, California 92037, USA
2 Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA

**Kruppel-like factor KLF10 deficiency predisposes to colitis through colonic macrophage dysregulation**

Konstantinos A. Papadakis, James Krempski, Prithvi Sivinen, Yuning Xiong, Olga E. Sarmento, Gwen A. Lomberk, Raul A. Urrutia, and William A. Fauzi

1 Divisions of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; and
2 Epigenetics and Chromatin Dynamics Laboratory, Departments of Medicine and Biochemistry and Molecular Biology, Epigenetic Translational Program, Center for Individualized Medicine, Mayo Clinic, Rochester, Minnesota

**Kruppel-like Factor KLF10 Targets Transforming Growth Factor-β1 to Regulate CD4+CD25− T Cells and T Regulatory Cells**

Role of TIEG in the musculoskeletal system

Muscle  Tendon  Os

Age-dependent changes in the mechanical properties of tail tendons in TGF-β inducible early gene-1 knockout mice

Published in final edited form as:

TIEG1-null tenocytes display age-dependent differences in their gene expression, adhesion, spreading and proliferation properties

Published in final edited form as:
Role of TIEG in the Musculoskeletal System

What type of changes?
- Mechanical?
- Morphological?

Sabine Bensamoun
Role of TIEG in the Skeletal Muscle

Morphological analysis

Functional analysis
Deletion of TIEG Results in Muscle Fiber Hypertrophy

Soleus WT

Soleus KO

100 µm
Deletion of TIEG leads to Disorganization of Muscle Ultrastructure

- Ultrastructure disorganization
- Absence of I band
- Smaller sarcomere
- Contracted behavior
- Changes in the shape of mitochondria
- Increase in myosin diameter
Deletion of TIEG Results in Altered Mitochondrial Activity

**Sabine Bensamoun**
Fundamental Research → Clinical Research

What is the mechanism of TIEG?

Scope → new concepts of understanding metabolic disorders

Can we identify mitochondrial pathologies?
Scope → new means of diagnosis for energy metabolism disorders

Gittan K. et al. Neuromuscular Disorders. 2011
Role of TIEG in Skeletal Muscle

Morphological analysis

Functional analysis

Muscle fiber
Platform for Multi-scale Characterization of Muscle Tissue

Fiber

Load cell (5mN)

14 mm

Solution  T = 25°C

Stretch

---

Impact of TIEG1 on the structural properties of fast and slow twitch skeletal muscle

Malek Kammoun, PhD1, Sandra Même, PhD2, William Même, PhD2, Malayanan Subramaniam, PhD3, John R. Hawse, PhD3, Francis Canon, PhD1, and Sabine F. Bensamoun, PhD1


---

**RESEARCH ARTICLE**

Impact of TIEG1 Deletion on the Passive Mechanical Properties of Fast and Slow Twitch Skeletal Muscles in Female Mice

Malek Kammoun1, Philippe Pouletaut1, Francis Canon1, Malayanan Subramaniam2, John R. Hawse2, Muriel Vayssade1, Sabine F. Bensamoun1 *
Two complementary mechanical tests

Longitudinal test

Transversal test (AFM)

Functional behaviour of the fiber

Organisation of the fiber structure
Transversal Mechanical Properties of TIEG KO Fibers

AFM technique indicated a less organized structure (lower resistance under the tip) which is revealed by a less rigid muscle composition for KO TIEG muscle fibers compare to WT muscle fibers.
Perspectives: Development of a Multi-scale Muscle Platform

Microscopic mechanical test

Macroscopic MRI elastography test

Microscopic test (AFM)

Tip
F = 2 nN

Fiber

25 µm

Tip
F = 2 nN

Macroscopic mechanical test

Tip
F = 2 nN

20 cm

Displacement (µm)

40
-40

Muscles

VM
Sr

Driver
2019: Building an International Research Network (ex GDRI)