Recent Developments and Future Challenges in Thyroidology

Basic Review

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Nothing to disclose
Thyroid hormone & Aging

Thyroid hormone & Food Intake
Cell Metabolism

Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging

Authors
Leanne M. Redman, Steven R. Smith, Jeffrey H. Burton, Corby K. Martin, Dora Il'yasova, Eric Ravussin

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In Brief
Calorie restriction (CR) has been shown to have health benefits and to extend lifespan in diverse species. Redman et al. conducted a 2-year CR trial in healthy, non-obese humans and found evidence that prolonged CR enhances resting energy efficiency, resulting in decreased systemic oxidative damage.
Caloric restriction is a dietary intervention with potential benefits for healthspan improvement and lifespan extension. Observational studies of human aging have shown higher mass-adjusted metabolic rate (24h energy expenditure or resting energy expenditure) is associated with disease burden and shorter life span.

2 year calorie restriction trial: Healthy non-obese humans, CR n=34, controls n=19

Redman LM, et al., Cell Metabolism 2018; 27:805-815
• Reduction in thyroid axis activity is a hallmark feature of the hypometabolic state with weight loss

• Drivers for maintaining metabolic adaptation or a consequence?

• Growing evidence that mechanisms of CR underlying increased life span work significantly through modulation of thyroid axis

Redman LM, et al., Cell Metabolism 2018; 27:805-815
Hypothalamic-Pituitary Axis Regulates Hydrogen Sulfide Production

Authors
Christopher Hine, Hyo-Jeong Kim, Yan Zhu, ..., Richard Miller, Anthony N. Hollenberg, James R. Mitchell

Correspondence
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In Brief
Reduced thyroid hormone (TH) and growth hormone (GH) activity are hallmarks of genetic models of longevity in mice. Here, Hine et al. find that TH and GH negatively regulate hepatic production of the longevity-associated gas hydrogen sulfide, which feeds back to negatively regulate circulating TH and IGF-1 levels.
Thyroid hormone & hepatic H₂S production

- Decreased thyroid hormone and growth hormone signaling are associated with longevity and metabolic fitness.
- Possible overlapping mechanisms with those of dietary restriction resulting in downregulation of TH/GH axis.
- Potential mediator is the longevity-associated gas H₂S, which is increased upon dietary restriction.

Hine C, et al., Cell Metabolism 2017; 25:1320-1333
Pleiotropic beneficial effects of H₂S

- Resistance to hypoxia
- Neuro-protection
- Modulation of inflammation
- Angiogenesis in cardiovascular system

Extension of longevity

Hine C, et al., Cell Metabolism 2017; 25:1320-1333
TSH and GH deficiency/inhibition promote hepatic H$_2$S production in vivo

Hine C, et al., Cell Metabolism 2017; 25:1320-1333
Hypothyroidism increases / thyroid hormone represses hepatic H\(_2\)S production \textit{in vivo} via TR\(\beta\)1

Hine C, et al., Cell Metabolism 2017; 25:1320-1333
TH / GH are negative regulators of H₂S production

TH / GH signaling could be the link between DR and H₂S production

H₂S is involved in negative regulation of TH / GH signaling, key longevity associated hormones = potential mechanism of H₂S action and mediator of its beneficial effects

Hine C, et al., Cell Metabolism 2017; 25:1320-1333
Thyroid hormone & key longevity associated hormone

Rotterdam Study

Figure. Life Expectancy (LE) With and Without Cardiovascular Disease (CVD) at Age 50 Years Among Thyrotropin and Free Thyroxine Tertiles, in Men and Women.
**Graphical Abstract**

**Food intake**

**Weight gain**

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**Authors**

Saira Hameed, Michael Patterson, Waljit S. Dhillo, ..., J.H. Duncan Bassett, Graham R. Williams, James V. Gardiner

**Correspondence**

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j.gardiner@imperial.ac.uk (J.V.G.)

**In Brief**

Hameed et al. report that selective knockdown of a thyroid hormone receptor in the mouse hypothalamus results in a phenotype of severe obesity, overeating, and reduced energy expenditure, which may be due to downstream changes in the expression of hypothalamic regulators of food intake.
• Improved understanding of the mechanisms that regulate appetite and body weight → design of anti-obesity therapies

• The TR-beta isoform (TRβ) is expressed in the ventromedial hypothalamus (VMH)- a brain area important for control of energy homeostasis

Hameed S, et al., Cell Reports 2017; 19:2202-2209
TRβ knockdown in the VMH results in a phenotype of hyperphagia comparable to some of the most extreme forms of monogenic obesity

Hypothalamic TRβ major physiological regulator of energy homeostasis

Hameed S, et al., Cell Reports 2017; 19:2202-2209
Non-classical thyroid hormone action
Novel thyroid hormone targets
Noncanonical thyroid hormone signaling mediates cardiometabolic effects in vivo

G. Sebastian Hönes\textsuperscript{a}, Helena Rakov\textsuperscript{b}, John Logan\textsuperscript{b}, Xiao-Hui Liao\textsuperscript{c}, Eugenie Werbenko\textsuperscript{b}, Andrea S. Pollard\textsuperscript{b}, Stine M. Præstholm\textsuperscript{d}, Majken S. Siersbæk\textsuperscript{d}, Eddy Rijntjes\textsuperscript{e}, Janina Gassen\textsuperscript{f}, Sören Latteyer\textsuperscript{a}, Kathrin Engels\textsuperscript{a}, Karl-Heinz Struckungsberg\textsuperscript{h}, Petra Kleinbongard\textsuperscript{f}, Denise Zwanziger\textsuperscript{e}, Jan Rozman\textsuperscript{s,h}, Valerie Gailus-Durner\textsuperscript{g}, Helmut Fuchs\textsuperscript{g}, Martin Hrabe de Angelis\textsuperscript{g,h,i}, Ludger Klein-Stepp\textsuperscript{g}, Josef Köhler\textsuperscript{e}, David L. Armstrong\textsuperscript{k}, Lars Grantved\textsuperscript{d}, U. H. Duncan Rassett\textsuperscript{b}, Graham R. Williams\textsuperscript{b}, Samuel Bofret\textsuperscript{b}, Dagmar Führer\textsuperscript{a}, and Lars C. Moeller\textsuperscript{a,1}

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Establishment of
- TR\textsubscript{\alpha GS} and TR\textsubscript{\beta GS} mice with loss of canonical TR signaling
- TR\textsubscript{\beta 147F} with abolished non-canonical TR\textsubscript{\beta} signaling

Hönes GS, et al., PNAS 2017; 114:E11323-E11332
Noncanonical TRβ signaling

Blood glucose

Serum and liver triglyceride concentration

Body temperature

Oxygen consumption

Hönes GS, et al., PNAS 2017; 114:E11323-E11332
Noncanonical TR signaling contributes significantly to physiologic actions of TH

Noncanonical TR signaling predominantly regulates energy homeostasis

Profound implications for the role of TRs in metabolism and physiology

Explain the pathophysiology in diseases caused by the various TR mutations

Paradigm shift for TH action

Hönes GS, et al., PNAS 2017; 114:E11323-E11332
Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function

Guoying Yu¹,¹¹, Argyris Tzouvelekis¹,²,¹¹, Rong Wang¹,¹⁰, Jose D Herazo-May¹, Gabriel H Ibarra¹, Anup Srivastava¹, Joao Pedro Werneck de Castro³,⁴, Giuseppe DeIuliis¹, Farida Ahangari¹, Tony Woolard¹, Nachelle Aurelien¹, Rafael Arrojo e Drigo⁵, Ye Gan¹, Morven Graham⁶, Xinran Liu⁶, Robert J Homer⁷,⁸, Thomas S Scanlan⁹, Praveen Mannam¹, Patty J Lee¹, Erica L Herzog¹, Antonio C Bianco³ & Naftali Kaminski¹
DIO2 expression and activity in IPF patient lungs

Thyroid hormone & lung fibrosis

DIO2 expression and activity in IPF mouse model (bleomycin model of lung fibrosis)

Aerosolized T3 treatment in IPF mouse models

- T3 blunts lung fibrosis
- T3 reverses bleomycin-induced mitochondrial changes
- T3 suppresses mitochondria-regulated apoptosis
- Upregul. of DIO2 = effort to boost local conversion of T4 to T3

New role of thyroid hormone as potential therapeutic agent in IPF

Thyroid cancer
Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers

Nikita Pozdeyev\textsuperscript{1,2,3}, Laurie M. Gay\textsuperscript{4}, Ethan S. Sokol\textsuperscript{4}, Ryan Hartmaier\textsuperscript{4}, Kelsi E. Deaver\textsuperscript{1}, Stephanie Davis\textsuperscript{1,5}, Jena D. French\textsuperscript{1,3}, Pierre Vanden Borre\textsuperscript{4}, Daniel V. LaBarbera\textsuperscript{3,6}, Aik-Choon Tan\textsuperscript{3,7}, Rebecca E. Schwepppe\textsuperscript{1,3}, Lauren Fishbein\textsuperscript{1,2,3}, Jeffrey S. Ross\textsuperscript{4,8}, Bryan R. Haugen\textsuperscript{1,3}, and Daniel W. Bowles\textsuperscript{3,7}
Genetic profiling of advanced DTC and ATC

PTC

Pozdeyev N, et al., Clin Cancer Res 2018; 24:3059-3068
Genetic profiling of advanced DTC and ATC

Pediatric PTC

Pozdeyev N, et al., Clin Cancer Res 2018; 24:3059-3068
Genetic profiling of advanced DTC and ATC

Table 3. Pathways and genes more frequently altered in ATC than in DTC

<table>
<thead>
<tr>
<th>Gene or group of genes</th>
<th>Prevalence, %</th>
<th>DTC</th>
<th>ATC</th>
<th>P*</th>
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<tbody>
<tr>
<td>Tumor suppressors</td>
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<td>21</td>
<td>74</td>
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<td>TP53</td>
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<td>NF2</td>
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<td>RB1</td>
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<td>NF1</td>
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<td>3</td>
<td>9</td>
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<tr>
<td>Cell-cycle pathway</td>
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<td>CDKN2A</td>
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<td>PI3K/AKT pathway</td>
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<td>SWI/SNF nucleosome modification pathway</td>
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<td>Hedgehog signaling pathway</td>
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<td>Histone modification</td>
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<td>Mutation-high genotype</td>
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</tr>
</tbody>
</table>

NOTE: Signaling pathways and groups of genes are highlighted in bold.

*P-values were adjusted for multiple comparisons using Benjamini-Hochberg method.

Pozdeyev N, et al., Clin Cancer Res 2018; 24:3059-3068
Genetic profiling of advanced DTC and ATC

Pozdeyev N, et al., Clin Cancer Res 2018; 24:3059-3068
Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hürthle Cell Carcinoma

Authors
Raj K. Gopal, Kirsten Kübler, Sarah E. Calvo, ..., Dora Dias-Santagata, Gad Getz, David G. McFadden

Correspondence
gadgetz@broadinstitute.org (G.G.), david.mcfadden@utswestern.edu (D.G.M.)

In Brief
Gopal et al. identify recurrent alterations in DAXX, TP53, NRAS, NF1, CDKN1A, ARHGAP35, and the TERT promoter, as well as in mtDNA-encoding complex I of the electron transport chain, in Hürthle cell carcinomas (HCC). Many HCCs harbor widespread chromosomal loss culminating in a near-haploid state.

Gopal RK, et al., Cancer Cell 2018; 34:242-255

Ganly I, et al., Cancer Cell 2018; 34:256-270
Hgf/Met activation mediates resistance to BRAF inhibition in murine anaplastic thyroid cancers

Jeffrey A. Knauf, Kathleen A. Luckett, Kuen-Yuan Chen, Francesca Voza, Nicholas D. Socci, Ronald Ghossein, and James A. Fagin

1 Human Oncology and Pathogenesis Program, 2Department of Medicine, 3Bioinformatics Core, and 4Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

5Department of Medicine, Weill-Cornell Medical College, New York, New York, USA.
Resistance to BRAF inhibition in ATC

Knauf JA, et al., J Clin Invest 2018; 128:4086-4097
Resistance to BRAF inhibition involves activation of HGF/Met signaling that can be targeted by MET inhibitors.

Knauf JA, et al., J Clin Invest 2018; 128:4086-4097
The miR-146b-3p/PAX8/NIS Regulatory Circuit Modulates the Differentiation Phenotype and Function of Thyroid Cells during Carcinogenesis

Garcilaso Riesco-Eizaguirre\textsuperscript{1,2,3}, León Wert-Lamas\textsuperscript{1}, Javier Perales-Patón\textsuperscript{1,4}, Ana Sastre-Perona\textsuperscript{1}, Lara P. Fernández\textsuperscript{1}, and Pilar Santisteban\textsuperscript{1}

https://doi.org/10.1038/s41388-017-0088-9

MicroRNA-146b promotes PI3K/AKT pathway hyperactivation and thyroid cancer progression by targeting PTEN

Julia Ramírez-Moya\textsuperscript{1} · León Wert-Lamas\textsuperscript{1} · Pilar Santisteban\textsuperscript{1,2}

Riesco-Eizaguirre G. \textit{et al.}, Cancer Res 2015; 75:4119-4130
miR-146b – a novel target for thyroid cancer therapy?

Riesco-Eizaguirre G, et al., Cancer Res 2015; 75:4119-4130
miR-146b – a novel target for thyroid cancer therapy?

Modulation of the PI3K signaling by miR-146b via PTEN silencing

Therapeutic efficacy of the hsa-miR-146b-5p mir-Vana® miRNA inhibitor

Ramirez-Moya J, et al., Oncogene 2018; 37:3369-3383
Regulation of mutant TERT by BRAF V600E/MAP kinase pathway through FOS/GABP in human cancer

Rengyun Liu¹, Tao Zhang¹, Guangwu Zhu¹ & Mingzhao Xing¹
Oncogene duet of BRAF V600E and TERT promoter mutations is a fundamental genetic background cooperatively driving progression/aggressiveness of cancers, i.e. PTC.

Molecular mechanism for synergistic oncogenic effect?

Upregulation of GABPB by BRAF V600E

GABPB complex a known activator of mut TERT promoter
FOS transcription factor of the GABPB gene

- BRAF/MAPK-induced FOS activation, a transcription factor activating GABPB promoter, a known activator of mut TERT promoter plays a key role in bridging the 2 oncogenes cooperatively driving oncogenesis

The sodium iodide symporter
NIS
An extremely high dietary iodide supply forestalls severe hypothyroidism in Na\(^+\)/I\(^-\) symporter (NIS) knockout mice

Giuseppe Ferrandino\(^1\), Rachel R. Kaspari\(^1\), Andrea Reyna-Neyra\(^1\), Nabil E. Boutagy\(^2\), Albert J. Sinusas\(^2,3\) & Nancy Carrasco\(^1\)
NIS knockout mouse model

Thyroid hormone is synthesized in NIS KO mice as long as I⁻ supply is sufficient to enter the thyroid most likely by diffusion via non-specific routes driven by a concentration gradient.

- I⁻ gradient (serum/thyroid) is maintained by upregulating genes involved in I⁻ organification.
- Enhanced oxidative environment in the thyroid (adaptive response).

A Novel Approach for Image-Guided $^{131}$I Therapy of Pancreatic Ductal Adenocarcinoma Using Mesenchymal Stem Cell-Mediated NIS Gene Delivery

Christina Schug$^1$, Aayush Gupta$^2$, Sarah Urnauer$^1$, Katja Steiger$^3$, Phyllis Fung-Yi Cheung$^{4,5}$, Christian Neander$^{4,5}$, Konstantinos Savvatakis$^{4,5}$, Kathrin A. Schmohl$^1$, Marija Trajkovic-Arsic$^{4,5}$, Nathalie Schwenk$^1$, Markus Schwaiger$^6$, Peter J. Nelson$^7$, Jens T. Siveke$^{2,4,5}$, and Christine Spitzweg$^1$
NIS gene therapy in pancreatic cancer
