Inflammatory responses and mTORC1 metabolism

Mark E. Wilson, PhD Reproductive Physiology

UNIVERSITY OF MINNESOTA
Driven to Discover®

Fight or Flight Response

- Events perceived as stressful have been found to affect susceptibility to infection[a]

- The sympathetic nervous system (SNS) is one of the three parts of the autonomic nervous system, along with the enteric and parasympathetic systems. Its general action is to mobilize the body's resources under stress; to induce the fight-or-flight response[b]

- It is constantly active at a basal level in order to maintain homeostasis[b]

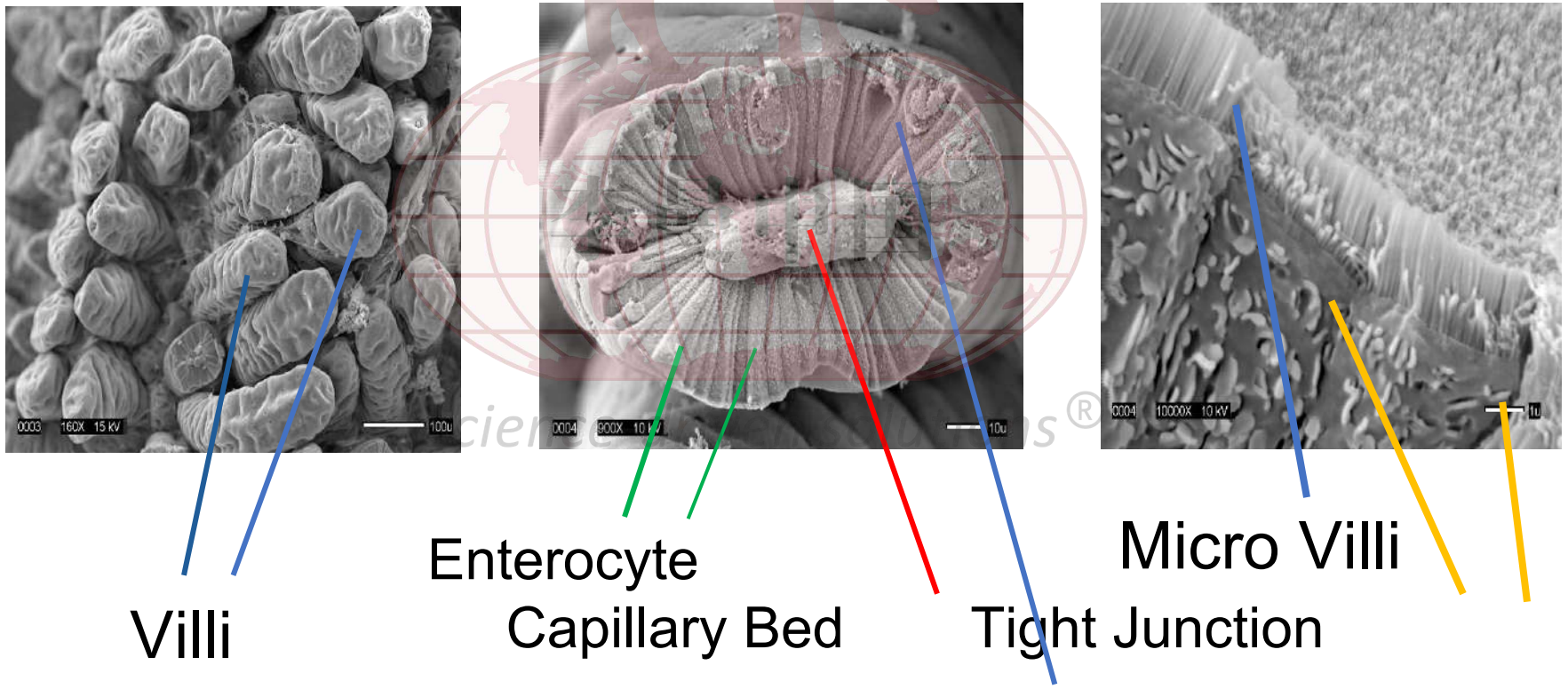
Stressors

- Psychological challenges
- Physical stressors
- Environmental stressors

[a] Freestone, P. and Lyte M. 2010. Animal 4:7, 1248-1257

[b] Brodal, Per. 2004. "The Central Nervous System: Structure and Function" (3 ed.). Oxford University Press US. pp. 369–396.

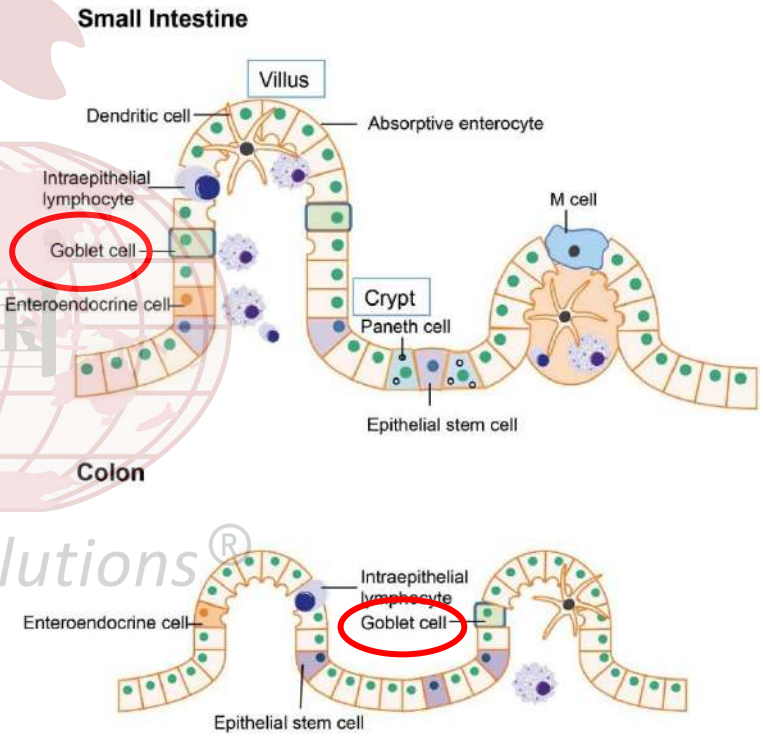
Intestinal anatomy



Epithelial Tissues – barrier functions

- Intestinal tract
- Skin
- Lungs
- Reproductive tract
- Eyes
- Claws

Goblet Cells



Source: https://www.frontiersin.org/files/Articles/149542/fmicb-06-00643-HTML/image_m/fmicb-06-00643-g001.jpg

Innate Immunity

First line of defense	Second Line of defense
Intact Skin Mucous membranes and their secretions Normal mcirobiota	Phagocytes, such as neutrophils, eosinophils, dendritic cells, and macrophages. Inflammation； Fever Antimicrobial substance

Injury and Inflammartion

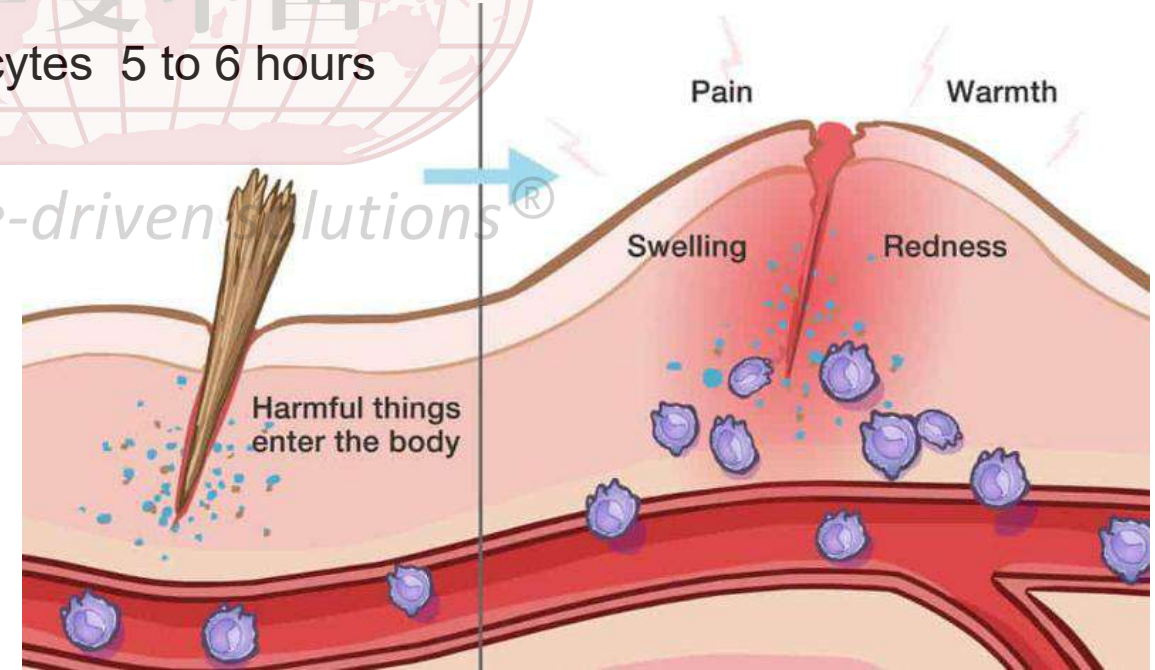
Clotting mechanism activates

Increased blood flow

Increased capillary permeability

Enhanced influx of phagocytic cells

- Neutrophils arrive in 30 -60 minutes
- Macrophages and lymphocytes 5 to 6 hours



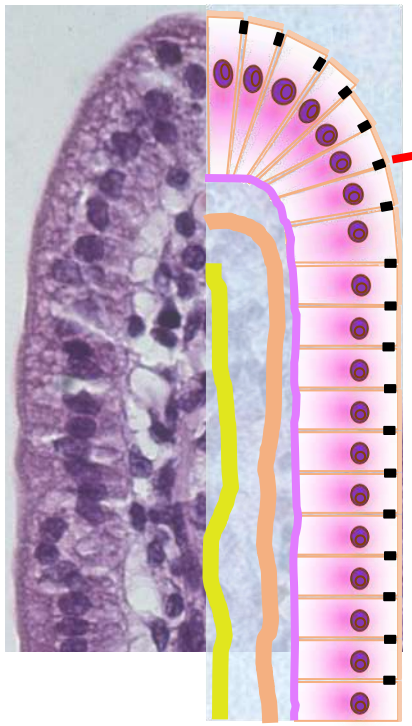
Innate and adaptive immunity

Common Pathway

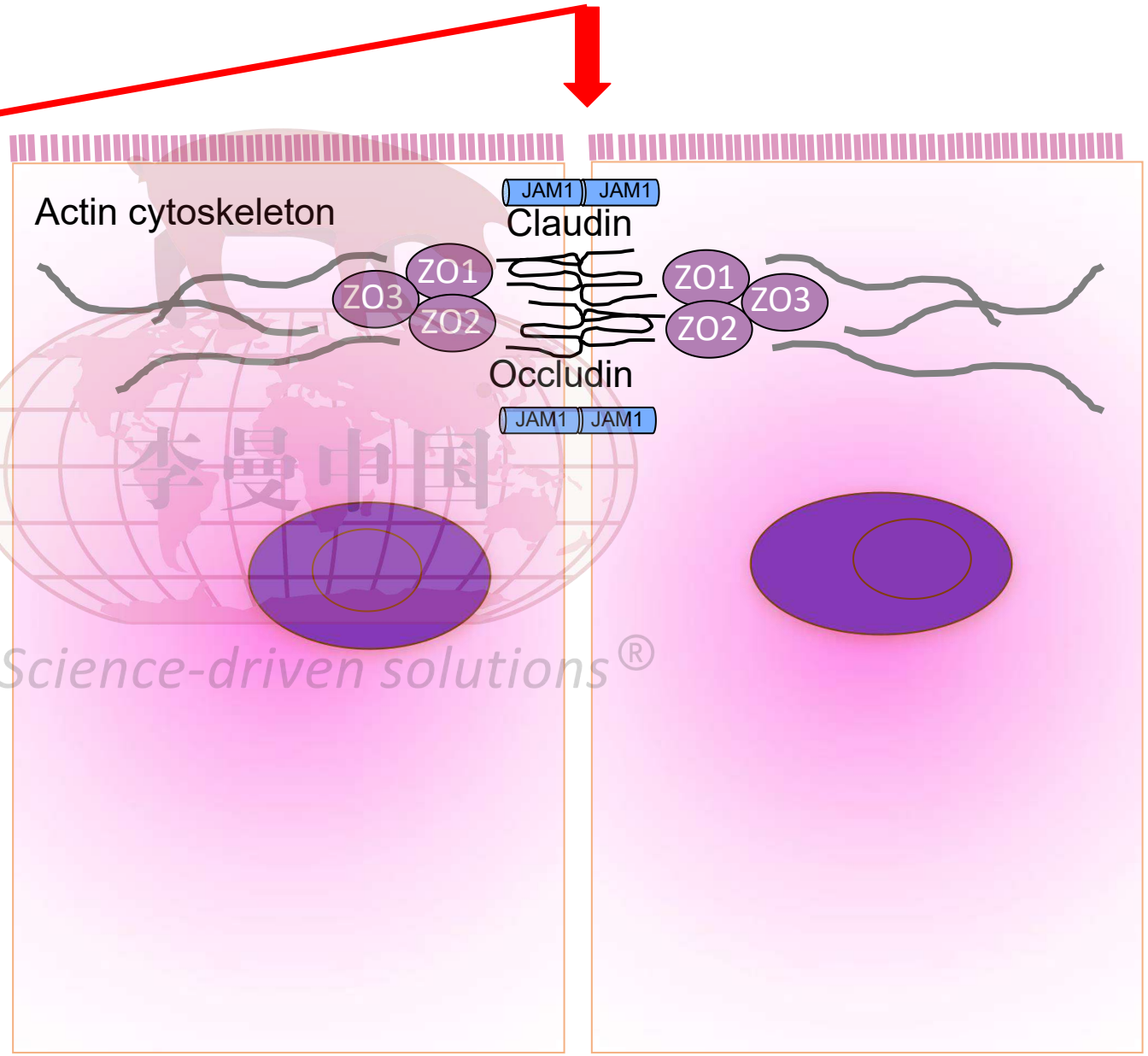
Natural Killer Cell NK T cell ⟷ Common lymphoid progenitor

Macrophage or Monocyte ⟷ Myeloid progenitor

Tight Junction Complex



Villi



Normal

Bacterial community

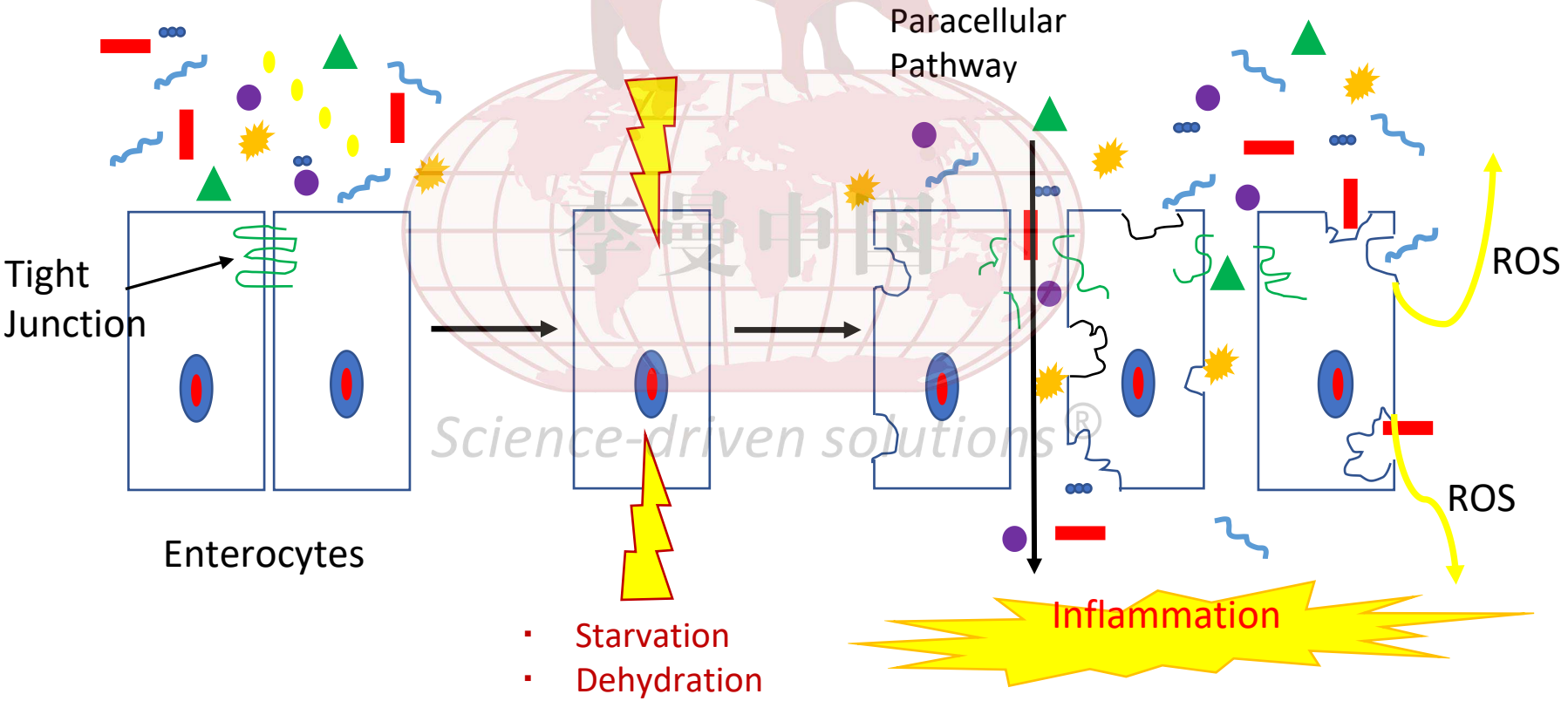
> 500 different species

Sources of metabolic stress

- Toxins
- Bacterial dysbiosis
- Infections
- Psychological stress

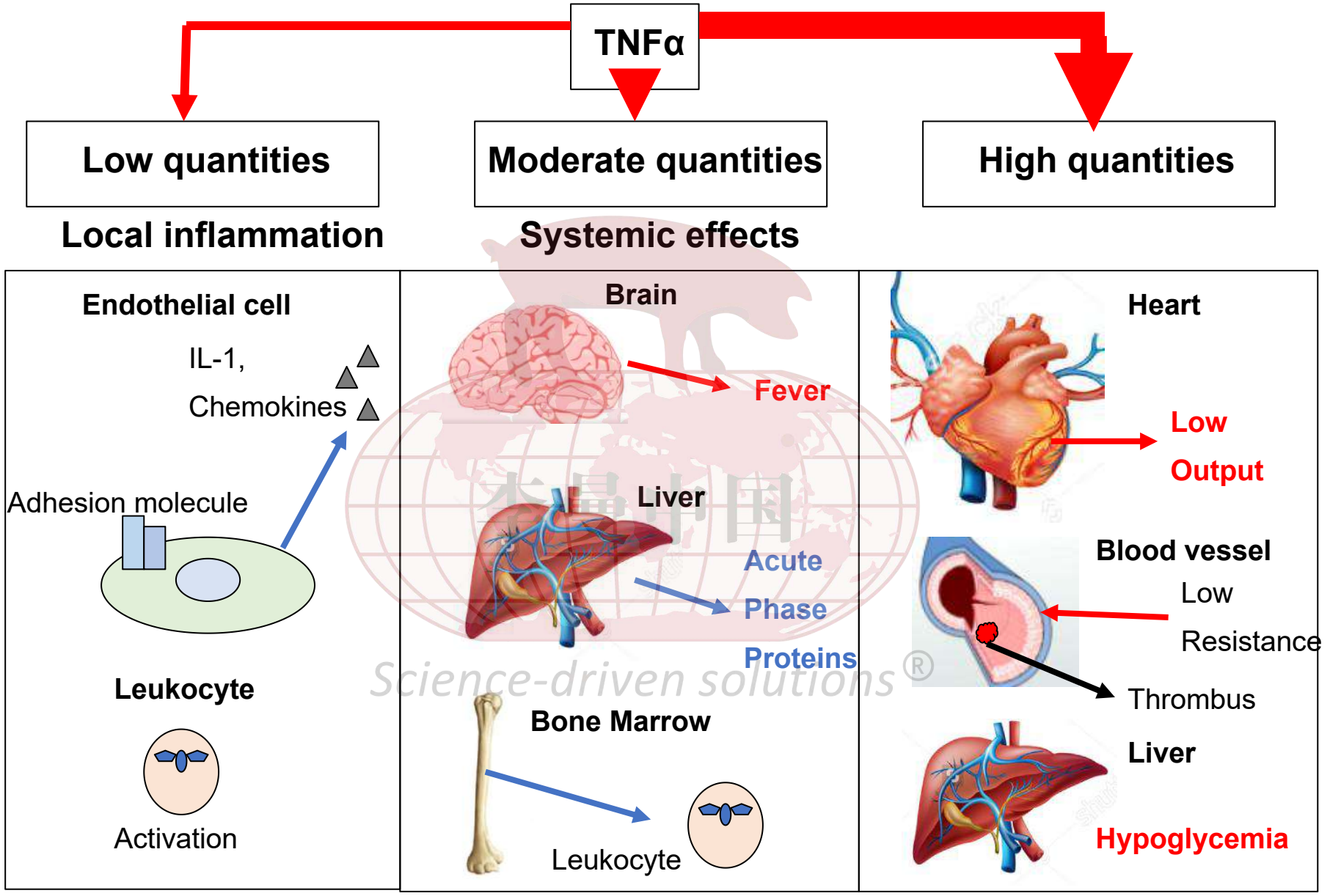
Effects of metabolic stress

"Gut Leakage"
Reactive Oxygen Species (ROS)
Cellular damage
Cytokines released



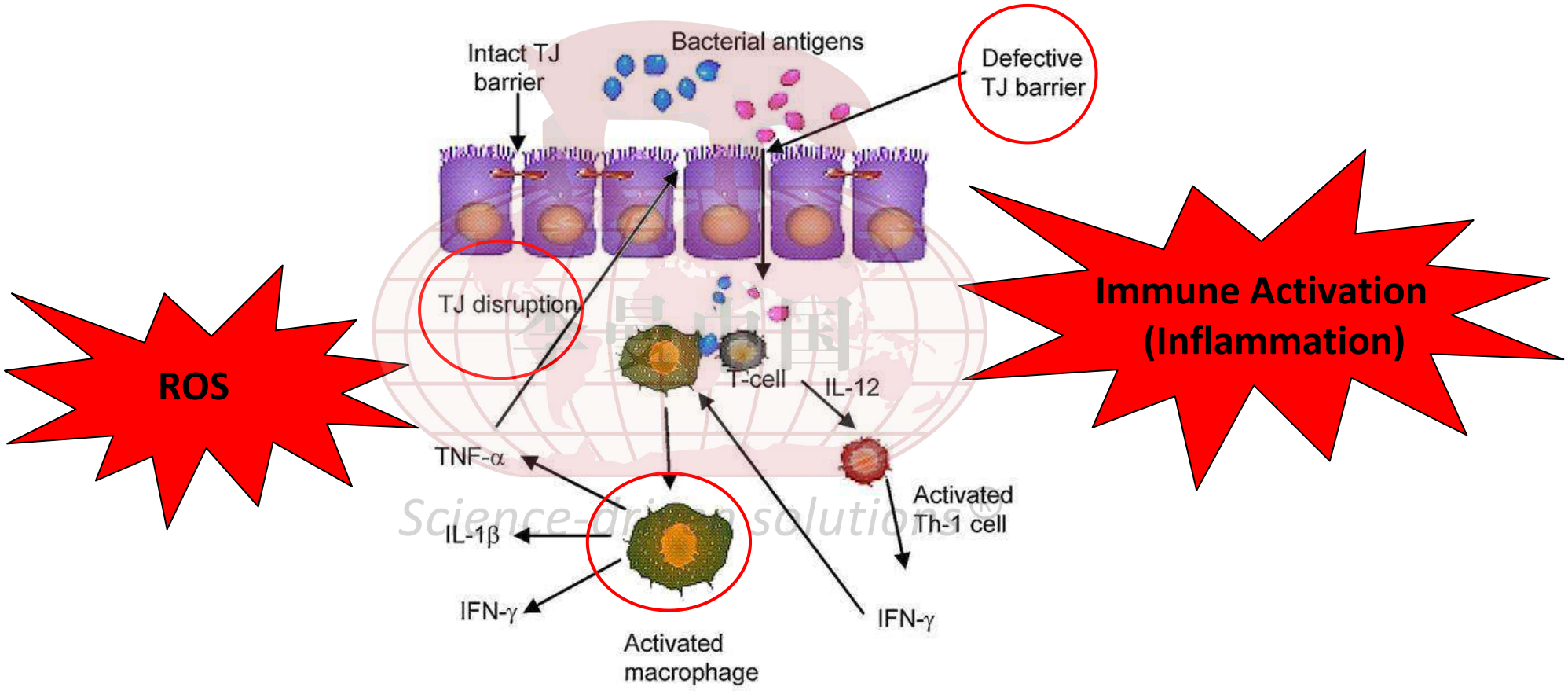
- Starvation
- Dehydration
- Inflammation
- Surgery

Inflammation In The Reproductive Tract

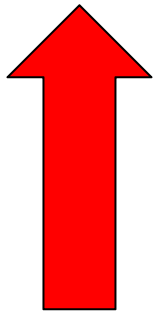


Modified from Cellular and molecurlar immunology, Suanders Elsiver Chapter 12 figure 12-5, pp. 277, 2007.

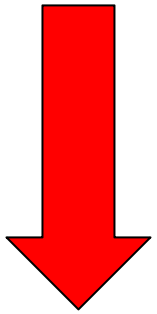
Tight Junction (TJ) Barrier Disruption Leads To Immune Activation



- Adapted from: Al-Sadi et al., 2009. Front. Biosci. 14:2765-2778

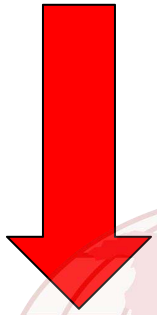


Inflammation



Intake

And/Or



Nutritient Utilization

Inflammation is Stealing Nutrients While You Are Not Looking

23 % increase in energy partitioning to the immune system

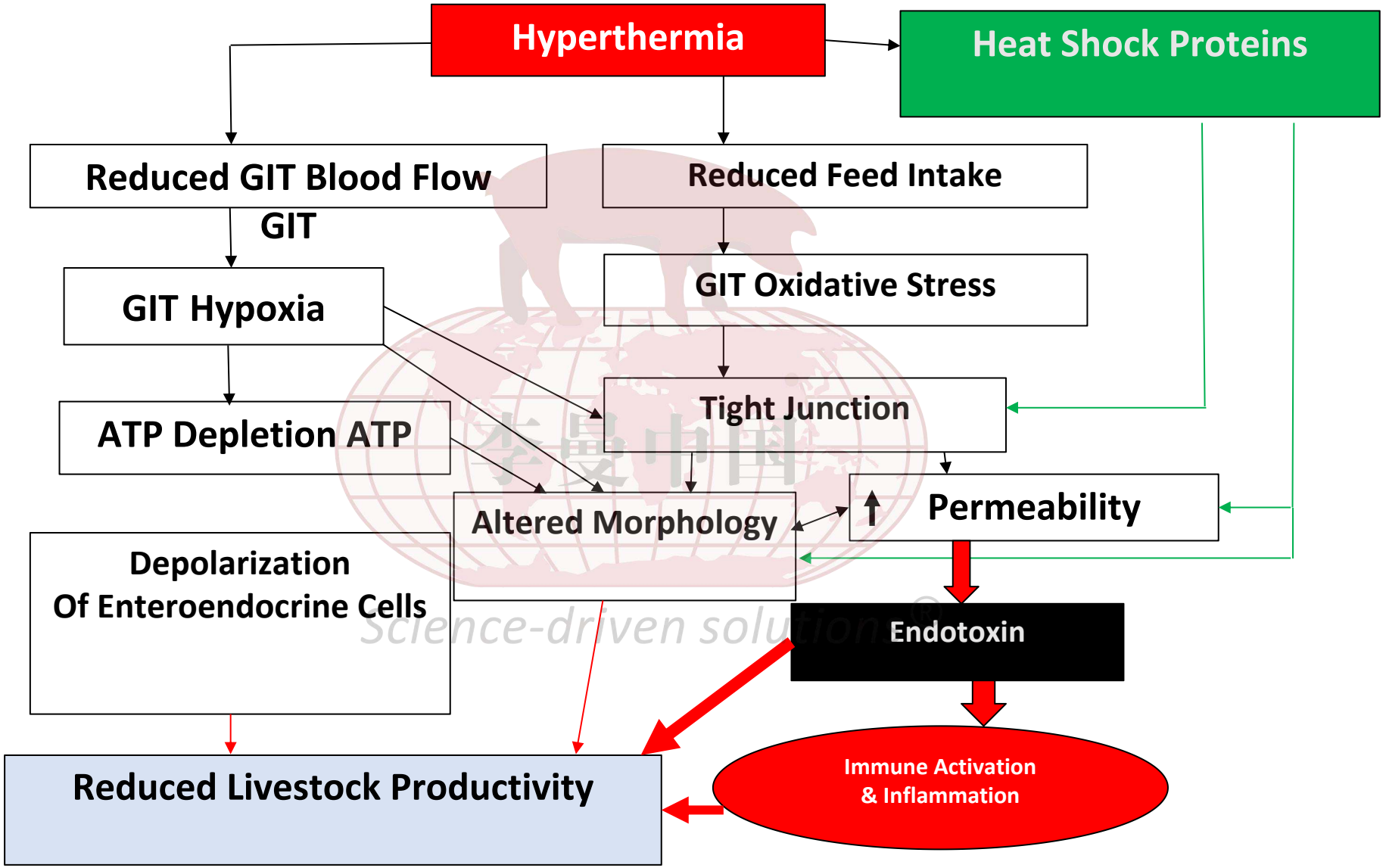
Heat Stress – Cost to US Swine Industry

- > $900 million dollars/year in the USA
- Grow-finish pigs: $450 million in losses

Sows: > $450 million in losses

[a]Pollmann, 2013

What Happens During Heat Stress



Baumgard et al., 2011

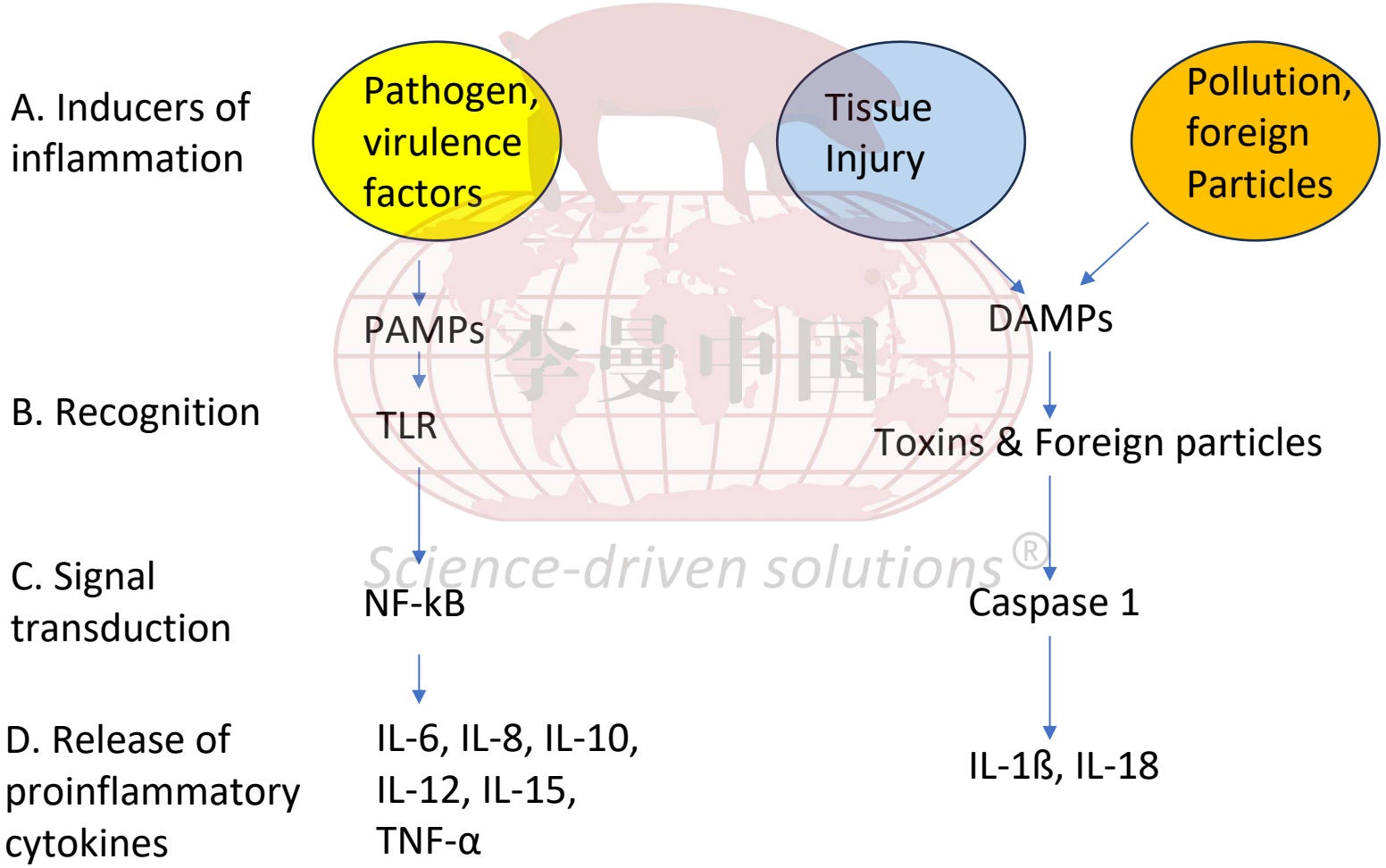
Scrotal Insulation in the Boar

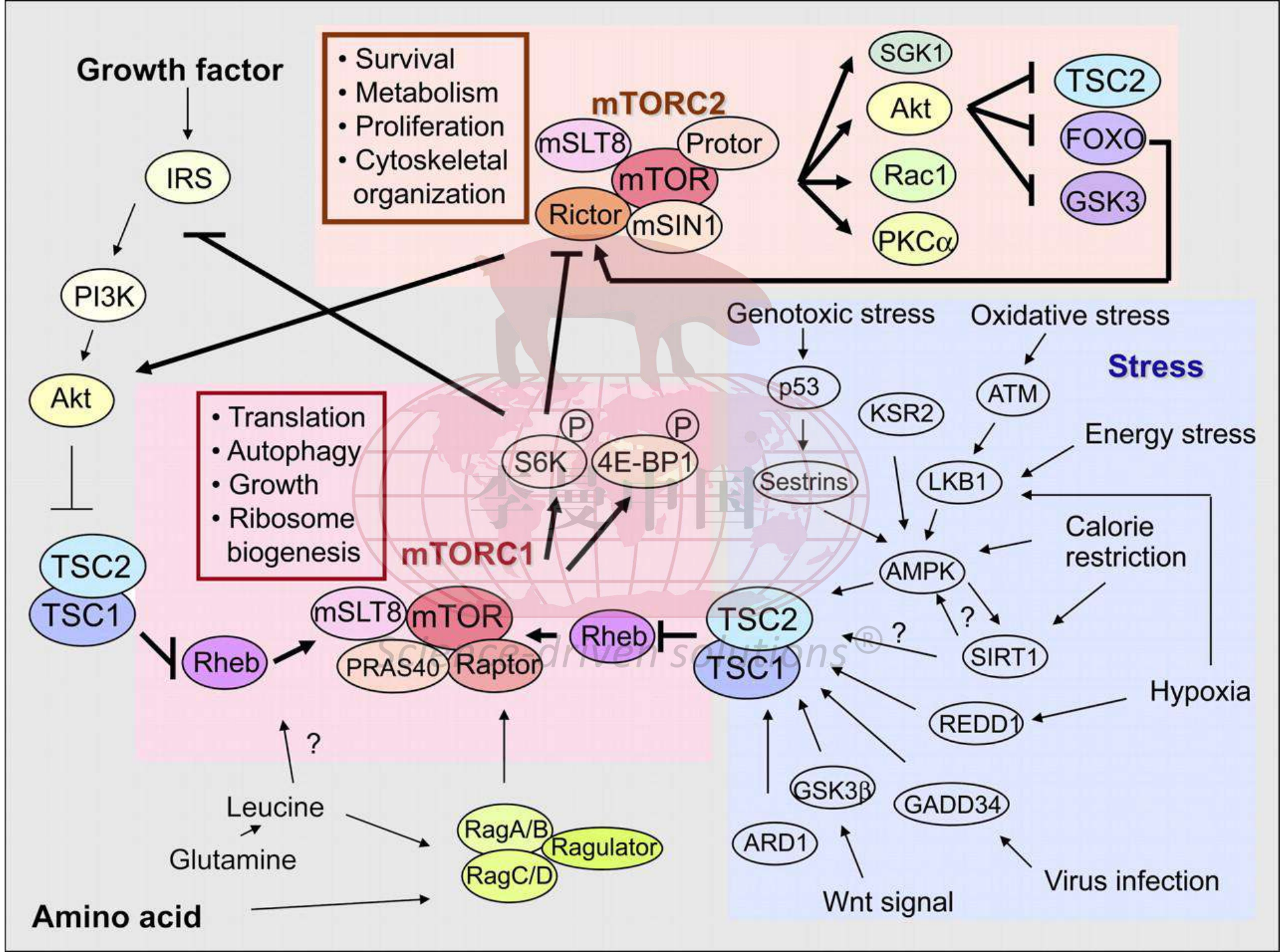
John Parrish,, University of Wisconsin

Feed And Nutrients May Help Mitigate Heat Stress

- Betaine
- Calmin (acid buff)
- Zn
- Chromium
- Synthetic amino acids
- Fats, and fatty acids
- (D. Rosario and D. Boyd, 2015)

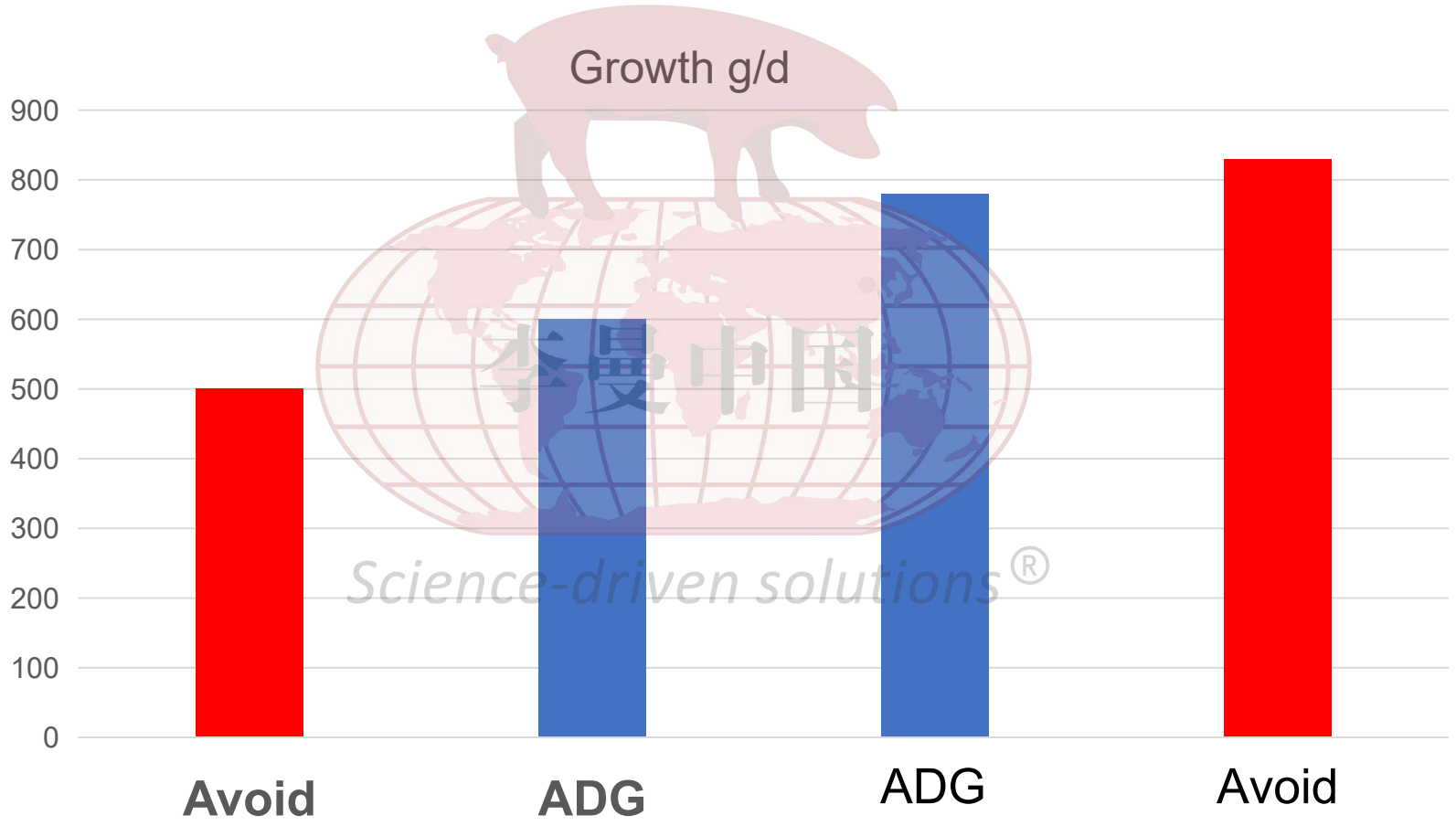
Lots of steps in the process of inflammation



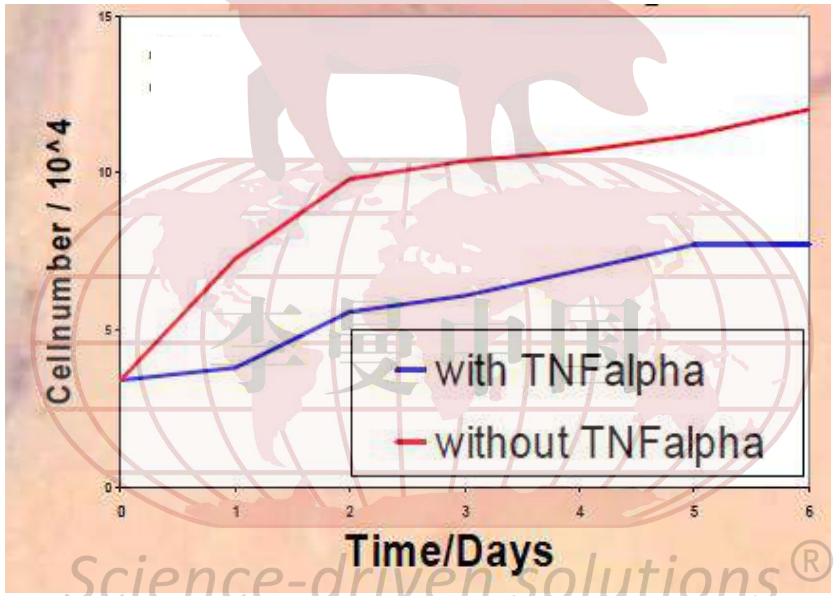

Growth factor
IRS
PI3K
Akt
TSC2
TSC1
Rheb
• Survival
• Metabolism
• Proliferation
• Cytoskeletal organization
mTORC2
mSLT8
Protor
mTOR
Rictor
mSIN1
SGK1
Akt
Rac1
PKCα
TSC2
FOXO
GSK3
• Translation
• Autophagy
• Growth
• Ribosome biogenesis
mTORC1
P
S6K
P
4E-BP1
mSLT8
mTOR
PRAS40
Raptor
Rheb
TSC2
TSC1
?
Leucine
Glutamine
RagA/B
Ragulator
RagC/D
Amino acid
Genotoxic stress
Oxidative stress
Stress
p53
ATM
KSR2
Energy stress
Sestrins
LKB1
Calorie restriction
AMPK
?
?
SIRT1
Hypoxia
REDD1
GSK3β
GADD34
ARD1
Wnt signal
Virus infection

Don’t
Jump
To
A
Conclusion
Too
Quickly

Avoid Gilts With Growth Rates Less Than 600 g/d And Greater Than 800 g/d



Impact of Inflammatory Mediators on Claw Horn Production



- Addition of TNF-α resulted in inhibition of keratinocyte proliferation vs. control over a period of 6d

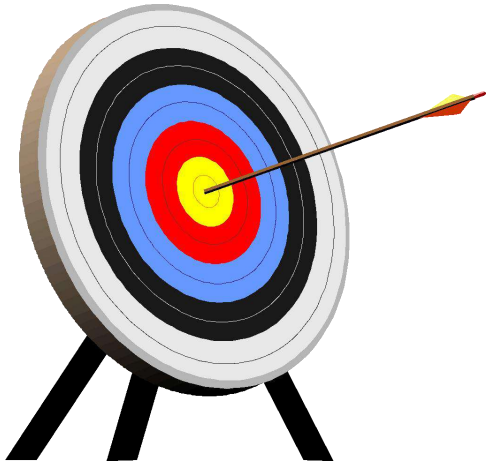
Mülling, CH., D. Hoffmann and K.-D. Budras. 2002. *In vitro* challenge studies on the effects of cytokines and growth factors on bovine keratinocytes. Institute of Veterinary Anatomy, Freie Universität Berlin, Koserstr. 20, D-14195 Berlin


李曼中国

Targets For Gilts

- >136 kg or up to 165 kg for breeding
- % weaned gilts converted to parity 2
- 2nd estrus prior to mating
- Early detection of onset of estrus
- > 60 pigs per sow lifetime
- > 16 pigs total born
- < 10 kg body weight loss after farrowing

weight loss between 5-7 kg for gilts



Key Economic Sensitivities For Large US Integrator

- REPLACEMENT RATE AND GILT PRODUCTION

- Replacement rate
  - 1% change = $315,000

- Gilt conversion rate
  - (% weaned pigs converted to parity 2)
  - 1% change = $409,000

- Noel Williams, 2013 Leman Swine Conference, Minnesota