We stand on the shoulders of Giants
ACADEMIC TREE
https://academictree.org/chemistry/tree.php?pid=384817

Christian Bohr
Copenhagen University

August Steenberg Krogh
Københavns Universitet

Knut Schmidt-Nielsen
Duke University

Peter W. Hochachka
University of British Columbia)

Kenneth B. Storey
Carleton University

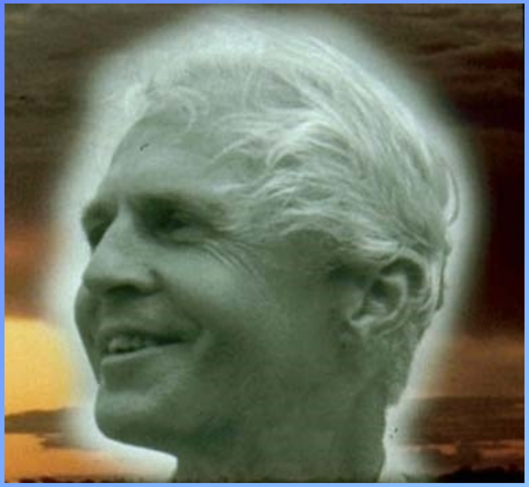
100 Graduate Students, 1000 publications, $$ & Decades
HYPOTHESES [not]

The Dawn of Comparative Physiology

1865: Claude Bernard

"There are also experiments in which it is proper to choose certain animals which offer favorable anatomic arrangements or special susceptibility to certain influences. This is so important that the solution to a physiological or pathological problem often depends solely on the appropriate choice of the animal for the experiment so as to make the result clear and searching."

Comparative Biochemistry Unfolds



1920: A. Krogh ~ Nobel Prize

Mid-1900's ~ Viking Physiologists

P. Scholander

K. Schmidt-Nielsen

K. Johansen

A Canadian ~ F. Fry

Biochemistry ~ F. Lippman

H. Krebs

O. Warburg

Comparative Textbook ~ E. Baldwin

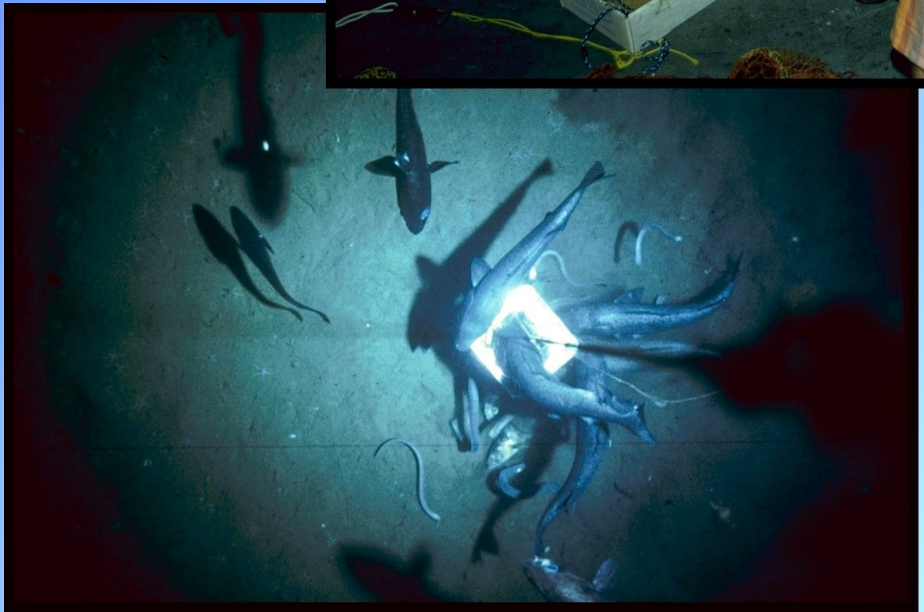
SYNTHETIC INTUITION

Something Old,

Something New,

Something Borrowed,

Some Glue.



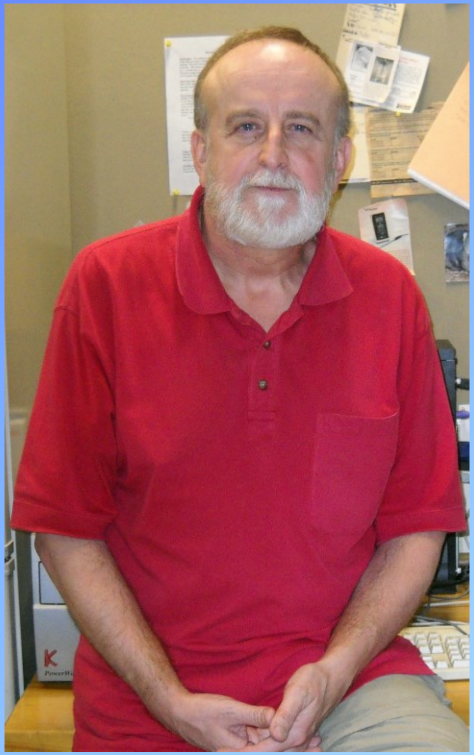
SYNTHETIC INTUITION

FILTER

~ Transducer
~ Organizer
~ *Revamp*
~ IDEA LENS

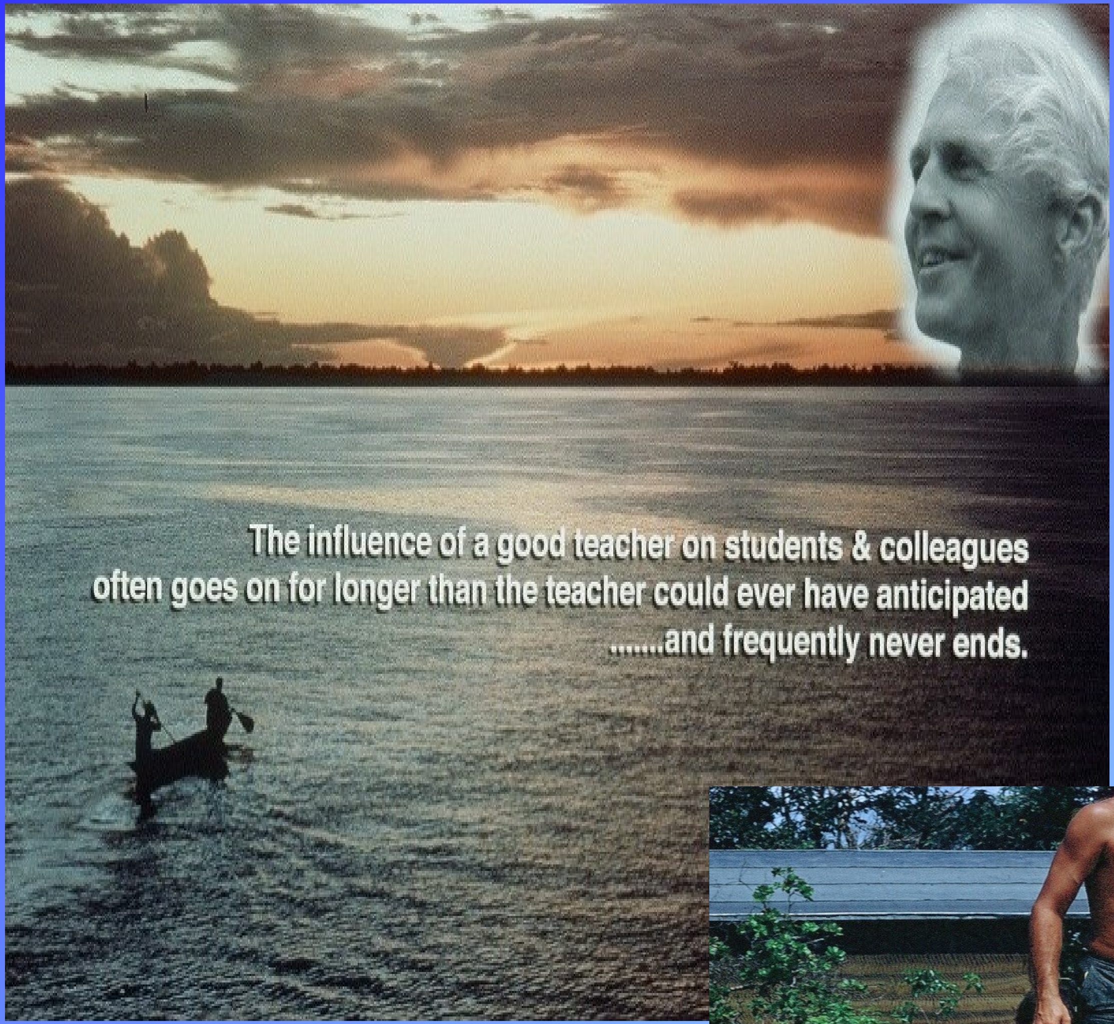
IDEAS IN

~ Ecology
~ Physiol. Ecology
~ PHYSIOLOGY
~ Metabolism
~ Methods of Biochemistry
~ Molecular Biology
~ Genetics

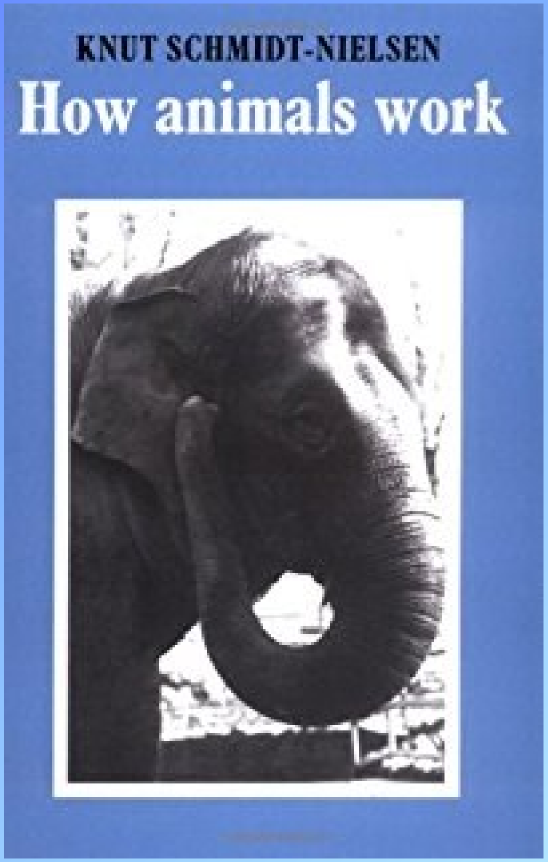


IDEAS OUT

~ Metabolic Arrangement
~ Reorganization of Metabolism
~ Adaptive Change at Pathway Level
~ Integration: multi-levels of Biological Organization

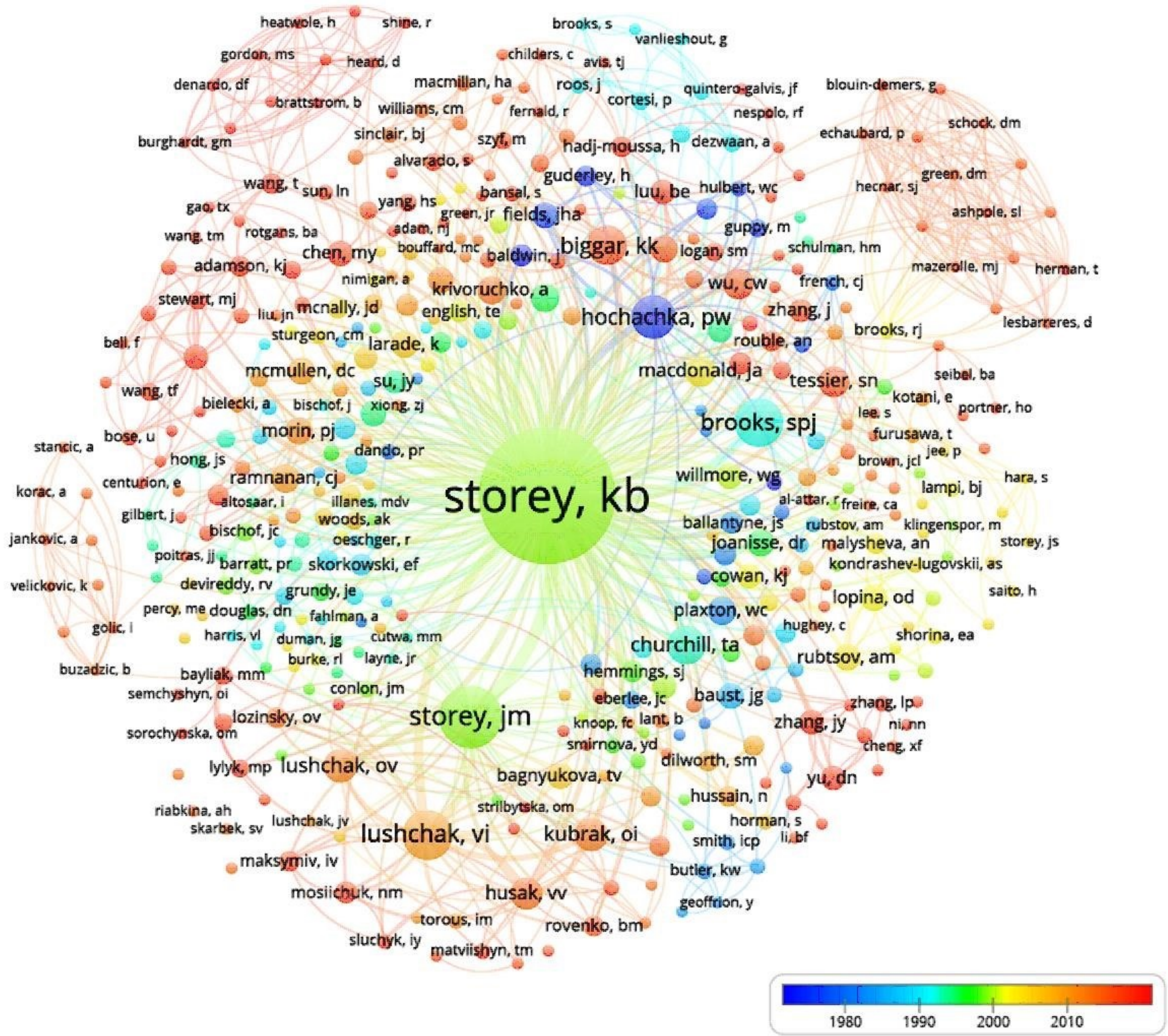


**Knut Schmidt-Nielsen:
A giant that Peter made
my faculty colleague**


KNUT SCHMIDT-NIELSEN
How animals work

Froze the first frog as a scientist

Kjell Johansen – Viking and Physiologist


heatwole, h
shine, r
brooks, s
vanlieshout, g
gordon, ms
heard, d
childers, c
avis, tj
denardo, df
macmillan, ha
roos, j
quintero-galvis, jf
blouin-demers, g
brattstrom, b
williams, cm
fernald, r
cortesi, p
nespolo, rf
schock, dm
burghardt, gm
sinclair, bj
szyf, m
hadj-moussa, h
dezwaan, a
echaubard, p
alvarado, s
green, dm
wang, t
sun, ln
guderley, h
luu, be
hulbert, wc
hecnar, sj
gao, tx
yang, hs
bansal, s
ashpole, sl
green, jr
fields, jha
guppy, m
wang, tm
rotgans, ba
adam, nj
biggar, kk
schulman, hm
chen, my
bouffard, mc
baldwin, j
logan, sm
adamson, kj
mazerolle, mj
herman, t
nimigan, a
wu, cw
french, cj
krivoruchko, a
stewart, mj
mcnally, jd
english, te
hochachka, pw
zhang, j
liu, jn
brooks, rj
lesbarreres, d
sturgeon, cm
bell, f
larade, k
rouble, an
mcmullen, dc
macdonald, ja
seibel, ba
su, jy
tessier, sn
wang, tf
kotani, e
bielecki, a
bischof, j
xiong, zj
portner, ho
lee, s
brooks, spj
morin, pj
furusawa, t
bose, u
dando, pr
stancic, a
jee, p
hong, js
brown, jcl
ramnanan, cj
willmore, wg
centurion, e
hara, s
korac, a
lampi, bj
storey, kb
al-attar, r
altosaar, i
illanes, mdv
freire, ca
gilbert, j
woods, ak
ballantyne, js
rubstov, am
klingenspor, m
bischof, jc
jankovic, a
oeschger, r
joanisse, dr
malysheva, an
storey, js
poitras, jj
barratt, pr
skorkowski, ef
kondrashev-lugovskii, as
devireddy, rv
cowan, kj
velickovic, k
grundy, je
saito, h
lopina, od
percy, me
douglas, dn
fahlman, a
plaxton, wc
golic, i
hughey, c
harris, vl
cutwa, mm
duman, jg
shorina, ea
churchill, ta
burke, rl
layne, jr
rubtsov, am
buzadzic, b
hemmings, sj
bayliak, mm
semchyshyn, oi
conlon, jm
baust, jg
eberlee, jc
zhang, lp
storey, jm
lozinsky, ov
knoop, fc
lant, b
zhang, jy
ni, nn
sorochynska, om
cheng, xf
smirnova, yd
dilworth, sm
lylyk, mp
lushchak, ov
yu, dn
bagnyukova, tv
hussain, n
riabkina, ah
strilbytska, om
horman, s
skarbek, sv
lushchak, jv
lushchak, vi
kubrak, oi
smith, icp
li, bf
maksymiv, iv
butler, kw
mosiichuk, nm
husak, vv
geoffrion, y
torous, im
rovenko, bm
sluchyk, iy
matviishyn, tm
1980
1990
2000
2010


Metabolic Arrest
"Life in Limbo"
Ken Storey
www.kenstoreylab.com

METABOLIC RATE DEPRESSION


Hibernation



Estivation

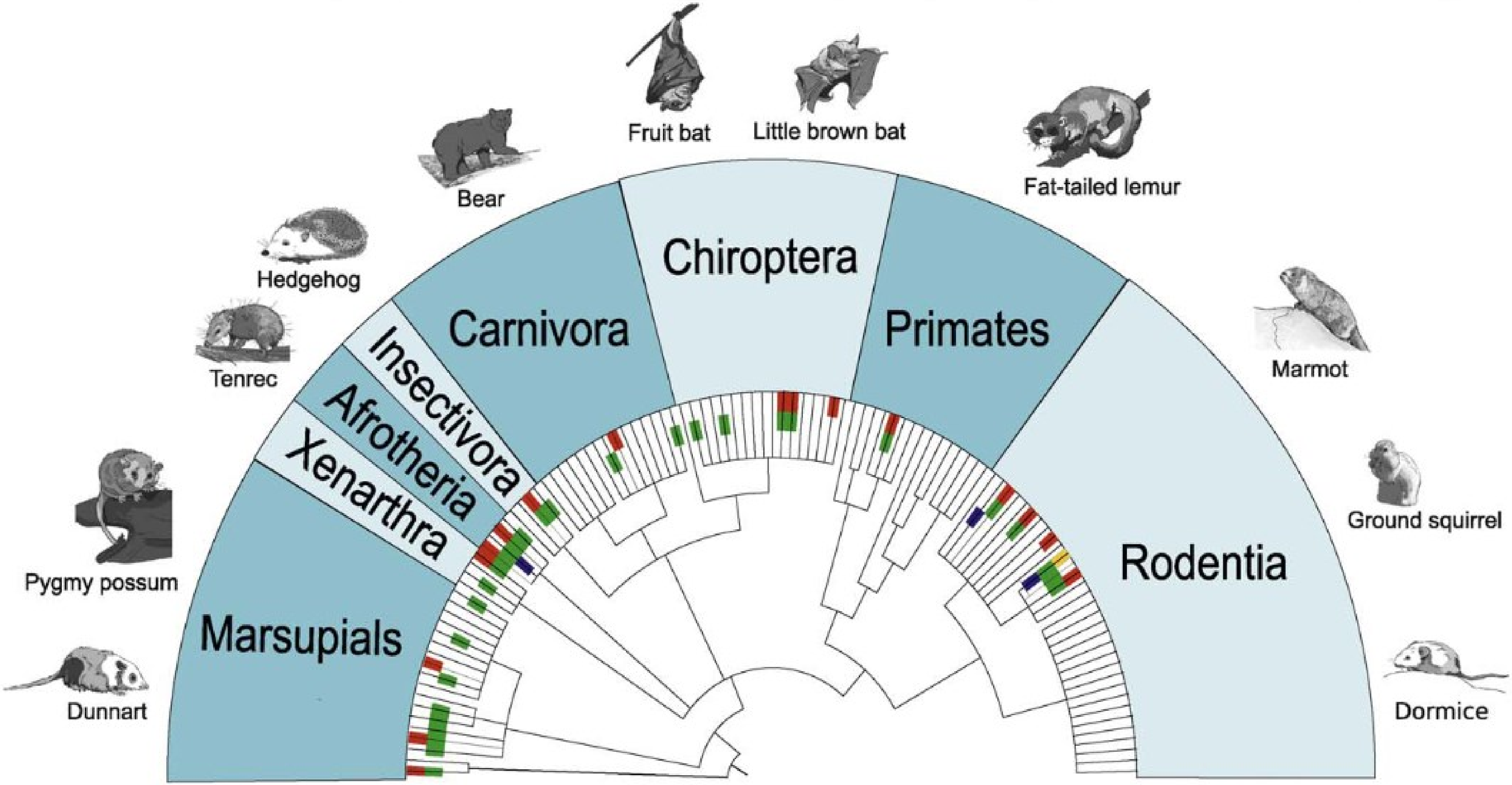


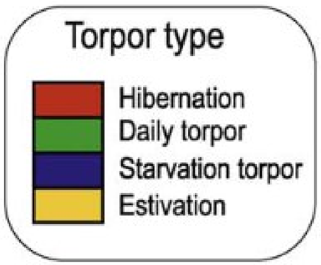
Anoxia



Freezing


Diapause





MAMMALIAN HYPOMETABOLISM

[redacted]

Model Hibernators

Spermophilus richardsonii, Richardson’s ground squirrel

Spermophilus tridecemlineatus, 13-lined ground squirrel

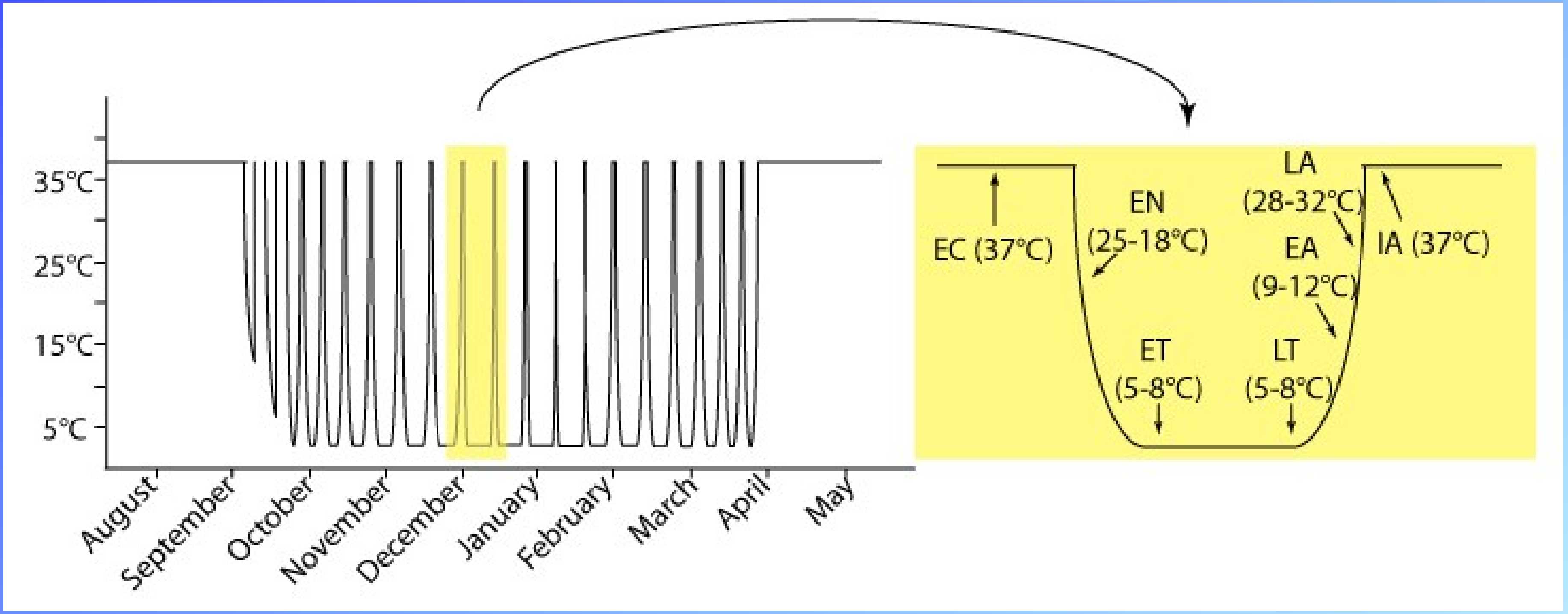
Myotis lucifugus, little brown bat

MONITO del MONTE

Dromiciops gliroides

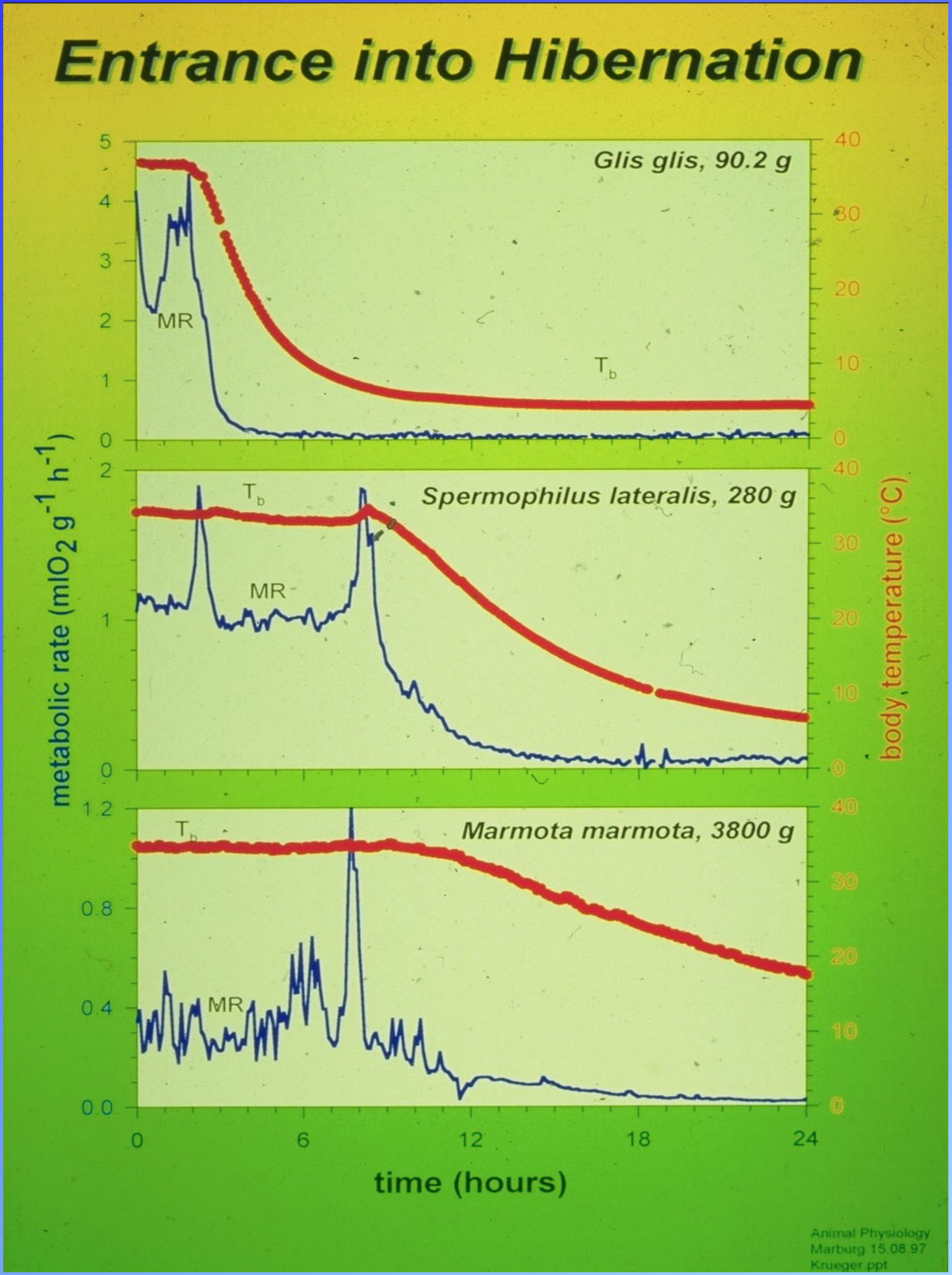
South American marsupial

TORPOR-AROUSAL IN HIBERNATORS



Animal studies by Dr. JM Hallenbeck and Dr. DC McMullen, NIH

Figure adapted from Nelson *et al.* 2009



- Metabolism inhibited causing Tb to fall
- Metabolic rate falls to <5% of normal
- Smaller animals cool down faster
- Q_{10} values up to 15
- Reversible in arousal
- Torpor bout duration 4 days to 2 weeks

COLD HIBERNATION

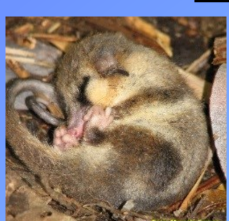
Pubmed: Storey kb

Lessons from mammalian hibernators: molecular insights into striated muscle plasticity and remodeling.
Tessier SN, **Storey KB**.
Biomol Concepts. 2016, 7(2):69-92. PMID: 26982616

Insight into post-transcriptional gene regulation: stress-responsive microRNAs and their role in environmental stress survival of tolerant animals.
Biggar KK, **Storey KB**.
J Exp Biol. 2015, 218(Pt 9):1281-9. PMID: 25954040

To be or not to be: the regulation of mRNA fate as a survival strategy during mammalian hibernation.
Tessier SN, **Storey KB**.
Cell Stress Chaper. 2014, 19(6):763-76. PMID: 24789358

Biochemical adaptations of mammalian hibernation: exploring squirrels as a perspective model for naturally induced reversible insulin resistance.
Wu CW, Biggar KK, **Storey KB**.
Braz J Med Biol Res. 2013, 46(1):1-13. PMID: 23314346



Out cold: biochemical regulation of mammalian hibernation - a mini-review.
Storey KB.
Gerontology. 2010, 56(2):220-30. PMID: 19602865

Life in the cold: links between mammalian hibernation and longevity.
Wu CW, **Storey KB**.
Biomol Concepts. 2016, 7(1):41-52. PMID: 26820181

Regulation of hypometabolism: insights into epigenetic controls.
Storey KB.
J Exp Biol. 2015, 218(Pt 1):150-9. PMID: 25568462

Biochemical adaptations of mammalian hibernation: exploring squirrels as a perspective model for naturally induced reversible insulin resistance.
Wu CW, Biggar KK, **Storey KB**.
Braz J Med Biol Res. 2013, 46(1):1-13. PMID: 23314346

The emerging roles of microRNAs in the molecular responses of metabolic rate depression.
Biggar KK, **Storey KB**.
J Mol Cell Biol. 2011, 3(3):167-75. PMID: 21177365

Metabolic rate depression: the biochemistry of mammalian hibernation.
Storey KB, Storey JM.
Adv Clin Chem. 2010, 52:77-108. PMID: 21275340

TORPOR Warm

Gray mouse lemur,
Microcebus murinus

BEARS !

PRINCIPLES OF HIBERNATION

1. **Metabolic rate reduction**
2. **Cold or Warm temperature**
3. **Most Genes & Processes OFF**
4. **miRNA Control of Pathways**
5. **Epigenetics as Central Controller**

Same for ALL MRD

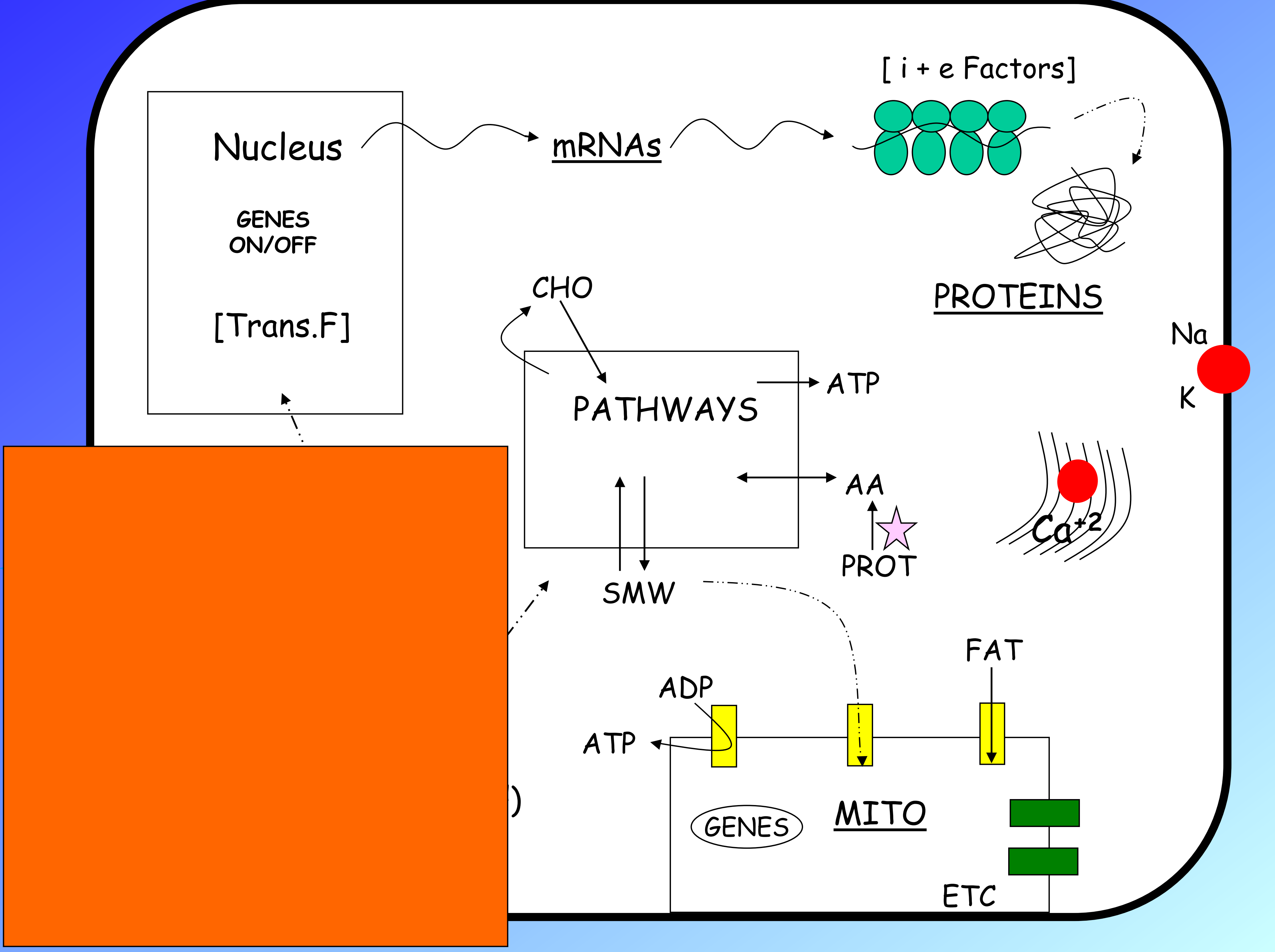
PRINCIPLES OF HIBERNATION

1. Metabolic rate reduction

2. Control by protein kinases
   (SAPKs, 2nd messenger PKs)

- p38, ERK (1/2), JNK, AMPK, AKT (mTOR)

Same for ALL MRD


[i + e Factors]
Nucleus
GENES
ON/OFF
[Trans.F]
mRNAs
PROTEINS
Na
K
CHO
PATHWAYS
ATP
AA
PROT
Ca^{+2}
SMW
FAT
ADP
ATP
GENES
MITO
ETC

Metabolic Rate Depression CHANGES

- ***Thousands of processes OFF***
- **Gene 'inactivation' (↓ mRNA)**
- **Few Genes activated (1-2%)**

TURNING OFF GENES: Role of Epigenetics

Epigenetics:

- **Stable changes in gene activity that do not involve changes in DNA sequence**

Common mechanisms:

- **DNA methylation**
- **Histone modification / histone variants e.g. acetylation, phosphorylation**
- **Regulatory non-coding RNAs**

Global changes in methylation of gene promoters to reduce transcription rates

Global changes in histone modifications to reduce accessibility to promoter regions by transcription machinery

Transcription and translation are ATP-expensive

Epigenetic modifications can alter rates of transcription/translation to produce energy savings in hypometabolism

MicroRNAs can coordinate expression of cell proteins via post-transcriptional action

Other post-transcriptional controls can apply –

- formation of stress granules &
- action of RNA binding proteins

DNA METHYLATION

DNA methylation and regulation of DNA methyltransferases in a freeze tolerant vertebrate.
Zhang J, Hawkins LJ, Storey KB. Biochem Cell Biol. 2020; 98, 145-153

Transcriptional regulation of metabolism in disease: From transcription factors to epigenetics.
Hawkins LJ, Al-Attar R, Storey KB. PeerJ 2018; 6: e5062.

Gene structure, expression, and DNA methylation characteristics of sea cucumber cyclin B gene during aestivation.
Zhu A, Chen M, Zhang X, Storey KB. Gene 2016; 594(1): 82-88

The role of DNA methylation during anoxia tolerance in a freshwater turtle (*Trachemys scripta elegans*).
Wijenayake S, Storey KB. J Comp Physiol B. 2016; 186(3) :333-42.

Dynamic changes in global and gene-specific DNA methylation during hibernation in adult thirteen-lined ground squirrels, *Ictidomys tridecemlineatus*. Alvarado S, Mak T, Liu S, Storey KB, Szyf M. J Exp Biol. 2015; 218: 1787-95.

DNA methylation levels analysis in four tissues of sea cucumber *Apostichopus japonicus* based on fluorescence-labeled methylation-sensitive amplified polymorphism (F-MSAP) during aestivation. .
Zhao Y, Chen M, Storey KB, Sun L, Yang H. Comp Biochem Physiol B. 2015; 181: 26-32.

Global DNA modifications suppress transcription in brown adipose tissue during hibernation.
Biggar Y, Storey KB. Cryobiology. 2014; 69(2): 333-8.

.

The dynamic nature of DNA methylation: a role in response to social and seasonal variation.
Alvarado S, Fernald RD, Storey KB, Szyf M. Integr Comp Biol. 2014; 54: 68-76.

Mammalian hibernation: differential gene expression and novel application of epigenetic controls.
Morin P Jr, Storey KB. Int J Dev Biol. 2009; 53(2-3): 433-42.

TURNING OFF GENES: Role of Epigenetics

Common mechanisms of epigenetic control:

- **DNA methylation**
- **Histone modification / histone variants**
  e.g. acetylation, phosphorylation
- **Regulatory non-coding RNAs [microRNA]**

HISTONE MODIFICTION

Hibernation impacts lysine methylation dynamics in the 13-lined ground squirrel, *Ictidomys tridecemlineatus.*
Watts AJ, Storey KB. J Exp Zool A Ecol Integr Physiol. 2019; 331: 234-244.

Transcriptional regulation of metabolism in disease: From transcription factors to epigenetics.
Hawkins LJ, Al-Attar R, Storey KB. PeerJ. 2018; 6: e5062.

Roles for lysine acetyltransferases during mammalian hibernation.
Rouble AN, Hawkins LJ, Storey KB. J Therm Biol. 2018; 74: 71-76.

Dynamic regulation of six histone H3 lysine (K) methyltransferases in response to prolonged anoxia exposure in a freshwater turtle. Wijenayake S, Hawkins LJ, Storey KB. Gene 2018; 649: 50-57.

Metabolic suppression in the pelagic crab, *Pleuroncodes planipes*, in oxygen minimum zones.
Seibel BA, Luu BE, Tessier SN, Towanda T, Storey KB. Comp Biochem Physiol B. 2018; 224: 88-97.

Histone methylation in the freeze-tolerant wood frog (*Rana sylvatica*).
Hawkins LJ, Storey KB. J Comp Physiol B. 2018; 188(1): 113-125.

The role of global histone post-translational modifications during mammalian hibernation.
Tessier SN, Luu BE, Smith JC, Storey KB. Cryobiology. 2017; 75: 28-36.

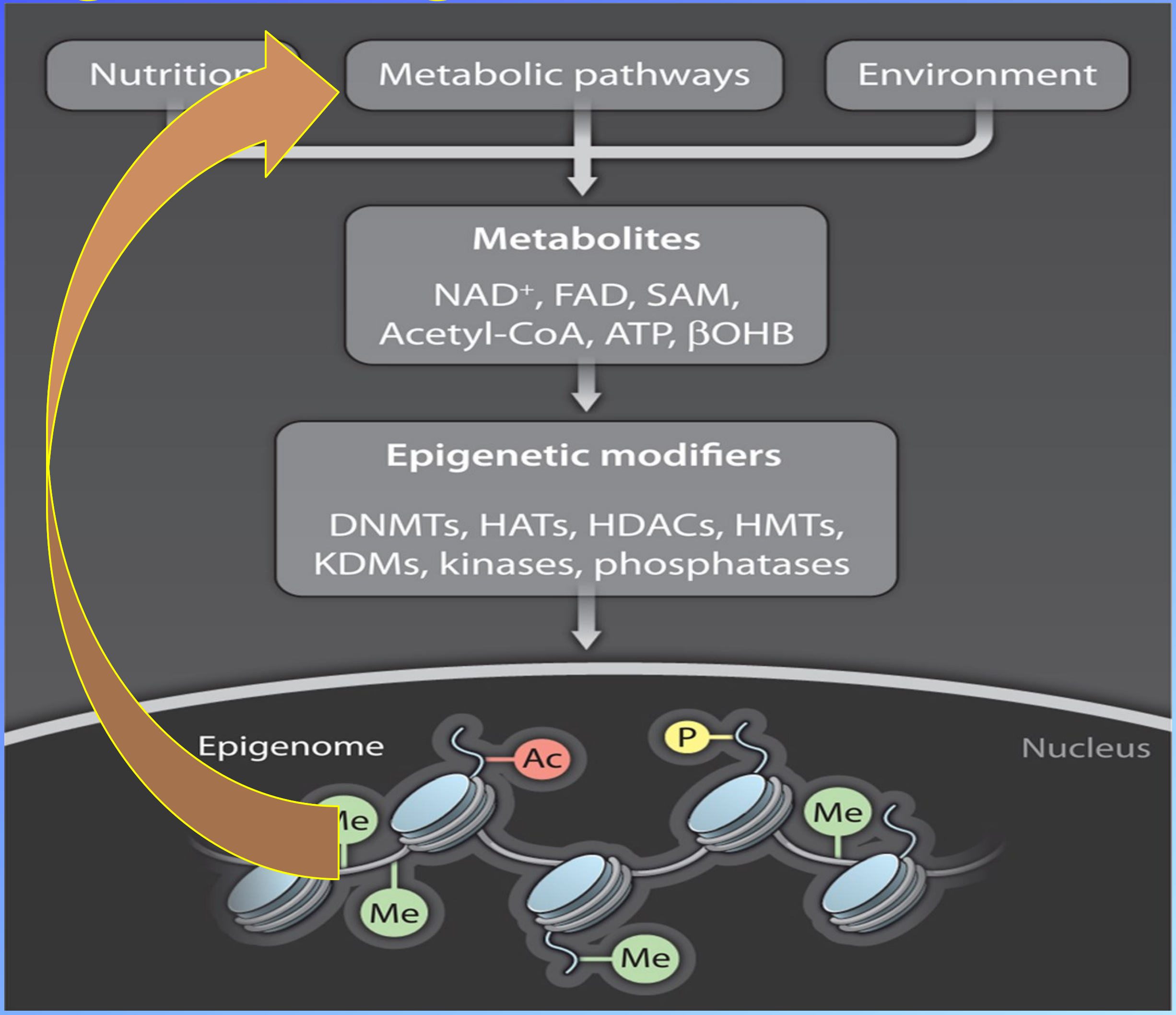
Regulation of torpor in the gray mouse lemur: transcriptional and translational controls and role of AMPK signaling.
Zhang J, Tessier SN, Biggar KK, Wu CW, Pifferi F, Perret M, Storey KB. Genom Proteom Bioinform. 2015; 13(2): 103-10.

Regulation of hypometabolism: insights into epigenetic controls.
Storey KB. J Exp Biol. 2015; 218: 150-9

Global DNA modifications suppress transcription in brown adipose tissue during hibernation.
Biggar Y, Storey KB. Cryobiology 2014; 69(2): 333-8.

Metabolic suppression during protracted exposure to hypoxia in the jumbo squid, *Dosidicus gigas*, living in an oxygen minimum zone. Seibel B, Häfker N, Trübenbach K, Zhang J, Tessier S, Pörtner H, Rosa R, Storey K. J Exp Biol. 2014; 217: 2555-68.

Principle: use epigenetic reprogramming to remodel chromatin



Sassone-Corsi Science 2013;339:148-150

Global changes in methylation of gene promoters to reduce transcription rates

Global changes in histone modifications to reduce accessibility to promoter regions by transcription machinery

Transcription and translation are ATP-expensive.

Epigenetic modifications can alter rates of transcription/translation to produce energy savings during hypometabolism.

MicroRNAs can coordinate expression of cell proteins via post-transcriptional action

Other post-transcriptional controls can apply –

- formation of stress granules &
- action of RNA binding proteins


MRD: Hibernation & MICRO RNA:


PUBMED:

Storey KB microRNA



Turning it all off

doi:10.1093/jmcb/mjx053
Published online January 9, 2018

Journal of Molecular Cell Biology (2018), 10(2), 93–101 | **93**

Review

Functional impact of microRNA regulation in models of extreme stress adaptation

Kyle K. Biggar and Kenneth B. Storey*

Institute of Biochemistry & Department of Biology, Carleton University, Ottawa, ON K1S 5B6, Canada
* Correspondence to: Kenneth B. Storey, E-mail: kenneth_storey@carleton.ca

Edited by Zefeng Wang

When confronted with severe environmental stress, some animals are able to undergo a substantial reorganization of their cellular environment that enables long-term survival. One molecular mechanism of adaptation that has received considerable attention in recent years has b
high-throughput e
Indeed, recent stu
are essential to pr
regulation of a me
frog and insect free
of microRNA stress
adaptation, this rev

Biochimica et Biophysica Acta 1779 (2008) 628–633

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Differential expression of microRNA species in organs of hibernating ground squirrels: A role in translational suppression during torpor

Pier Jr. Morin, Adrian Dubuc, Kenneth B. Storey *

Institute of Biochemistry and Department of Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, Ontario, Canada K1S 5B6

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Keywords:
MicroRNA
Hibernation
Spermophilus tridecemlineatus
Dicer
Reversible control of translation

ABSTRACT

Mammalian hibernation includes long periods of profound torpor where the rates of all metabolic processes are strongly suppressed in a reversible manner. We hypothesized that microRNAs (miRNAs), small non-coding transcripts that bind to mRNA, could play a role in the global suppression of mRNA translation when animals enter torpor. Selected miRNA species (4–9 of the following: mir-1, mir-24, mir-15a, mir-16, mir-21, mir-122a, mir-143, mir-146 and mir-206) were evaluated in four organs of euthermic versus hibernating ground squirrels, *Spermophilus tridecemlineatus* using RT-PCR. Levels of mir-24 transcripts were significantly reduced in heart and skeletal muscle of torpid animals as were mir-122a levels in the muscle. Mir-1 and mir-21 both increased significantly in kidney during torpor by 2.0- and 1.3-fold, respectively. No changes were found for the four miRNA species analyzed in liver. Protein levels of Dicer, an enzyme involved in miRNA processing were also quantified in heart, kidney and liver. Dicer protein levels increased by 2.7-fold in heart during hibernation but decreased by 60% in kidney. These data are the first report that differential regulation

miRNAs & Dicer enzyme show organ-specific changes in mammalian hibernation

Regulatory non-coding RNAs

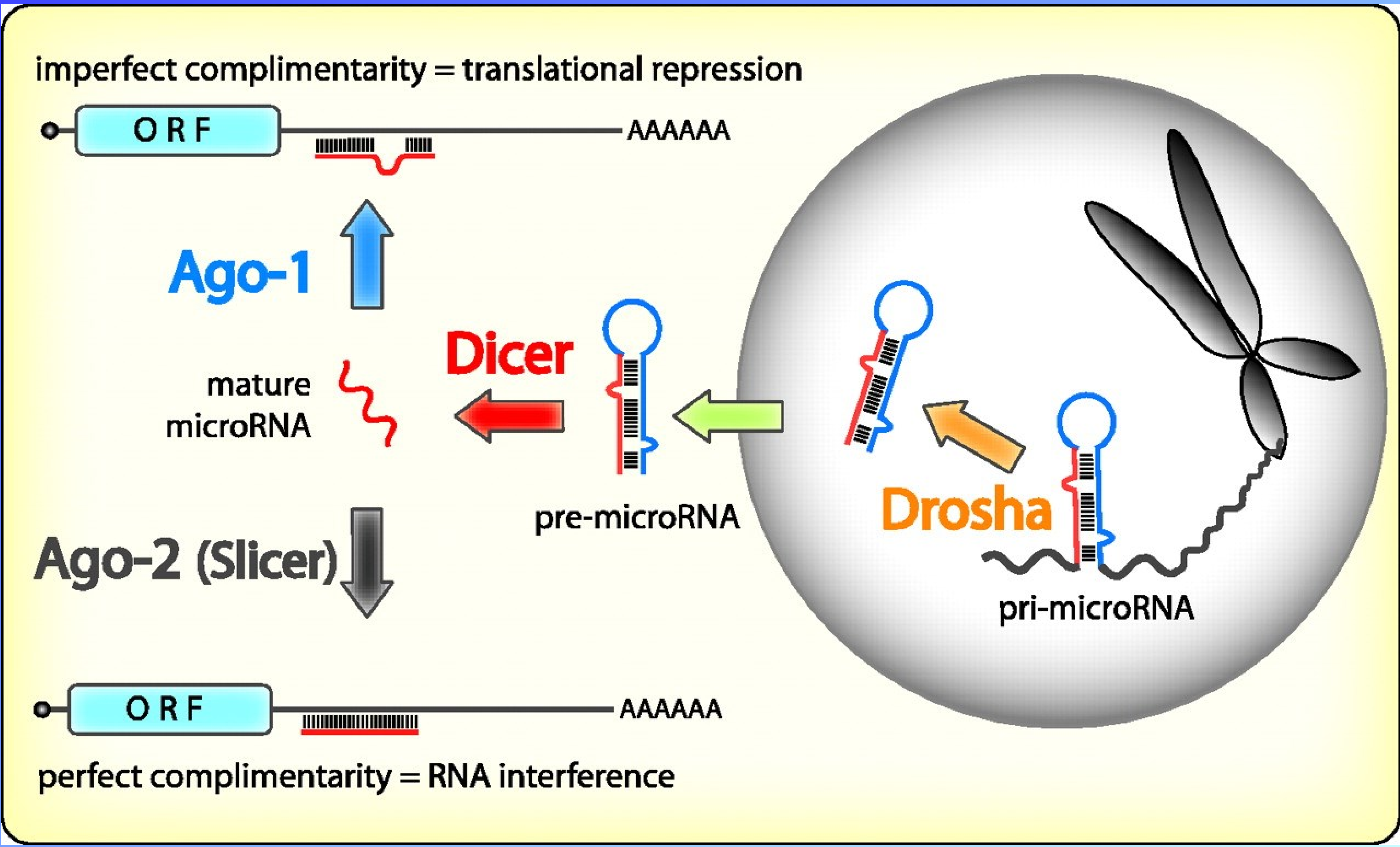
microRNA

- **Small RNAs of ~22 nucleotides in length**
- **Highly conserved across species**
- **<u>Reach out to control genes of ALL cell processes</u>**
- **Could be 1000, affect 85 % of genes**
- **Disease involvement**
- **Act to :**

  - Block translation of mRNA

  - Target mRNA for degradation

MICRO RNA: Drosha & Dicer



Cuellar TL, McManus MT. J Endocrinol. 187(3):327-332, 2005.

MicroRNA & Hibernation

Physiol Genomics 48: 388–396, 2016.
First published April 15, 2016; doi:10.1152/physiolgenomics.00005.2016.

Analysis of microRNA expression during the torpor-arousal cycle of a mammalian hibernator, the 13-lined ground squirrel

Cheng-Wei Wu, Kyle K. Biggar,* Bryan E. Luu,* Kama E. Szereszewski, and Kenneth B. Storey
Institute of Biochemistry and Department of Biology, Carleton University, Ottawa, Ontario, Canada

Submitted 6 January 2016; accepted in final form 4 April 2016

Wu CW, Biggar KK, Luu BE, Szereszewski KE, Storey KB. Analysis of microRNA expression during the torpor-arousal cycle of a mammalian hibernator, the 13-lined ground squirrel. *Physiol Genomics* 48: 388–396, 2016. First published April 15, 2016; doi:10.1152/physiolgenomics.00005.2016.—Hibernation is a highly regulated stress response that is utilized by some mammals to survive harsh winter conditions and involves a complex metabolic reprogramming at the cellular level to maintain tissue protections at low temperature. In this study, we profiled the expression of 117 conserved microRNAs in the heart, muscle, and liver of the 13-lined ground squirrel (*Ictidomys tridecemlineatus*) across four stages of the torpor-arousal cycle (euthermia, early torpor, late torpor, and interbout arousal) by real-time PCR. We found significant differential regulation of numerous microRNAs that were both tissue specific and torpor stage specific. Among the most significant regulated microRNAs was *miR-208b*, a positive regulator of muscle development that was found to be upregulated by fivefold in the heart during late torpor (13-fold during arousal), while decreased by 3.7-fold in the skeletal muscle, implicating a potential regulatory role in the development of cardiac hypertrophy and skeletal muscle atrophy in the ground squirrels during torpor. In addition, the insulin resistance marker *miR-181a* was upregulated by 5.7-fold in the liver during early torpor, which supports previous suggestions of hyperinsulinemia in hibernators during the early stages of the hibernation cycle. Although microRNA expression profiles were largely unique between the three tissues, GO annotation analysis revealed that the putative targets of upregulated microRNAs tend to enrich toward suppression of progrowth-related processes in all three tissues. These findings implicate microRNAs in the regulation of both tissue-specific processes and general suppression of cell growth during hibernation.

tional level, with reversible protein phosphorylation shown to play an integral role in the regulation of key glycolytic enzymes, histone modifications, RNA polymerase II activity, and protein translation initiation (17, 30, 39).

Recent discoveries of microRNAs (miRNAs) have introduced a new dimension of cellular regulation that is highly conserved among species ranging from nematodes, fruit flies, to human (3). MiRNAs are small noncoding RNA transcripts that are ~22 nucleotides in length and are known to exert posttranscriptional control by binding to target mRNAs near the 3′-untranslated region (UTR) to promote translational silencing through either sequestration or degradation. Transcripts targeted by miRNAs have been shown to localize to cytoplasmic foci, which can serve as sites for mRNA storage or degradation leading to translational repression (23). We have recently shown evidence for the formation during hibernation of stress-induced granules that comprised RNA-binding proteins, and these could serve as potential mRNA storage foci that would complement the regulatory roles of miRNAs during torpor (40). A single miRNA can regulate hundreds of genes, and a single gene can be targeted by multiple miRNAs, creating a complex network that is thought to regulate up to 60% of all protein-coding genes in human (21). We have previously reported the regulatory roles of miRNAs during hibernation and have begun to show miRNA regulation as part of a global response to other environmental stressors that include estivation, anoxia, and freezing, with select miRNAs

- **Skeletal muscle atrophy**
- **Cardiac hypertrophy**
- **Insulin resistance**
- **Suppression of cell growth**

MARSUPIAL TORPOR

SCIENTIFIC REPORTS

SCIENTIFIC REPORTS | 6:24627 | DOI: 10.1038/srep24627

OPEN

The hibernating South American marsupial, *Dromiciops gliroides*, displays torpor-sensitive microRNA expression patterns

Received: 08 January 2016
Accepted: 31 March 2016
Published: 19 April 2016

Hanane Hadj-Moussa[1,*], Jason A. Moggridge[1,*], Bryan E. Luu[1], Julian F. Quintero-Galvis[2], Juan Diego Gaitán-Espitia[3], Roberto F. Nespolo[2] & Kenneth B. Storey[1]

When faced with adverse environmental conditions, the marsupial *Dromiciops gliroides* uses either daily or seasonal torpor to support survival and is the only known hibernating mammal in South America. As the sole living representative of the ancient Order Microbiotheria, this species can provide crucial information about the evolutionary origins and biochemical mechanisms of hibernation. Hibernation is a complex energy-saving strategy that involves changes in gene expression that are elicited in part by microRNAs. To better elucidate the role of microRNAs in orchestrating hypometabolism, a modified stem-loop technique and quantitative PCR were used to characterize the relative expression levels of 85 microRNAs in liver and skeletal muscle of control and torpid *D. gliroides*. Thirty-nine microRNAs were differentially regulated during torpor; of these, 35 were downregulated in liver and 11 were differentially expressed in skeletal muscle. Bioinformatic analysis predicted that the downregulated liver microRNAs were associated with activation of MAPK, PI3K-Akt and mTOR pathways, suggesting their importance in facilitating marsupial torpor. In skeletal muscle, hibernation-responsive microRNAs were predicted to regulate focal adhesion, ErbB, and mTOR pathways, indicating a promotion of muscle maintenance mechanisms. These tissue-specific responses suggest that microRNAs regulate key molecular pathways that facilitate hibernation, thermoregulation, and prevention of muscle disuse atrophy.

- Activation of mTOR
- Activation of MAPKs
- Tissue-specific responses:
  - Hibernation
  - Thermal regulation
  - Disuse atrophy

Monito del Monte
from Chile

Genomics Proteomics Bioinformatics 13 (2015) 77–80

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PREFACE

The Gray Mouse Lemur: A Model for Studies of Primate Metabolic Rate Depression

CrossMark

Kenneth B. Storey *,a

Institute of Biochemistry and Department of Biology, Carleton University, Ottawa

Received 15 April 2015; accepted 11 June 2015
Available online 21 June 2015

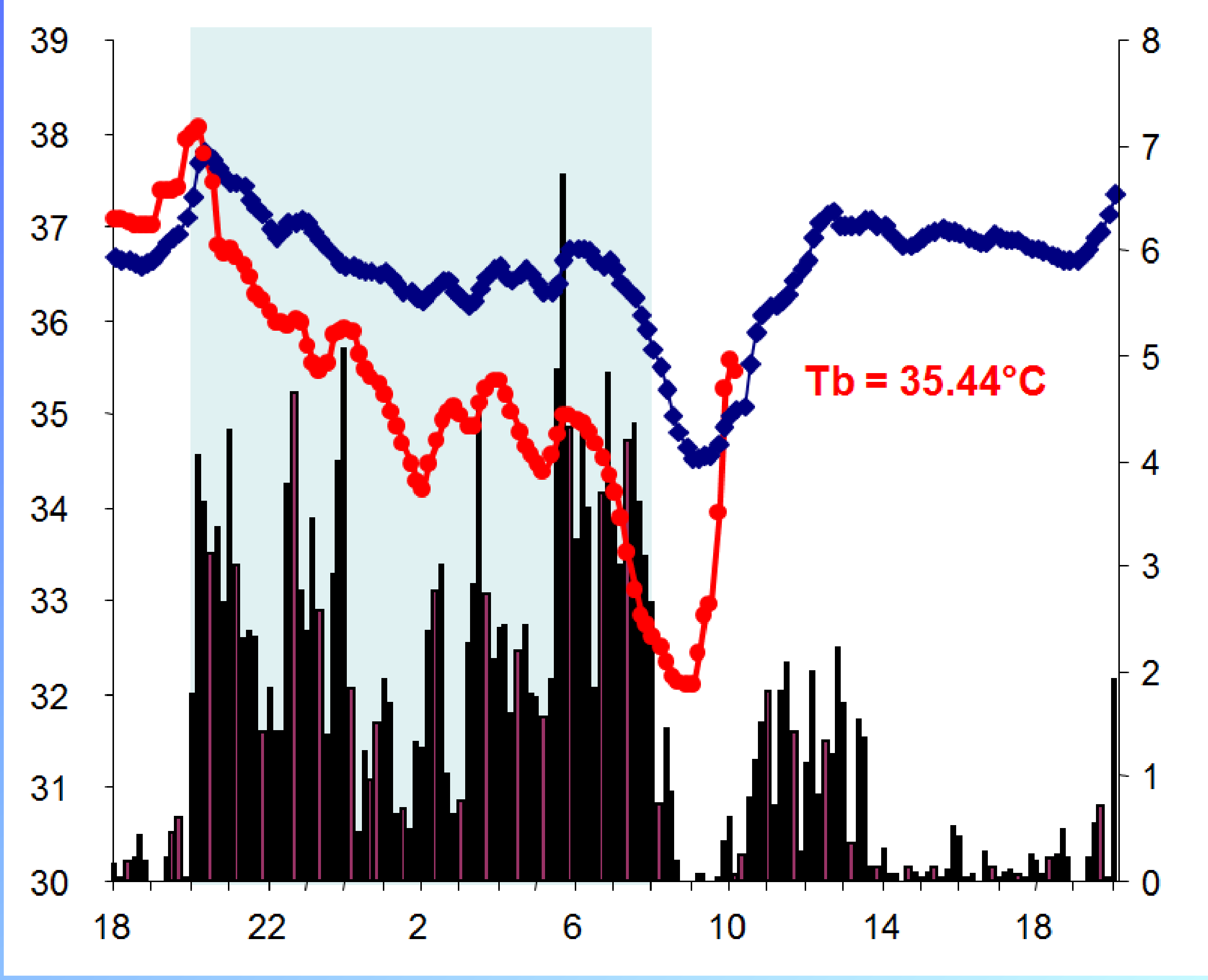
Overview: Fewer cell changes needed when torpor is at higher body temperature !

Gray mouse lemur, *Microcebus murinus* - Native to Madagascar

LEMUR model

- Primates, native to Madagascar
- Use daily torpor while sleeping
- Hibernate long term to deal with chronic food shortages in the dry season
- The most closely related species to man that exhibit natural hypometabolism
- Enter torpor at high ambient temperatures (T_b ~28-32°C) i.e. not confounded by the additional biochemical adaptations needed for low temperature function

PRIMATE TORPOR: GRAY MOUSE LEMUR



DAILY TORPOR

Primate Torpor Series

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PREFACE

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Kenneth B. Storey [*,a]

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Stress response & signal transduction

Genomics Proteomics Bioinformatics 13 (2015) 119–126

ORIGINAL RESEARCH

Induction of Antioxidant and Heat Shock Protein Responses During Torpor in the Gray Mouse Lemur, *Microcebus murinus*

Cheng-Wei Wu [1,3,#,a], Kyle K. Biggar [1,4,#,b], Jing Zhang [1,5,c], Shannon N. Tessier [1,6,d], Fabien Pifferi [2,e], Martine Perret [2,f], Kenneth B. Storey [1,*,g]

Genomics Proteomics Bioinformatics 13 (2015) 81–90

ORIGINAL RESEARCH

Primate Torpor: Regulation of Stress-activated Protein Kinases During Daily Torpor in the Gray Mouse Lemur, *Microcebus murinus*

Kyle K. Biggar [1,3,#,a], Cheng-Wei Wu [1,4,#,b], Shannon N. Tessier [1,5,c], Jing Zhang [1,6,d], Fabien Pifferi [2,e], Martine Perret [2,f], Kenneth B. Storey [1,*,g]

[1] *Institute of Biochemistry and Department of Biology, Carleton University, Ottawa, ON K1S 5B6, Canada*

Regulation of gene/protein expression

Genomics Proteomics Bioinformatics 13 (2015) 103–110

ORIGINAL RESEARCH

Regulation of Torpor in the Gray Mouse Lemur: Transcriptional and Translational Controls and Role of AMPK Signaling

Jing Zhang [1,2,#,a], Shannon N. Tessier [1,3,#,b], Kyle K. Biggar [1,4,c], Cheng-Wei Wu [1,5,d], Fabien Pifferi [6,e], Martine Perret [6,f], Kenneth B. Storey [1,*,g]

Genomics Proteomics Bioinformatics 13 (2015) 111–118

ORIGINAL RESEARCH

Modulation of Gene Expression in Key Survival Pathways During Daily Torpor in the Gray Mouse Lemur, *Microcebus murinus*

Kyle K. Biggar [1,3,#,a], Cheng-Wei Wu [1,4,#,b], Shannon N. Tessier [1,5,c], Jing Zhang [1,6,d], Fabien Pifferi [2,e], Martine Perret [2,f], Kenneth B. Storey [1,*,g]

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Metabolism, fuel use & cytokines

Genomics Proteomics Bioinformatics 13 (2015) 91–102

ORIGINAL RESEARCH

Regulation of the PI3K/AKT Pathway and Fuel Utilization During Primate Torpor in the Gray Mouse Lemur, *Microcebus murinus*

Shannon N. Tessier [1,3,#,a], Jing Zhang [1,4,#,b], Kyle K. Biggar [1,5,c], Cheng-Wei Wu [1,6,d], Fabien Pifferi [2,e], Martine Perret [2,f], Kenneth B. Storey [1,*,g]

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Genomics Proteomics Bioinformatics 13 (2015) 127–135

ORIGINAL RESEARCH

Cytokine and Antioxidant Regulation in the Intestine of the Gray Mouse Lemur (*Microcebus murinus*) During Torpor

Shannon N. Tessier [1,3,#,a], Barbara A. Katzenback [1,4,#,b], Fabien Pifferi [2,c], Martine Perret [2,d], Kenneth B. Storey [1,*,e]

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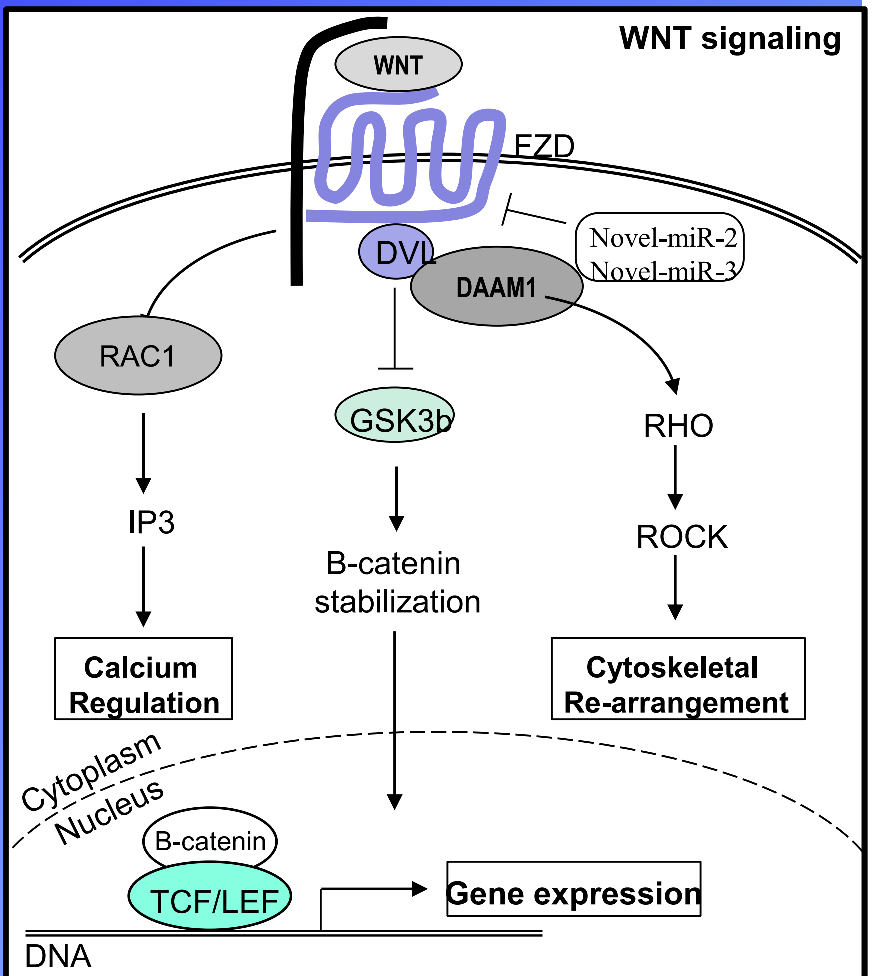
LEMUR model

- Enter torpor at high ambient temperatures (T_b may only fall to ~28-32°C) so MRD is not confounded by adaptations needed to endure T_b at 0-5°C as during hibernation in most mammals
- Fewer Changes [5% of changews of cold hibernation]
- Ex. lack of “stress response” & shock proteins
- Translation Arrest occurs : mTOR, eIF4E
- AMPKinase increases for fuel shifting
- **miRNA responses** = pathway control

LEMUR miRNA



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Profiling torpor-responsive microRNAs in muscles of the hibernating primate *Microcebus murinus*

Hanane Hadj-Moussa[a], Jing Zhang[b,c], Fabien Pifferi[d], Martine Perret[d], Kenneth B. Storey[a,*]

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ARTICLE INFO

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Gray mouse lemur
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ABSTRACT

When food scarcity is coupled with decreased temperatures, gray mouse lemurs (*Microcebus murinus*) depress their metabolic rates and retreat into bouts of either daily torpor or multi-day hibernation, without dramatically dropping body temperatures like other 'traditional hibernators'. Rapid and reversible mechanisms are required to coordinate the simultaneous suppression of energetically expensive processes and activation of pro-survival pathways critical for successful torpor-arousal cycling. MicroRNAs, a class of endogenous non-coding small RNAs, are effective post-transcriptional regulators that modulate all aspects of cellular function. The present study hypothesizes that miRNAs are intimately involved in facilitating the molecular reorganization events necessary for lemur skeletal muscle torpor. Small RNA-Sequencing was used to compare miRNA profiles from skeletal muscles of torpid and control primates. We characterized 234 conserved miRNAs, of which 20 were differentially expressed during torpor, relative to control. Examples included downregulation of key muscle-specific (myomiR) members, miR-1 and miR-133, suggesting a switch to muscle-specific energy-saving strategies. *In silico* target mapping and logistic regression-based gene set analysis indicated the inhibition of energy costly pathways such as oxidative phosphorylation and muscle proliferation. The suppression of these metabolic pathways was balanced with a lack of miRNA inhibition of various signaling pathways, such as MAPK, mTOR, focal adhesion, and ErbB. This study identifies unique miRNA signatures and 'biomarkers of torpor' that provide us with primate-specific insights on torpor at high body temperatures that can be exploited for human biomedical concerns.

PRIMATE TORPOR: Shutting down primates, LIKE YOU !!

The FEBS Journal

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VIEWPOINT

Bringing nature back: using hibernation to reboot organ preservation

Hanane Hadj-Moussa and Kenneth B. Storey

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Keywords
biostasis; metabolic rate depression; microRNA; normothermic perfusion; organ transplantation; torpor; warm preservation

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Recently, organ transplant therapy has received a major boost from a change in perspective – a move away from damaging, cold static organ storage to the use of *warm* normothermic perfusion. The concept for warm preservation is one that has been borrowed from Nature, and it is only fitting that we go back to the wild for more 'tricks' to further improve warm organ stabilization. Current warm preservation strategies are designed to mimic natural conditions in the human body as closely as possible, but what if we could mimic these conditions while simultaneously inducing a reversible state of torpor that would further extend the viability window of donor organs? Indeed, the original driver for using cold organ storage was its ability to strongly reduce metabolic rate many-fold when organs were cooled from 37 to 5 °C. Herein, we discuss the adaptations that allow warm hibernators such as bears and lemurs (fellow primates) to naturally depress their metabolic rate and retreat into states of suspended animation, and how these can be applied to improve organ transplant therapy. Can we look to Nature for instructions to induce torpor in human organs? This article discusses the possibilities.

The $1,000,000 Question → What is needed for long term human MRD ?

- Many less genes & fewer tissues affected in RT torpor than in long-term hibernation at cold body temperatures.
- <u>Organs</u>: identify key processes in each organ that need adjusting
- Warm preservation may be the least injurious

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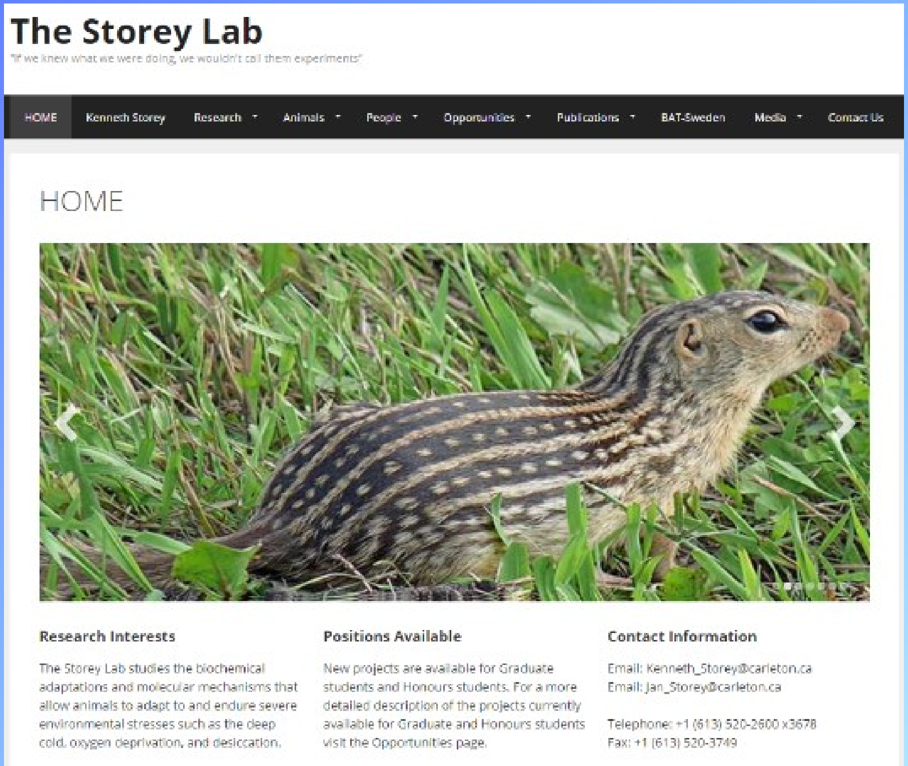

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Global changes in methylation of gene promoters to reduce transcription rates

Global changes in histone modifications to reduce accessibility to promoter regions by transcription machinery

Transcription and translation are ATP-expensive.

Epigenetic modifications can alter rates of transcription/translation to produce energy savings in hypometabolism

MicroRNAs can coordinate expression of cell proteins via post-transcriptional action

Other post-transcriptional controls can apply

- **formation of stress granules &**
- **action of RNA binding proteins**