Some Calpain History- Part 2: GENETICS and EVOLUTION

The information for **calpain genetics** is organized by genes for

- component subunits of calpain-1 (***Capn1*** and ***Capns1****),* calpain-2 (***Capn2*** and ***Capns1***) and calpastatin (*Cast*)
- ***Capn3*** – a genetic link to human disease- Limb-Girdle Muscular Dystrophy type IIA
- ***Capn10***- a genetic link to human disease- type 2- diabetes
- ***Capn5*** -a genetic link to human disease- ADNIV
- Gene targeting in mice: insights into biological function of ***Capn8, Capn9*** **and** ***Capn6***

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Ubiquitous calpains 1 and 2 and calpastatin: mouse models

2000 **Targeted deletion of *Capns1* (*Capn4* ,** the shared small subunit for calpains 1 and 2) **is embryonic lethal**

Disruption of the murine calpain small subunit gene, *Capn4*: calpain is essential for embryonic development but not for cell growth and division. **Arthur, JSC, Elce, JS,** Hegadorn, C, Williams, K and **Greer, PA** **Mol. Cell Biol.** 20, 4474- 4481

The calpain small subunit gene is essential: its inactivation results in embryonic lethality. **Zimmerman, UJ,** Boring, L, Pak, JH, Mukerjee, N**,** **Wang, KK** **IUBMB 1, 63-68**

2001 **Targeted deletion of Capn1** (catalytic subunit of calpain 1/μ-calpain) **mice show modest phenotypic changes**

Disruption of the mouse - μ-calpain gene reveals an essential role in platelet function. Azam, M, Andarabi, SS,Sahr, KE, Kamath, L, Kuliopulos, A**,** **Chishti, A.** **Mol. Cell Biol. 21 2213-2220**

2005 **Targeted deletion of *Cast*** **(**calpastatin- the inhibitor of calpains 1 and 2)has **minimal or no overt phenotype but altered responses to systemic stressors**

Calpain mediates excitotoxic DNA fragmentation via mitochondrial pathways in adult brains: evidence from calpastatin mutant mice. **Takano,J,** Tomioka, M, Tsubuki, S, Higuchi,M, Iwata, N, Itohara,S, **Maki, M, Saido, TC** **J. Biol. Chem**. 280:16175–16184

2006 **Targeted deletion of *Capn2*** (catalytic subunit of calpain 2) **is embryonic lethal**

m-Calpain is required for preimplantation embryonic development in mice. Dutt, P, **Croall, DE**, **Arthur, JSC**, DeVeyra, T, Williams, K, **Elce, JS, Greer, PA** **BioMed Central Developmental Biology** 6, 3

2011 **Systematic analysis of single/double knockouts of calpains 1 and 2 with/without calpastatin knockout**

Vital Role of the Calpain-Calpastatin System for Placental-Integrity-Dependent Embryonic Survival. **Takano, J**, Mihira, N, Fujioka, R, Hosoki,E, **Chishti, AH , Saido, TC**. **Mol Cell Bio** 31, 4097–4106

Some key findings:

- ⇒ ***Capn2*** deletion limited to embryo – **lethal at 15.5 d**
- ⇒ ***Capn2*** deletion with deletion of ***Cast*** produced normal phenotype
- ⇒ i.e. the lethality of ***Capn2*** deletion was rescued by coincident deletion of ***Cast*****.**

Capn3- Human disease Limb Girdle Muscular Dystrophy type 2A (LGMD-2A) and mouse models

1996 **Juvenile limb-girdle muscular dystrophy: Clinical, histopathological and genetic data from a small community living in the Reunion Island.** M. Fardeau, D. Hillaire, C. Mignard, N, Feingold, J, Feingold, D, Mignard, B, de Ubeda, H, Collin, FMS, Tomé, **I. Richard**, and **J. Beckmann** **Brain 119: 295 - 308**.

1997 **Calpain-3 deficiency causes a mild muscular dystrophy in childhood**. H Topaloglu, P Dincer, **I Richard**, Z Akcoren, D Alehan, S Ozme, M Caglar, A Karaduman, JA Urtizberea, and **JS Beckmann** **Neuropediatrics, 28(4): 212-216.**

1998 **Functional Defects of a Muscle-specific Calpain, p94, Caused by Mutations Associated with Limb-Girdle Muscular Dystrophy Type 2A.** **Ono, Y,** Shimada, H, **Sorimachi, H, Richard, I, Saido,TC, Beckmann, JS, Ishiura, S, Suzuki, K** **J. Biol. Chem. 273: 17073 – 17078**

2000 **Targeted deletion/mutation of *Capn3* causes muscular dystrophy**

Loss of calpain 3 proteolytic activity leads to muscular dystrophy and to apoptosis-associated IkBa/nuclear factor kB pathway perturbation in mice. **Richard, I**, Roudaut, C, Marchand, S, Baghdiguian, S, Herasse, M, Stockholm, D, **Ono, Y**, Suel, L, Bourg, N, **Sorimachi, H**, Lefranc, G, Fardeau, M, Sebille, A, **Beckmann, JS** **J. Cell Biol**. 151:1583 - 1590.

2004 **Null mutation of calpain 3 (p94) in mice causes abnormal sarcomere formation in vivo and in vitro.** Kramerova, I, Kudryashova, E, Tidball, JG, **Spencer, MJ** **Hum. Mol. Genet.** 13:1373-1388.

Bidirectional transcriptional activity of the Pgk1 promoter and transmission ratio distortion in *Capn*3-deficient mice. Taveau, M, Stockholm, D, Marchand, S, Roudaut, C, Le Bert, M, **Richard, I** **Genomics** 84:592-595.

2005 **Calpain 3 participates in sarcomere remodeling by acting upstream of the ubiquitin-proteasome pathway.** Kramerova, I, Kudryashova, E, Venkatraman, G, **Spencer, MJ** **Hum Mol Genet** 14: 2125-2134.

2006 **Regulation of the M-cadherin-beta-catenin complex by calpain 3 during terminal stages of myogenic differentiation.** Kramerova, I, Kudryashova, E, Wu, B, **Spencer, MJ** **Mol Cell Biol** 26:8437-8447.

A mouse model for monitoring calpain activity under physiological and pathological conditions. Bartoli, M, Bourg, N, Stockholm, D, Raynaud, F, Delevacque, A, Han, Y, Borel, P, Seddik, K, Armande, N, **Richard, I** **J Biol Chem** 281:39672-39680.

2008 **Novel role of calpain-3 in the triad-associated protein complex regulating calcium release in skeletal muscle.** Kramerova, I, Kudryashova, E, Wu, B, Ottenheijm, C, Granzier, H, **Spencer, MJ** **Hum Mol Genet** 17:3271-3280.

NF-κB-dependent expression of the antiapoptotic factor c-FLIP is regulated by calpain 3, the protein involved in limb-girdle muscular dystrophy type 2A. Benayoun, B, Baghdiguian, S, Lajmanovich, A, Bartoli, M, Daniele, N, Gicquel, E, Bourg, N, Raynaud, F, Pasquier, MA, Suel, L, Lochmuller, H, Lefranc, G, **Richard, I** **FASEB J** 22:1521-1529.

2009 **Mitochondrial abnormalities, energy deficit and oxidative stress are features of calpain 3 deficiency in skeletal muscle.** Kramerova, I, Kudryashova, E, Wu, B, Germain, S, Vandenborne, K, Romain, N, Haller, RG, Verity, MA, **Spencer, MJ** **Hum Mol Genet** 18:3194-3205.

2010 **Removal of the calpain 3 protease reverses the myopathology in a mouse model for titinopathies.** Charton, K, Danièle, N, Vihola, A, Roudaut, C, Gicquel, E, Monjaret, F, Tarrade, A, Sarparanta, J, Udd, B, **Richard, I** **Hum Mol Genet** 19:4608-4624.

Dynamic distribution of muscle-specific calpain in mice has a key role in physical-stress adaptation and is impaired in muscular dystrophy. Ojima, K, Kawabata, Y, Nakao, H, Nakao, K, Doi, N, Kitamura, F, **Ono, Y,** Hata, S, Suzuki, H, Kawahara, H, Bogomolovas, J, Witt, C,

Ottenheijm, C, Labeit, S, Granzier, H, Toyama-Sorimachi, N, Sorimachi, M, Suzuki, K, Maeda, T, Abe, K, Aiba, A, **Sorimachi, H** **J. Clin. Invest.** 120:2672 - 2683.

2011 **Pathogenicity of some limb girdle muscular dystrophy mutations can result from reduced anchorage to myofibrils and altered stability of calpain 3.** Ermolova, N, Kudryashova, E, DiFranco, M, Vergara, J, Kramerova, I, **Spencer, MJ** **Hum Mol Genet** 20:3331-3345.

2012 **Impaired calcium calmodulin kinase signaling and muscle adaptation response in the absence of calpain 3.** Kramerova, I, Kudryashova, E, Ermolova, N, Saenz, A, Jaka, O, López de Munain, A, **Spencer, MJ** **Hum Mol Genet** 21:3193-3204.

Capn10 and diabetes (and more?)

2000 **Genetic variation in the gene encoding calpain-10 is associated with type 2 diabetes mellitus.** Y Horikawa, N Oda, NJ Cox, X Li, M Orho-Melander, M Hara, Y Hinokio, TH Lindner, H Mashima, PE Schwarz, L del Bosque-Plata, Y Horikawa, Y Oda, I Yoshiuchi, S Colilla, KS Polonsky, S Wei, P Concannon, N Iwasaki, J Schulze, LJ Baier, C Bogardus, L Groop, E Boerwinkle, CL Hanis, and **GI Bell** **Nat Genet** 26(2): 163-75.

2002 **Variation within the Type 2 Diabetes Susceptibility Gene Calpain-10 and Polycystic Ovary Syndrome.** L Haddad, JC Evans, N Gharani, C Robertson, K Rush, S Wiltshire, TM Frayling, TJ Wilkin, A Demaine, A Millward, AT Hattersley, G Conway, NJ Cox, **GI Bell**, S Franks, and MI McCarthy **J. Clin. Endocrinol. Metab.,** 87: 2606 - 2610.

2010 **Targeted deletion of *Capn10* shows its involvement in obesity-related QTL**

Calpain-10 is a component of the obesity-related quantitative trait locus *Adip1*. Cheverud, JM, Fawcett, GL, Jarvis, JP, Norgard, EA, Pavlicev, M, Pletscher, LS, Polonsky, KS, Ye, H, **Bell, GI**, Semenkovich, CF **J. Lipid Res.** 51:907-913.

2012 *Capn5* and human disease- ADNIV

(Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy)

Calpain-5 Mutations Cause **Autoimmune Uveitis, Retinal Neovascularization, and Photoreceptor Degeneration** **VB Mahajan**, JM Skeie, AG Bassuk, JH Fingert, TA. Braun HT Daggett, JC Folk, VC Sheffield, **EM Stone** **PLoS Genet 8(10): e1003001**.

Approaching biological functions of other calpains through genetic manipulation of mice

2004 **Targeted deletion of *Capn5* is dispensable for development**

***Capn5* is expressed in a subset of T cells and is dispensable for development.** Franz T, Winckler L, Boehm T, **Dear TN** **Mol. Cell. Biol.** 24:1649 - 1654**.**

2010 **Targeted deletion/mutation of *Capn8/9* causes ethanol-induced gastric ulcer**

Calpain 8/nCL-2 and calpain 9/nCL-4 constitute an active protease complex, G-calpain, involved in gastric mucosal defense. Hata, S, Abe, M, Suzuki, H, Kitamura, F, Toyama-Sorimachi, N, Abe, K, Sakimura, K, **Sorimachi, H** **PLoS Genet.** 6:e1001040.

2013 **Targeted deletion of *Capn6* in mice promotes muscle development and regeneration**

Calpain-6 deficiency promotes skeletal muscle development and regeneration. Tonami, K, Hata, S, Ojima, K, **Ono, Y**, Kurihara, Y, Amano, T, Sato, T, Kawamura, Y, Kurihara, H, **Sorimachi, H** **PLoS Genet.** 9:e1003668.

Evolutionary relationships within the CALPAIN Family

1989-1993 **The discovery of calpain family members *Capn3 and Capn9* by H. Sorimachi and K. Suzuki triggered speculation and investigations of the evolutionary relationships between the calpain family members.**

1997 **A new subfamily of vertebrate calpains lacking a calmodulin-like domain:implications for calpain regulation and evolution.** **N Dear,** K Matena, M Vingron, and T Boehm **Genomics 45(1): 175-84.**

1999 **Evolutionary pathways were proposed by** G Jekely and **P Friedrich**

The evolution of the calpain family as reflected in paralogous chromosome regions

G Jekely and **P Friedrich** **J Mol Evol, 49 : 272-81.**

2001 **Both the conserved and the unique gene structure of stomach-specific calpains reveal processes of calpain gene evolution.** S Hata, K Nishi, T Kawamoto, HJ Lee, H Kawahara, T Maeda, Y Shintani**, H Sorimachi, and K Suzuki** **J Mol Evol; 53: 191-203.**

2001 **a single transmembrane calpain identified in plants**

Identification, classification and expression pattern analysis of sugarcane cysteine proteinases. GC Correa, M Margis-Pinheiro, and R Margis Genet. Mol. Biol. 24: 275-283.

2002 **The *defective kernel 1* (*dek1*) gene required for aleurone cell development in the endosperm of maize grains encodes a membrane protein of the calpain gene superfamily.** SE Lid, D Gruis, R Jung, JA Lorentzen, E Ananiev, M Chamberlin, X Niu, R Meeley, S Nichols, and **O-A Olsen** **PNAS; 99: 5460 - 5465.**

Calpains- kinetoplastid parasites, placental mammals and C. elegans

2005 **Evolutionary relationships and protein domain architecture in an expanded calpain superfamily in kinetoplastid parasites.** **K Ersfeld,** H Barraclough, **and K Gull** **J Mol Evol, 61: 742-57.**

2010 **A Newly Classified Vertebrate Calpain Protease, Directly Ancestral to *Capn1* and *2*, Episodically Evolved a Restricted Physiological Function in Placental Mammals.** **DJ Macqueen,** ML. Delbridge, S. Manthri, and IA. Johnston **Mol. Biol. Evol. 27: 1886 - 1902.**

2012 **The atypical calpains: evolutionary analyses and roles in *Caenorhabditis elegans* cellular degeneration.** PI Joyce, R Satija, M Chen, and **PE Kuwabara** **PLoS Genet; 8: e1002602.**

Massive expansion of the calpain gene family in unicellular eukaryotes. **S Zhao,** Z Liang, V Demko, R Wilson, W Johansen**, O-A Olsen and K Shalchian-Tabrizi** **BMC Evol Biol 12:193**