

## EXPLORING BIOCHEMICAL ADAPTATION:

*Synthetic Intuition  
on a Family Farm*



[www.carleton.ca/~kbstorey](http://www.carleton.ca/~kbstorey)

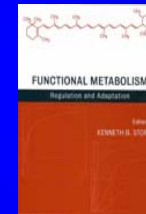
## Biochemical Adaptation - How Animals Work

- Search to identify principles of biochemical regulation across the animal kingdom
- Biochemical unity
- Chemistry bkgd., NO Biology (ever)
- Elastic limits of biochemistry



**There are so many songs and  
only the three cords.**

- John Hiatt



## A Life of Science Adventure

### Mentors

**Peter  
Hochachka**



**Dave  
Jones**

Knut Schmidt-Neilsen, Ladd Prosser,  
Kjell Johansen, **Ken Davey**, Hans Krebs,  
Gene Huber, Les Copley, **Geoff Eales**, A. Helix



**DO YOUR WORK, THEN STEP BACK.  
THE ONLY PATH TO SERENITY.**

- "Tao Te Ching" by Lao Tzu

## Storey Family Farm





## SYNTHETIC INTUITION

1) A new mix of ideas leads to a new field:

Chemistry

Mol. Biol.

Biochem.

}

Diverse  
Techniques

→

Comparative  
Experiments


*NMR, MRI, DSC, AFM, DSF, UV difference, Protein purification, etc.*

2) Models: Zoology, Ecology, Field Trips

3) Any new set of data reorganizes itself through UNRELATED pieces of the puzzle and returns as UNIQUE.


4) Salvage Solutions from Chaos:  
ex. Thesis Ideas, "DATA KNOTS"


5) Time Vampire: "Students Match Projects"



## SYNTHETIC INTUITION


Something Old,  
Something New,  
Something Borrowed,  
Some Glue





## SYNTHETIC INTUITION

| <u>INPUT</u>  | <u>FILTER</u>   | <u>OUTPUT</u>  |
|---|---|--|
| <ul style="list-style-type: none"> <li>~ Ecology</li> <li>~ Natural History</li> <li>~ PHYSIOLOGY</li> <li>~ Chemistry Analytical</li> <li>~ Biochem methods</li> <li>~ Mol Biol methods</li> <li>~ Genes – BioInform.</li> <li>~ NOT Metabolism</li> <li>~ Equipment Expos</li> <li>~ Catalogues</li> <li>~ Tools:               <ul style="list-style-type: none"> <li>- PHONE (1980)</li> <li>- EMAIL (1990→)</li> </ul> </li> <li>~ Jan Writing</li> <li>~ Touring (R&amp;R)</li> </ul> | <ul style="list-style-type: none"> <li>~ Transducer</li> <li>~ Organizer</li> <li>~ "Revamp"</li> <li>~ IDEA LENS</li> <li>~ Non-sci. Stability</li> <li>~ Never "Circle the Wagons"</li> <li>~ COST / BENEFIT</li> </ul> | <ul style="list-style-type: none"> <li>~ Metabolic Arrangement</li> <li>~ Reorganization of Metabolism</li> <li>~ Adaptive Change at Pathway Level</li> <li>~ Integration: multi-levels of biol. organization</li> <li>~ Model Organisms as raw material</li> <li>~ Intracellular: from membrane to Nucleus</li> </ul> <p style="text-align: center; color: yellow;">BIOCHEMICAL UNITY</p> |



## Why Am \*I\* Here



**" My lab is full"**

>> Said to KBS when turned down by PWH for a spot in his lab.

...15 minutes ( discussion) later ...

**" Take that desk"**

>> Said to KBS when Peter discovered that Ken had a scholarship that paid both salary and research expenses.

## And, Students 50 MSc, 36 PhD, 11 PDFs

### PDF

J Ballantyne  
S Rahman  
B Michaelidis  
R Ferguson  
SPJ Brooks  
M Hermes-Lima  
C Frank  
Q Cai  
I Moineau  
M Batrukova  
E Kotani



### PhD

W Plaxton  
T Churchill  
D Joannis  
Y Su  
J Grundy  
H Mehrani  
C Holden  
W Willmore  
B Thatcher  
K Cowan  
J MacDonald  
T Bilgen  
S-B Wu  
T English  
A Fahlman  
D McNally  
K Larade  
S Eddy

D Hittel  
D McMullen  
A de Croos  
P Morin  
K Abnous  
M Hapsatou  
C Ramnathan  
C Dieni  
A Malik  
A Krivoruchko  
B Lant  
K Biggar  
J Zhang  
C-W Wu  
N Dawson  
R Bell  
A Letourneau  
S Tessier

### MSc

K Male, D Miller, S Korycan, R Cole, A Chakrabarti, J Duncan, R Whitwam  
D Kelly, D Schafhauser, C Holden, E Russell, D Douglas, A Muise, T Pannunzio,  
P Schade, S Greenway, M de la Roche, T English, D Lobsinger, L Jurgensen,  
S Lautru, T Pfister, S Saeedi, M Castellari, E Sepchr, K Yan, J Ni, L Zhenhong,  
A Woods, S McFadyen, J Du, J Zhang, J Zhou, L Xie, M Bouffard, J Niles, L-H  
Yao, J Lama, R Bell, M Mathialagan, O Aguilar, N Dawson, C Brooks, R Roufayel,  
S Tessier, A Letourneau, M Allan, A Holden, K Sullivan, A Mahmud, J Wu

**+ 105  
Undergrads**

## WHY I PERSISTED

- Synthetic Intuition
- JANET
- Talented Team (PhD, MSc, UG)
- Strategy (Student Wrangling)
- PDF ( Few but Key) + **Luck**
- Constant NSERC funding
- Occasional Equipment grants
- Big Scores (timely) CFI-OIT, NIH
- Cardboard Enemies /  
Big Talent Support



## My Presentation : R&R ? Or Comedy ?

- At Rock Shows, you want the group to play the **OLD** songs just like on the album
- At Comedy Shows, if you hear an **OLD** joke, you boo. You want the **NEW**, fresh material.

**Answer: Science talks are about tomorrow**

## Greatest Hits: (Vol 1) “High Tides & Green Grass” The early days

- Comparative regulation of glycolysis
- Methods in Enzymology (purification)
- Exercise muscle metabolism: insects & cephalopods
- Octopine (**Storey cycle**), alanopine & strombine
- Glycolytic Enzyme Complex
- Bound water in metabolism
- Reversible phosphorylation control of metabolic enzymes ( Novel)
- Phosphagen effects on enzymes
- PFK polymers &  $F_{2,6}P_2$



## Greatest Hits: (Vol 2) Anoxia Tolerance

- Anti-Pasteur Effect (Anti-Temperature !)
- Coordinated Metabolic Rate Depression (MRD)
- Anabolism follows Catabolism in MRD
- Reversible phosphorylation of glycolytic enzymes: Gly phos, PFK, PK, etc.
- Protein kinases: PKA, PKG, MAPKs, AMPK, etc.
- Anoxia-induced gene expression
- Antioxidants – adaptation to variable oxygen



## Greatest Hits: (Vol. 3) Cold & Freezing Survival

- Deep supercooling by cold-hardy insects
- Freeze tolerance:
  - insects & molluscs
  - frogs, turtles, lizards, snakes
- Biochemistry of cryoprotectants
- Adaptive evolution from underlying anoxia & dehydration tolerances
- Freeze responsive gene expression
- Novel proteins



## Unique Animal Stress Model

Vertebrate  
whole-body  
freeze tolerance

Tissue  
cryopreservation



Tolerance of extreme  
ischemia and  
hyperglycemia



## Greatest Hits: (Vol. 4) Hibernation

- Regulated MRD drives body temperature down
- Reversible enzyme control in torpor-arousal cycles
- Cold adaptation of mammalian enzymes
- Polysome dissociation, mRNA storage
- Micro RNA
- Gene screening, epigenetic controls
- Antioxidant defense (Tf)
- Atrophy resistance



## Greatest Hits: (Vol. 5) Estivation

- MRD parallels estivation = low oxygen / anoxia
- Phosphorylation also controls
  - ion motive ATPases (NaK, Ca)
  - novel enzymes
  - protein synthesis flux generators
  - transcription factors
- Involvement of protein kinases – Akt, AMPK, MAPKs, PKA/PKG
- Role of FOXO transcription factors
- Urea effects on enzymes



## Greatest Hits: Full Collection

- Animal stories
- Publications
- Research Interests
- Students & projects
- Media

• Textbook with former students

[www.carleton.ca/kbstorey](http://www.carleton.ca/kbstorey)

**Kenneth B. Storey**  
Ph.D., F.R.S.C.  
Canada Research Chair in Molecular Physiology  
Professor of Biochemistry  
Institute of Biochemistry  
and Departments of  
Biology and Chemistry

**Click on photo**

**THE LAB**

**Research Interests**

**GRADUATE STUDENTS** - positive website

**RESEARCH STUDENTS** 4000 and summer projects available

**PEOPLE** in the Storey lab, Past and Present

**Free computer programs**

**Animals** info on housing (CNS) animals

**PHOTO GALLERY** our animals & their studies

**Publications**

**Publications** 1991 - 2000

**Publications** 2001 - 2005

**Publications** 2006 - 2010

**Publications** 2011 - 2015

**Publications** 2016 - 2020

**Publications** 2021 - 2025

**Publications** 2026 - 2030

**Publications** 2031 - 2035

**Publications** 2036 - 2040

**Publications** 2041 - 2045

**Publications** 2046 - 2050

**Publications** 2051 - 2055

**Publications** 2056 - 2060

**Publications** 2061 - 2065

**Publications** 2066 - 2070

**Publications** 2071 - 2075

**Publications** 2076 - 2080

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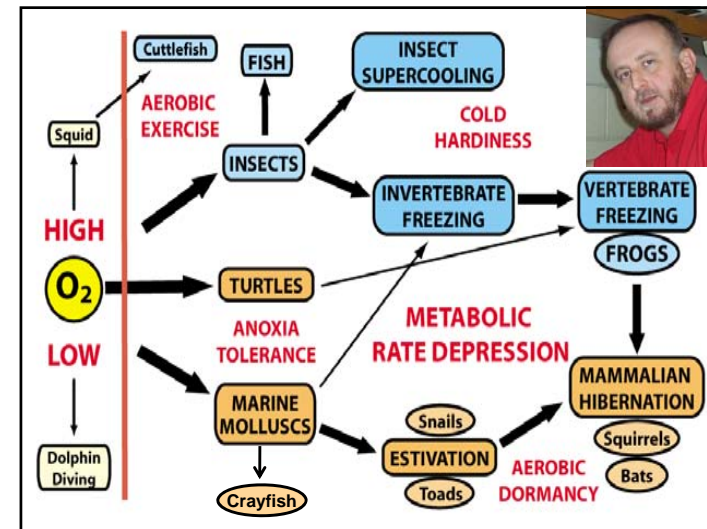
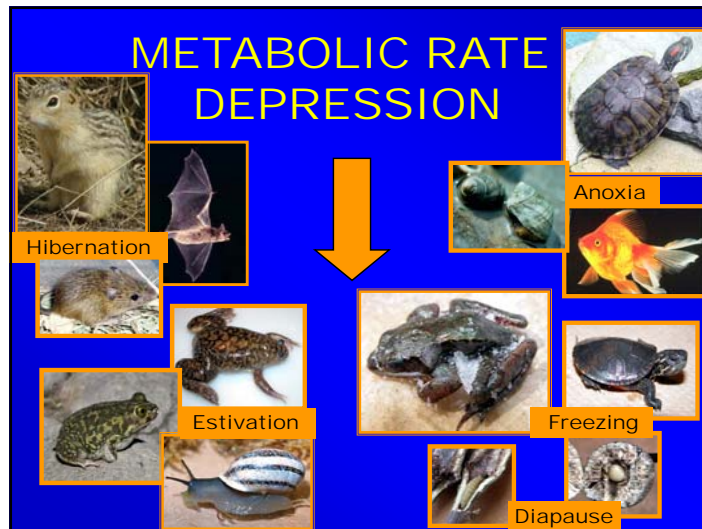
**Publications** 2986 - 2990

**Publications** 2991 - 2995

**Publications** 2996 - 3000

## Best Experiment EVER !



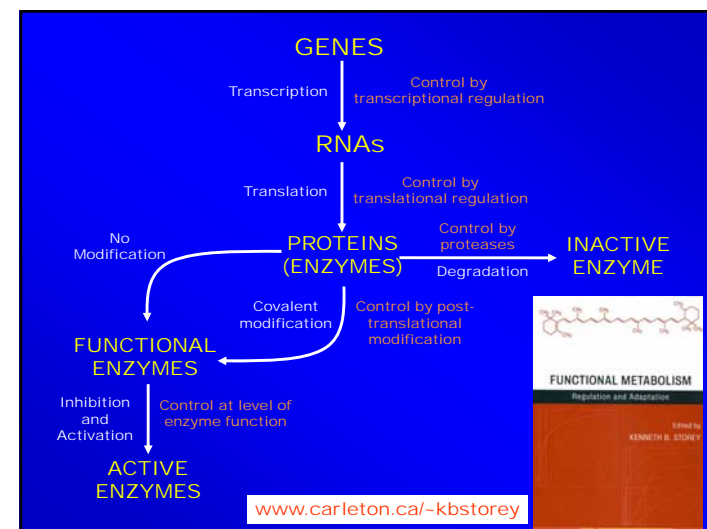


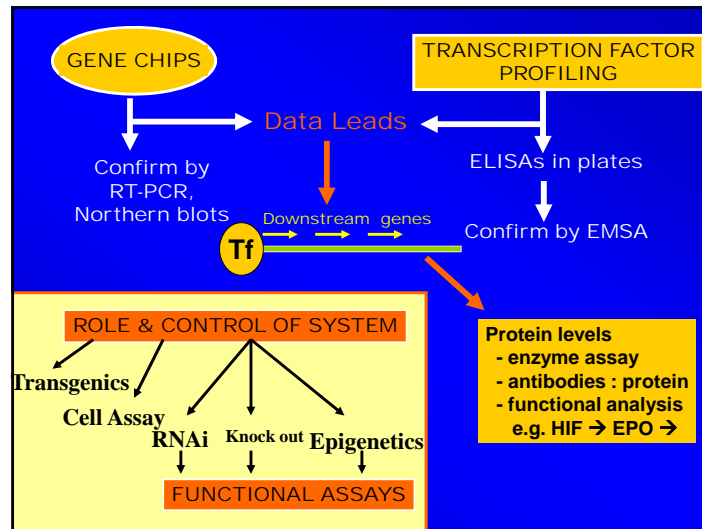
## Principles of Metabolic Rate Depression

- Transcriptional + translational + PTM
- Anabolism follows Catabolism in MR
- Coordinated suppression: gene expression, protein synthesis, biosynthesis, cell cycle, etc.
- Reversible phosphorylation of key enzymes, ion channels, transcription factors, etc.
- Stress-activated protein kinases

**Cell preservation in hypometabolism**

- Antioxidant defenses, iron sequestered
- Chaperone proteins





## Where do we go from here?

- Human applications of MRD research
- Novel phosphorylations
- Atrophy, hypertrophy -- autophagy for survival
- Turning it all off -- microRNA
- Epigenetics & adaptation
- Life span extension
- Antioxidant defense
- Cell cycle suppression
- Unity through evolution



**NOW: finally !!! NEW DIRECTIONS**

## Hibernation and medicine

*Adv. Clin. Chem.* 2010;52:77-106.  
**Metabolic rate depression: the biochemistry of mammalian hibernation.**  
 Storey KB, Storey JM  
 Institute of Biochemistry, Carleton University, Ottawa, Ontario, Canada. kenneth\_storey@carleton.ca

**Abstract**  
 During winter hibernation, small mammals fall into long periods of deep cold torpor where metabolic rate is suppressed by >90% and core body temperature can fall to near 0 degrees C. Studies with hibernators illustrate the molecular regulatory mechanisms that coordinate the suppression of metabolic functions during torpor, reprioritize energy use, and preserve/stabilize macromolecules to support long-term viability during cold torpor. This review explores mechanisms including posttranslational modification of proteins, differential regulation of enzymes, global suppression of transcription and translation including a role for transcription factors. The review is intended to be useful to researchers in comparative physiology, evolutionary biology, and atrophy/resistance.

**Out cold: biochemical regulation of mammalian hibernation - a mini-review.**

Storey KB  
 Institute of Biochemistry, Carleton University, Ottawa, Ont., Canada. kenneth\_storey@carleton.ca

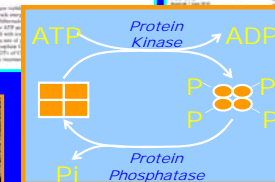
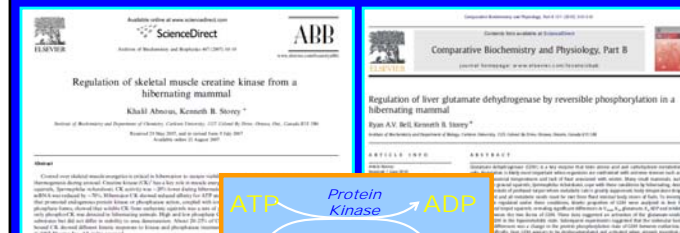
**Abstract**  
 Hibernating mammals offer an intriguing example of natural torpor and illustrate the regulatory mechanisms that control cell preservation strategies that support long-term viability in a hypometabolic state. These include the hypothermic preservation of human organs for transplant, and guidelines that serve as an intervention strategy in human medicine. Recent advances in hibernation research contribute to metabolic depression by orchestrating the global suppression of ATP production including multiple forms of post-translational modification of proteins/enzymes (ubiquitination, mTORC1 storage mechanisms, and differential expression of microRNA species), also contributed new advances in understanding the range of cell functions that are maintained. Some critical preservation strategies that aid long-term viability in a torpid state. These include the suppression of the unfolded protein response, and the enhancement of autophagy to control the actions of extracellular proteases in clotting and inflammation responses.



**Primates !!**



## Novel phosphorylations



# Atrophy – Hypertrophy

Int Cell Biomech. 2010 Nov;34(41-2):191-42. Epub 2010 Jul 9.

**Expression of myocyte enhancer factor-2 and downstream genes in ground squirrel skeletal muscle during hibernation.**

Tessier GJ, Storey KB

Institute of Biochemistry & Department of Biology, Carleton University, Ottawa, ON, Canada.

**Abstract**

Myocyte enhancer factor-2 (MEF2), transcription factors regulate the expression of a variety of genes encoding contractile proteins and other proteins associated with muscle performance. We proposed that changes in MEF2 levels and expression of selected downstream targets would alter the skeletal muscle of brown-lined ground squirrels (*Spermophilus tridecemlineatus*) in meeting metabolic challenges associated with winter hibernation, e.g., cycles of torpor-arousal, body temperature that can fall to near 0°C, long periods of inactivity, that could lead to atrophy. MEF2A protein levels were significantly elevated when animals were in torpor (mainly); 2-fold higher than in active (awake) mice and the amount of phosphorylated active MEF2A, Thr312 increased during entrance into torpor. MEF2C levels also rose significantly during entrance and torpor as did the amount of phosphorylated MEF2C Ser387. Furthermore, both MEF2 members showed elevated amounts in the nuclear fraction during torpor as well as enhanced binding to DNA indicating that MEF2-mediated gene expression was up-regulated in torpid animals. Indeed, the protein products of two MEF2 downstream gene targets *uncoupled in muscle during torpor*, glucose transporter isoforms 4, GLUT4; or early arousal (myogenic differentiation, MyoD). MyoD mRNAs transcribed levels correlated with the rise in protein product levels and provided MEF2-mediated gene expression in the hibernator. Transcript levels of Irf2a3 and TACC3 with levels of both being highest during arousal from torpor. The data suggest a gene transcription in the selective adjustment of muscle protein complement over the

The diagram shows a sequence of four heart illustrations connected by arrows, representing the cycle of hibernation and arousal. The first heart is labeled 'Falling heart' and has a blue arrow pointing down next to it. The second heart is labeled 'Hibernation (torpor)' and has a blue arrow pointing left next to it. The third heart is labeled 'Arousal (wakefulness)' and has a blue arrow pointing right next to it. The fourth heart is labeled 'Physiological hypertrophy' and has a blue arrow pointing up next to it. Below each heart, there are three labels: 'Decrease myocardial mass', 'Protein synthesis - repressible', and 'Nuclei reduction and late protein repletion post-arousal'. These labels are repeated under each heart stage, indicating the state of the heart during that phase.

# Epigenetics in Adaptation

*SciCell Systems*, 2010 Sep 24(2):1-2, 193-61. Epub 2010 May 1.

## Epigenetics in anoxia tolerance: a role for histone deacetylases.

*Epigenetics* 15, 2010: 938-948.

Institute of Biochemistry, Carleton University, Ottawa, ON, Canada. [kmorin@uottawa.ca](mailto:kmorin@uottawa.ca)

### Abstract

The importance of epigenetics has been established in many key biological mechanisms to animal survival of low oxygen conditions has never been examined. Mechanisms that could be involved in natural anoxia tolerance, we have examined transcriptional silencers, histone deacetylases (HDACs), in tissues of a unique turtle *Trachemys scripta elegans*. Transcript and protein levels of all five HDACs in skeletal muscle in response to 20 h of anoxia exposure. In addition, HDAC response to 20 h of anoxia and levels of acetylated histone H3 (Lys 9 or Lys 26) were displayed a milder response with HDAC1, -4, and -5 protein levels increased acetylated histone H3 levels also decreased to 55-75% of control values. Ost heart, HDAC5 protein levels increased 2-3 fold and HDAC5 protein rose

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

**ScienceDirect**

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**CRYOBIOLOGY**

[www.elsevier.com/locate/cryobiology](http://www.elsevier.com/locate/cryobiology)

### Evidence for a reduced transcriptional state during hibernation in ground squirrels<sup>1</sup>

Pier Jr Morin<sup>1</sup>, Kenneth B. Storey<sup>1</sup>

<sup>1</sup>Department of Chemistry, Carleton University, 1125 Colonel By Drive, Ottawa, ON, Canada K1S 5B6

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Available online 13 September 2010

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# Life span extension

Dev Biol Cell. 2010 May-Jun;3(3):186-86.



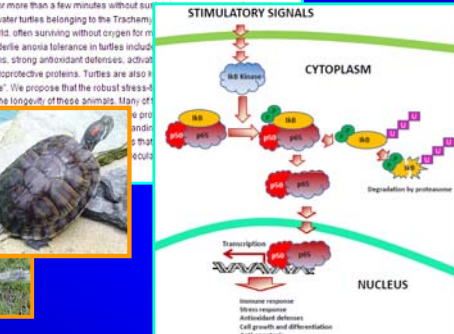
## Forever young: mechanisms of natural, physiological and environmental longevity.

[Kouyama A. Storey KB](#)

Institute of Biochemistry and Department of Medicine, Carleton University, Ottawa, ON, CA.

### Abstract

While mammals cannot survive oxygen deprivation for more than a few minutes without suffering, some animals have mastered anaerobic life. Freshwater turtles belonging to the Trachemydidae, champion facultative anaerobes of the vertebrate world, often surviving without oxygen for many months. Physiological and biochemical mechanisms that underlie anoxia tolerance in turtles include depression, post-translational modification of proteins, strong antioxidant defenses, activation of transcription factors, and enhanced expression of cytoprotective proteins. Turtles are also known to display characteristics of "negligible senescence". We propose that the robust, albeit long-term anaerobiosis by turtles may help support the longevity of these animals. Many of the natural anoxia tolerance, such as hypometabolism, may be applicable to other organisms to play important roles in mammalian oxygen-restricted environments. This review could aid in the understanding and treat in the present review we discuss the recent advances and the potential links between this topic.

**STIMULATORY SIGNALS**

**CYTOPLASM**

**NUCLEUS**

Insulin resistant  
Shows response  
Antioxidant defense  
Cell growth and differentiation  
Anti-apoptosis



**Cytotoxicity of chromium ions may be connected with induction of oxidative stress**  
Olga Yu. Vaytikh\*, Olya I. Kuzak\*, Kenneth B. Storey\*, Volodymyr I. Lushchak\*\*

*Department of Biochemistry, Princeps School of Health Sciences, 100 University Ave., Toronto, Ontario, M5S 1A5, Canada*

**ARTICLE INFO**  
Received 19 March 2010  
Received in revised form 11 May 2010  
Accepted 19 May 2010  
Available online 14 June 2010

**Keywords:**  
Chromium  
Oxidative stress  
Cellular toxicity  
Antioxidant defense

**Ukrainian connection  
- Metal & herbicide  
effects on fish  
- Antioxidant defense**

**Abstract**  
Chromium ions are toxic to fish, and their toxicity is related to oxidative stress. In this study, we investigated the effects of Cr(VI) on the antioxidant defense system of goldfish (*Carrasius auratus*). The results show that Cr(VI) induces oxidative stress in goldfish tissues, leading to a decrease in the levels of antioxidant enzymes (SOD, CAT, GPx) and an increase in the levels of malondialdehyde (MDA). These findings suggest that Cr(VI) may be a potential environmental pollutant that can cause oxidative stress in fish.

**Low toxic herbicide Roundup induces mild oxidative stress in goldfish tissues**  
Olya I. Kuzak\*, Olya I. Kuzak\*, Janet M. Storey\*, Kenneth B. Storey\*, Volodymyr I. Lushchak\*\*

*Department of Biochemistry, Princeps School of Health Sciences, 100 University Ave., Toronto, Ontario, M5S 1A5, Canada*

**ARTICLE INFO**  
Received 19 March 2010  
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Available online 17 May 2010

**Keywords:**  
Roundup  
Oxidative stress  
Cellular toxicity  
Antioxidant defense

**Abstract**  
The herbicide Roundup is widely used in agriculture. It is considered to be low toxic to the World Health Organization, but it may cause oxidative stress and antioxidant defense in fish. In this study, we investigated the effects of Roundup on the antioxidant defense system of goldfish (*Carrasius auratus*). The results show that Roundup induces oxidative stress in goldfish tissues, leading to a decrease in the levels of antioxidant enzymes (SOD, CAT, GPx) and an increase in the levels of malondialdehyde (MDA). These findings suggest that Roundup may be a potential environmental pollutant that can cause oxidative stress in fish.




# Unavoidable metabolic costs


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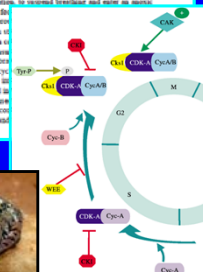
**Perspectives in Cell Cycle Regulation: Lessons from an Anoxic Vertebrate**



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**Abstract:** The ability of an animal, usually dependent on aerobic respiration, to survive in anoxic conditions is a fascinating feat, and has been the focus of intense research. Anoxia is a state of oxygen deprivation, and animals take a place in order to facilitate vital reductions in ATP consumption. Such adaptations, as well as the implementation of tolerance and transcriptional changes, it is clear that anoxic survival relies on the suppression of ATP consumption. Several anoxic vertebrates remain active. Several anoxic vertebrates enter a state of anoxia-tolerant diapause, where metabolic activity is reduced to a minimum. Understanding how vertebrates respond to anoxia can have implications for understanding how vertebrates respond to hypoxia and anoxia. Understanding how vertebrates respond to anoxia can have implications for understanding how vertebrates respond to hypoxia and anoxia.





# Unity through Evolution

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**Review**  
**An Overview of Stress Response and Hypometabolic Strategies in *Caenorhabditis elegans*: Conserved and Contrasting Signals with the Mammalian System**

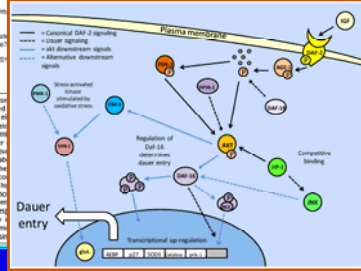
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**Abstract**  
Studies of the molecular mechanisms of stress response and hypometabolic strategies in *Caenorhabditis elegans* have long been used as model organisms. *C. elegans* is a 'dauer' stage. This period of development is a metabolic state, triggered by environmental conditions and stress. The suppression of cellular metabolism of nematodes through the dauer stage is a fundamental survival strategy. In general, mammalian systems are highly sensitive to environmental stress, and the suppression of cellular metabolism is a common response to stress. This review provides an overview of the stress response and hypometabolic strategies in *C. elegans*, and discusses the conserved and contrasting signals with the mammalian system.

**WWCeD**



# ONWARDS !

**Temperature Adaptation in a Changing Climate**

EDITED BY KENNETH B. STOREY AND KAREN LANTINO

