SUN-309/TUMOR BIOLOGY Cytokine Signaling by Thyronine and NAD in Colon and Pancreas - Case reports Highlighting Stem Cell Differentiation and Insulin Regulation

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T. Bilash reports no conflict of interest

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#5128 Cytokine Signaling by Thyronine and NAD in Colon and Pancreas - Case reports Highlighting Stem Cell Differentiation and Insulin Regulation

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I. ABSTRACT

There has been an explosion of interest in Thyroid dysfunction since the chemiluminescent free hormone assays, advanced imaging and biophysical techniques (Phasor FLIM) have evolved over the last 15 years. Research now identifies peripheral metabolism as intimate to Thyroid Physiology, adding cellular (non-genomic/cytoplasmic) to well studied nuclear (genomic) processes. Carrier proteins, Enzyme Converters (Deiodinase), and Trans-membrane Transport Proteins create a complex web communicating across distinct Thyroid compartments. Feedback, conversion, local accommodation among and inside cells results in precise control. There is currently not one Thyroid test accurate enough to define Thyroid Status, although Thyroid Stimulating Hormone (TSH), Thyroxine (T4 - Total and Free), and Triiodothyronine (T3 - Total and Free) are shown to be clinically determinant in function.

This work reports case studies for two patients with distinct, serious medical issues in the presence of Hypothyroxinemia: Diabetes Mellitus in a Pregnant female treated with Levothyroxine, and Advanced Stage Adenocarcinoma of the Colon in a male treated with Levothyroxine and Liothyronine, leading to successful clinical outcomes. T4 vs T3 and NAD vs NADP impact sources of cellular energy; in gradient for Colon stem cell differentiation (Wnt/bcatenin/ PDK-1/NF-κB/STAT3) and for Insulin production in Pancreatic Beta Cells (MAPK/ERK). Support for the Serum FreeT3/FreeT4 Ratio as an important clinical parameter is offered.

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II. Patient Case1 - Diabetes Mellitus in Pregnancy

The Patient is a 28 y/o pregnant female followed in her first pregnancy since the first trimester. She presented to the Hospital in Preterm Labor with Acute Pyelonephritis at 28 weeks. She was placed on Insulin and Thyroxine for elevated blood sugars over 200, with Laboratory and Clinical evidence of Hypothyroxinemia (sub-normal Free T4). She responded well, continued on Levothyroxine with one increase in dose, then weaned from Insulin advancing to vaginal delivery at term without incident. A Fetal Hydronephrosis noted prenatally resolved at birth.

Case 1
21 y/o first pregnancy
29 wk Preterm Labor, Pyelopnehritis
Eating disorder
Depression in Therapy
TOB 1/2 PPD
Milk Protein allergy
Renal CT neg
Peripheral Glucose 226 post prandial, normal fasting
UTI Recurrent Treated @28 weeks
Bacterial Vaginosis Treated
H/O high grade Pap Treated, Repeat negative
Placed on 2300 cal ADA Diet
Required Insulin 25 units/day, tapered off at 1 wk
Placed on Levothyroxine 50 mcg daily
1 hr glucola @30 weeks on L-thyroxine 136 (Fasting 80)
Fetal Dilated Renal Ureters - NI @Birth

	TSH	FREE T4	Free T3	TOT T4	TBG	Urinary Iodide	TGab	TRAB	Glucose	2 hr Glucola
Lab NL Range	0.49-4.67 4.18	0.71-1.85 1.04	2.3-4.2 1.9	4.5-12.0 7.5	13-39				90-105	<135
29 weeks 0 LT4	0.51 0% nl	0.76 5% nl	2.8 5% nl	11.8 97%		Decreased			226 Hi	
30 weeks (on LT4 50)	0.79 7% nl	0.8 9% nl			50 Hi		0	0		136

III. Patient Case2 - Adenocarcinoma of the Colon Stage 3/4

The Patient is a 60 y/o male diagnosed at surgery for a ruptured viscous with a Stage 3 Adenocarcinoma in the left descending Colon. At the time of surgery he was on Levothyroxine and Triiodothyronine for Hypothroxinemia with otherwise stable Thyroid symptoms. A single 2 cm moderately differentiated tumor was removed at successful segmental resection (colostomy revised 9 months later), with 1/13 adjoining lymph nodes 95% replaced with moderately differentiated Adenocarconoma of the Colon. Later revisit found B-Cell Lymphoma in all 13 nodes. Patient declined Intravenous Chemotherapy for the Stage 3 Carcinoma, noting complete resection and clear surgical margins. Oral Capecitabine therapy was offered, then discontinued after 2 months secondary to foot-hand syndrome. Adjuvant Curcumin as Turmeric and Epigallocatechin-3 gallate (EGG) supplementation was continued for 6 months. Pre-diagnosis Thyroid replacement dose for Hypothyroxinemia was adjusted, decreasing

Levothyroxine T4 which is demonstrated to stimulate solid tumor growth, and increasing Triiodothyronine known to differentiate Colon Stem Cells. Pre-diagnosis Vitamin D3 supplementation was also augmented.

Subsequent MRI and PET-CT imaging at 9 months identified two, isolated adjacent 2&3 cm lesions in the Left Lobe of the Liver, c/w Stage 4 metastatic tumor, and little change over 9 months on comparison with non-contrast imaging. Resection of the Left Lobe of the liver and Cholescystectomy was performed at 1 year post diagnosis.

Additional Follicular Cell Lymphoma in multiple locations was identified at 9 months (Collision Tumor). At 2 years a Retroperitoneal 4-cm ParaCaval Lymph Node was removed robotically (B-cell Lymphoma CD10 POS (64%), CD19, CD20, CD10, lamda light chain, CD23, CD38) and Biopsy of a ParaProstate Nodule indicated Hybrid Schwannoma.

Colonoscopy at 3 years resected a 0.8cm Transverse Colon Tubular Adenoma Polyp, and at 5 years a 0.3 cm Cecal Adenoma. Repeat Pet scan at 5 years showed no Colon tumor residual or metastasis and stable imaging. Patient is doing well ten years post diagnosis.

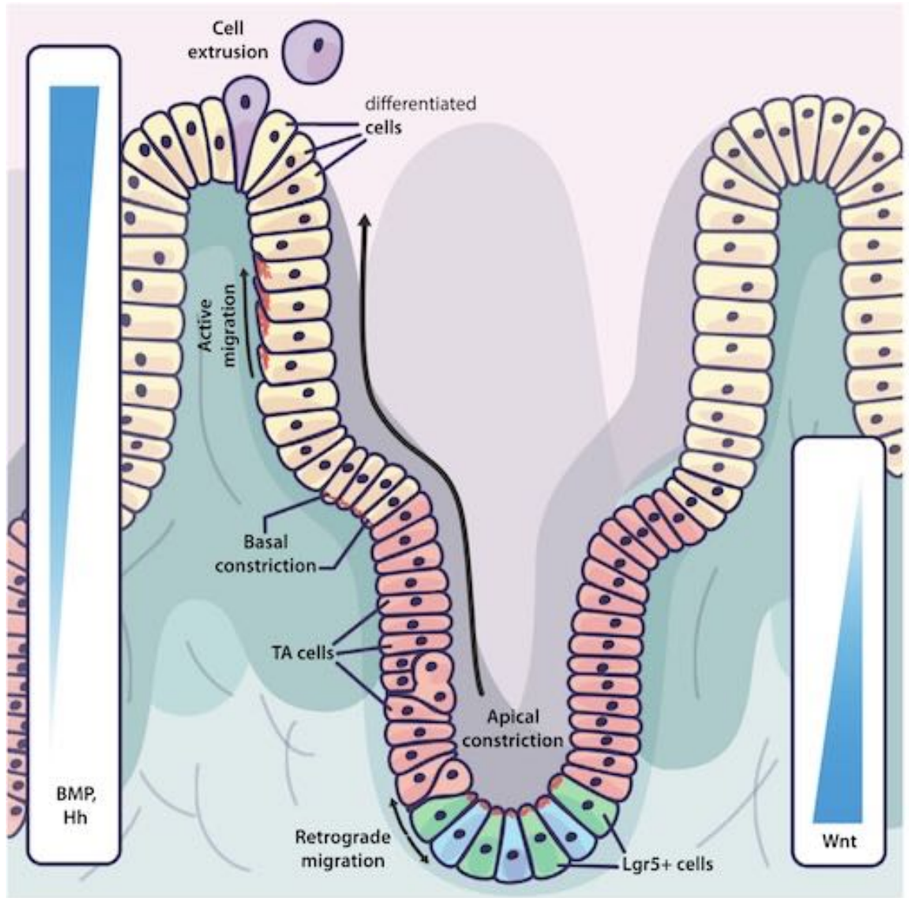
IV. INTRODUCTION

Peripheral metabolism and local control with feedback loops are demonstrated in Thyroid Physiology. Free hormone assays are now available. Carrier proteins, Enzyme Iodinase and Trans-membrane Transporters identify feedback and fine controls. Thyroxine (T4 - Total and Free), TSH, and now Triiodothyronine (T3 - Total and Free) are clinically useful. This work introduces some of the common pathways involved in Colon Cancer and Diabetes Mellitus.

V. Thyroid Hormone Physiology

THs are transported to distal organs carried on serum proteins such as Thyroid Binding protein (TBP), Transthyretin (Pre-Albumin) and Albumin. At the cells, transmembrane transporters (MCT, OATP, and LAT) facilitate the entry of TH into cells, which follow the gradient of free hormone between the extracellular fluid and cytoplasm. T4 and (T3 from T4) bind to intracellular receptors; TRα and TRβ initiate nuclear TH signaling, regulating target genes and metabolic pathways (genomic). Local (peripheral) mechanisms dominate and compartmentalise hormonal control thru non-genomic actions.

VI. INTESTINAL CELL WALL RENEWAL



Intestinal epithelium demonstrate a proliferation zone for Stem Cell activity and Progenitor proliferation at the base (crypts). A differentiation zone defines the region where Progenitors enter and differentiate while migrating toward the top of the vertical axis. Differentiated cells reside at the lumen and finally die by apoptosis and are shed into the lumen.

Adapted from Optimal Thyroid Hormone Replacement, Jacqueline Jonklaas, Endocr Rev. 2021 Sep 20;43(2):366–404

VII. THYROID HORMONES

Thyroxine- T4 binds to cell membrane Integrin αvβ3, proliferating cancer cells; in colon adenocarcinoma cell lines T4 increases AMPK and inhibits mTOR resulting in increased tumor progression by interfering with anti-tumor immune responses, activating PD-L1 thru the ERK1/2 pathway; induces serine phosphorylation of ERα. These T4 pro-mitogenic effects are in sharp contrast to intracellular T3.

Triiodothyronine- The biological activity of T3 is largely determined by its intracellular concentration. T3 promotes cell growth and differentiation; enhances glycolysis to Pyruvate in the Cytosol; increases OXPHOS; induces Mitochondrial Calcium uptake & Mitochondrial Dehydrogenase; induces differentiation of Stem Cells towards secretory lineages and reduces proliferation in colon cancer cells; improves mitochondrial health, cristae structure & membrane potential; activates tumor-suppressive E-cadherin, triggering plasma-membrane localization of Beta-catenin, which prevents its solublization and nuclear transit; suppresses cyclin-CDK complexes,

effecting G1 cell cycle arrest and downregulation of cyclins D1 and E.

Thyroid Stimulating Hormone -TSH stimulates NAD+ Kinase, increases reoxidation of NADP from NADPH ; TSH stimulates peroxisome activity.

Binding Proteins- THs are transported to distal organs bound to serum proteins. Most hormone is bound and inactive: Thyroid Binding protein (TBP), Transthyretin (PreAlbumin), Albumin; Vitamin D Binding Protein (VDBP), Retinol Binding Protein (RBP) also transport.

Effector Proteins- Important effector proteins are Beta-catenin which functions as membrane bound in complex with E-Cadherin in a zinc finger complex. Soluble nuclear beta catenin stimulates solid tumor cancers; SIRT1 induces NAD+ mediated gene repression. T3 inibits mTOR, important for intestinal regeneration and preservation of “reserve SCs” from DNA damage.

Central and Peripheral Deiodinase Enzymes- DIO1 and DIO2 activate, converting intracellular T4 to T3. DIO3 (T3>T2 and T3>rT3) is inactivate.

VIII. THYROID HORMONE GENOMIC AND NON-GENOMIC RECEPTORS

Genomic Thyroid Receptors (TR) are mainly locate in the nucleus. In the absence of Thyroid binding, TR act as repressors: TRα1 in the undifferentiated crypt compartment in Stem Cells (SC), modulating the expression of cell division and cell cycle regulators thru Wnt and Notch; binding T4. TRβ1 is downregulated in CRC mucosa, and its overexpression inhibits proliferation and migration.

Retinoid X Receptors (RXRs) form heterodimers with other nuclear receptors like RAR, PPAR, VDR, and TR. RXR binds T3 with high affinity to mediate feedback regulation. which may have a stronger effect than nutrient composition.

Some TH target genes fall under epigenomic regulation, which modifies their transcription; Sirtuin-mediated regulate the metabolic state of intestinal SCs far away (centrally) from as well as in the niche (locally).

IX. NON-GENOMIC THYROID RECEPTORS

Integrin αvβ3 is embedded in the cell membrane exposed to the outside of the cell and cytoplasmic interior; in plasma membranes (T4), in cytoplasmic membranes (T3), in mitochondrial membranes (T3). Integrins play a crucial role in cell adhesion by binding to extracellular matrix (ECM) proteins as a sensor for the ECM. S1 subunit binding by T3 leads to PI3K/Akt pathway activation; S2 subunit binding by T4 activates both PI3K/Akt and MAPK.

Non-genomic actions are are dependent on nuclear uptake of T3 and T3–TR complexes with other nucleoproteins: MAPKs, PKC, AKT, and PI3-K-AKT. Crypt-base columnar cells (CBCs) are considered the active Stem Cells of the intestinal epithelium. NRF-1, NRF-2, (PPAR)γ are intermediate factors; coactivators (PGC)-1α and PGC-1β are downstream.

X. THYROID HORMONE SIGNALING AND REGULATION

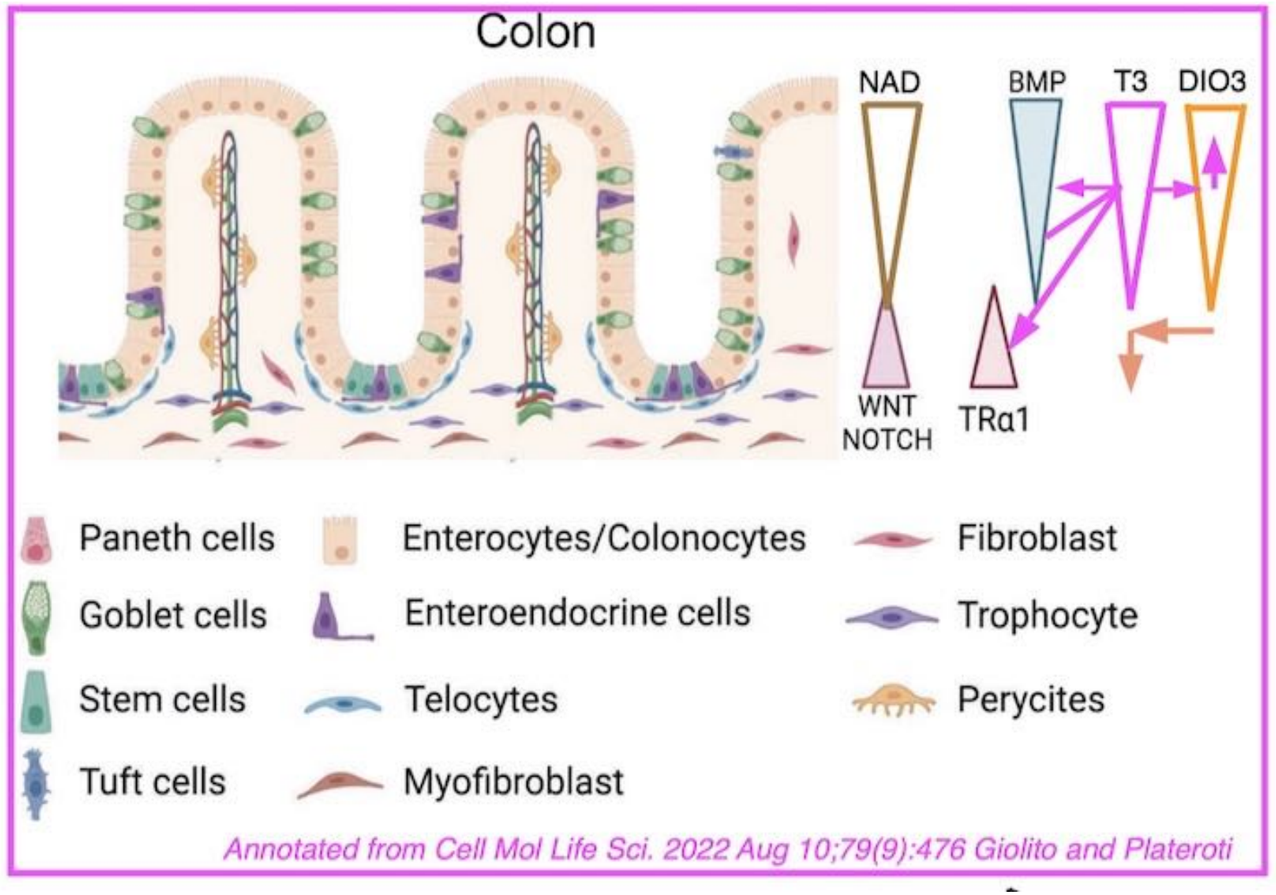
Thyroid Hormones participate in multiple reactions: Proliferation/Division, Differentiation, Migration, Invasion, Growth. Interplay occurs between classical cell signaling (coordinating modification) and metabolic pathways

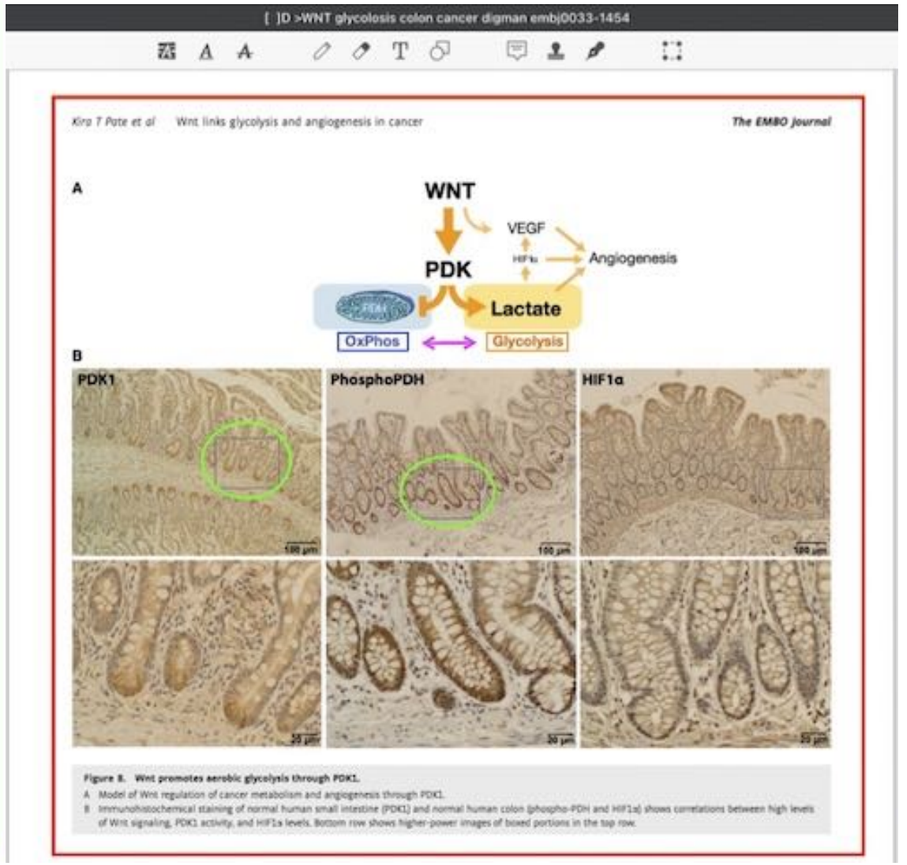
(energy) utilizing the mitochondria in Stem Cell maintenance/ differentiation.

XI. MICROENVIRONMENT AROUND THE CELL

There is concentration and activity gradients of along the Colon villus axis. TRα1, Wnt, Notch decrease towards the villi; while BMP, Hedgehog, and Triiodothyronine (T3) increase. These non-nuclear signaling pathways balance cell proliferation and cell differentiation. Crosstalk between the epithelium and the underlying mesenchyme is absolutely required for intestinal maturation and stem cell emergence.

DIO3 is expressed at the base of the crypts, and decreases towards the tip of the villus: it is maximally expressed in proliferating cells lowering T3, and decreasing with differentiation. T3 is a differentiating agent: in CaCo-2 cells, external T3 reduces growth rate and Cyclin D1, a marker for the G1-S phase transition (Dentice et al 2012).





The schematic^ from Giolito and Plateroti and Stained Slides from Pate et al illustrate the enzyme gradient for NADK related to the NAD/NADH Ratio.

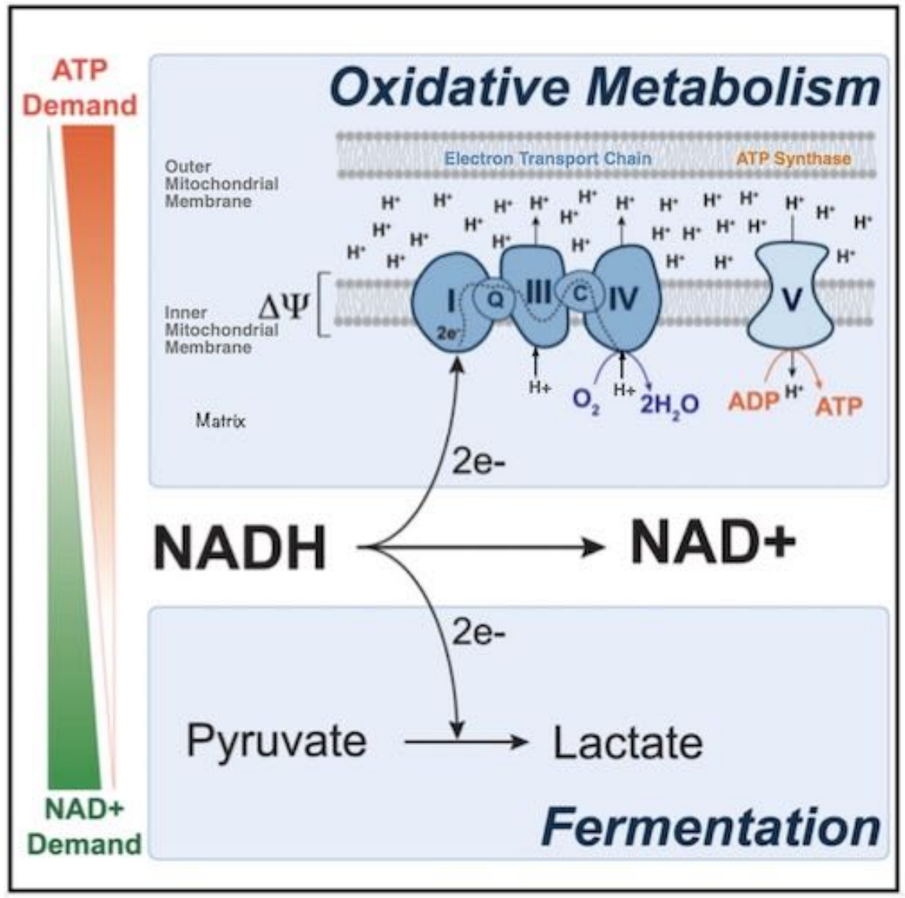
NOTCH

Notch signaling is a critical regulator of the tumor microenvironment, influencing various cellular and molecular processes that contribute to cancer progression, metastasis, and drug resistance.

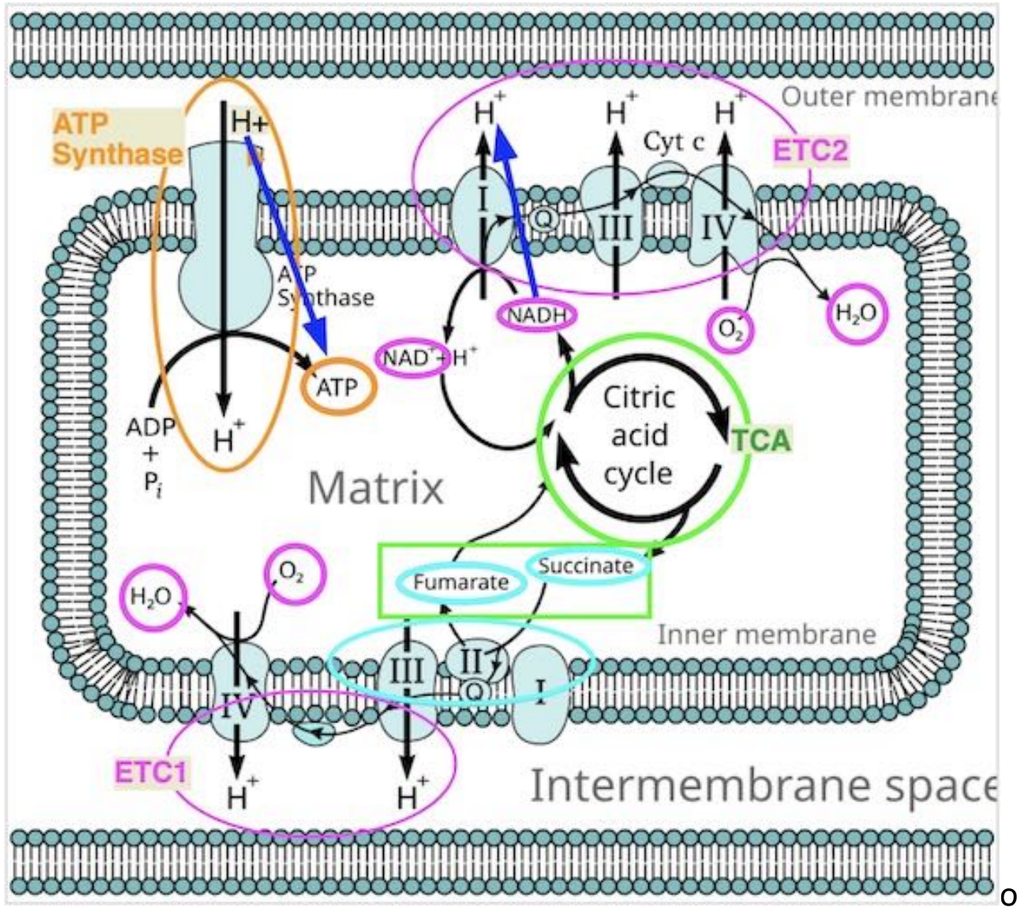
XII. OXPHOS NADH PRODUCTION AND THE MITOCHONDRIAL INNER MEMBRANE PROTON GRADIENT

Active Stem Cells rely highly upon Oxidative Phosphorylation (OXPHOS), in “blocks” of reactions within the Mitochondria Membrane:
1) Oxidation of substrates generates Hydrogen Ion H+ gradients that couples with the ETC.
2) Dissipating Hydrogen Ion H+ gradients for synthesis exports ATP (ATP Sythase and Adenosine Nucleotide Translocase ANT, into the cytoplasm.
4) Phosporylation reactions provde the Energy for this.

Proton Gradients in Mitochondria- "The Electron Transport Chain generates ATP and NADH through proton flux across the membrane, though this process is not fully coupled to ATP synthesis." A “proton leak” dissipates part the energy of the H+ gradient as heat, balancing the redox pumps generating the gradient. Hyperthyroidism increases electron flow through the respiratory chain, modulated by genomic and non-genomic actions of TH.



(Adapted from Luengo et al NCI Jan 13, 2021 https://frederick.cancer.gov/news/new-clarity-warburg-effect)



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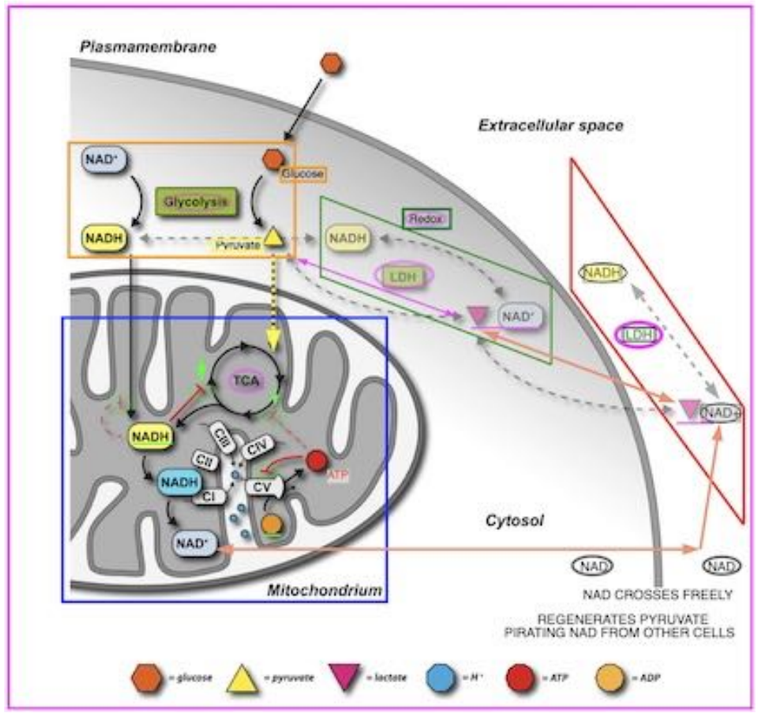
(Adapted from https://en.wikipedia.org/wiki/Oxidative_phosphorylation)

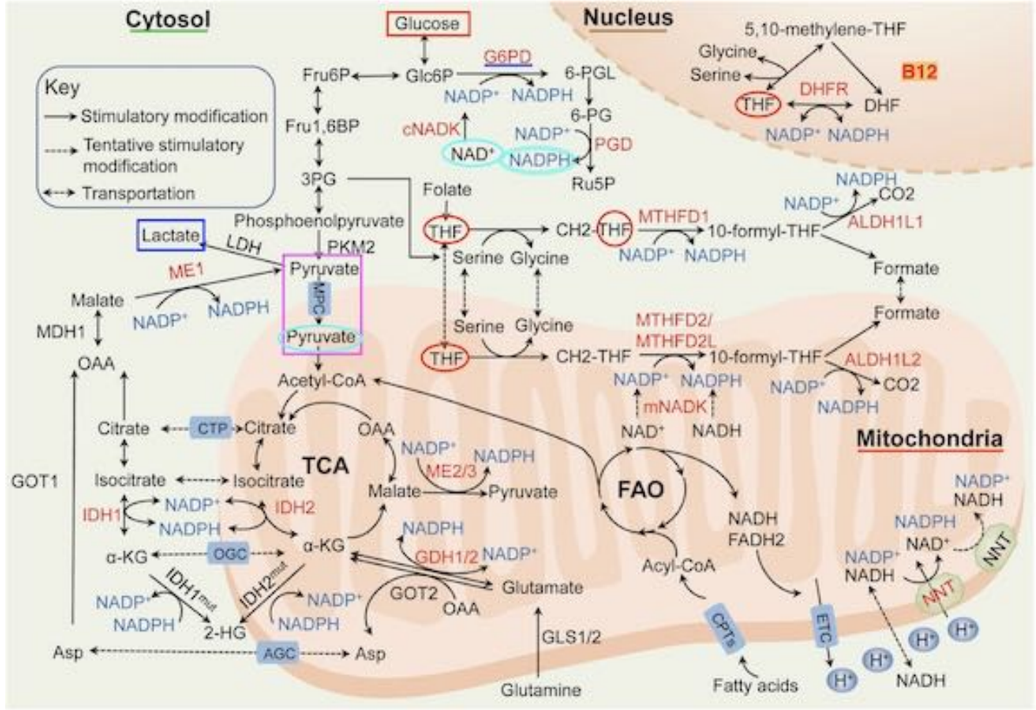
Energy production in the cell can involve direct oxidation of Glucose to Pyruvate in the Cytosol (Glycolysis); with the additional step of Fermentation to Lactate or Oxidation to Pyruvate for NADH in the Cytosol and ATP or NADH in the Mitochondria. Oxidative Phosphorylation described in the

Lunego and Wiki articles diagrammed above identify the distinct parts. TCA itself does not require Oxygen, but nedds to dispose of its products to continue producing energy.

NAD/NADH/NADPH



(adapted from Schaefer et al (2018) NADH NADH Autofluorescence - A Marker on its Way) https://onlinelibrary.wiley.com/doi/full/10.1002/cyto.a.23597



(adapted from Ju, Lin, Tian, Xie, Xu (2020) NADPH homeostasis in Cancer https://www.nature.com/articles/s41392-020-00326-0)

The above from Schaefer et al and Ju et al introduce newer concepts in Energy Metabolism for Cancer Cells. Substances such as Lactate and NAD are shared among cell compartments and nearby/distant cells to produce the high energy needed for cell reproduction. Thus Cancer cells pirate it's fuel from nearby cells and muscle in particular which can process using oxygen.

XIV. BLOOD SUGAR

TRα-T3 binding impairs glucose-stimulated insulin secretion by acting directly at the level of the pancreatic islets. TH cell-signaling induces carbohydrate response element-binding protein (ChREBP), stimulating glycolysis and lipogenesis (production of energy compounds) in response to low glucose and insulin in a TRα- and TRβ- dependent manner; reduced insulin levels stimulates ChREBP expression which in turn influences glucose response and insulin secretion.

Triiodothyronine (T3) increases hepatic glucose production, stimulates glucose uptake in peripheral tissues (GLUT4 in skeletal muscle) and SLGT1 (in intestine) that slows down the movement of food increasing nutrient and

water absorption). This increases GLP-1 and insulin secretion, ultimately leads to a net decrease in blood glucose levels.

A recent study found that free triiodothyronine (FT3) concentration was inversely associated with microangiopathic complications and metabolic control in euthyroid patients with type 1 diabetes mellitus (T1DM). After adjusting for confounding factors, Zhang et al found in their study that serum FT3 was inverse to HbA1c.

XV. COLON CANCER

T3 and TRα1 (T4) control the metabolic state of SCs and regulate their self-renewal capacity.

Depletion of DIO3 in adenocarcinoma downregulating Wnt is pro-differentiation. High T3 stimulates excess ROS in a stressed cell, yet normal surrounding microenvironment would function normally and absorb the High T3 effects. T3 promotes cell growth (increased size) and differentiation (complete the mesenchymal transition). Colon cancer actions of TH are mainly mediated through Serum T4, promoting cell proliferation/division at the membrane receptor αvβ3. T4 binding favors an increase of AMPK and the inhibition of mTOR resulting in increased tumor cell aggressivity.

XVI. Free T3/ FreeT4 Ratio

Table 2. Coefficients of linear fit: y = Ax + B among the variables $\log_e$ of TSH (mIU/L), FT3 (pmol/L) and FT4 (pmol/L) in euthyroidism, hypothyroidism and hyperthyroidism. The included errrors are standard errors in slope and intercept, and the P-value for F-test is obtained from the linear regression analysis

Thyroid status	*Values*	*ln(TSH) vs FT4*	*ln(TSH) vs FT3*	*FT3 vs FT4*
Euthyroidism (N = 2413)	Slope (A)	-0.02±0.003	-0.02±0.01	0.03±0.006
	Intercept (B)	0.99±0.05	0.84±0.06	5.00±0.08
	Pearson's r	-0.11	-0.03	0.11
	P-value	<0.001	0.07	<0.001
Subclinical hypothyroidism (N = 649)	Slope (A)	-0.005±0.004	-0.04±0.02	0.06±0.01 ↑
	Intercept (B)	2.02±0.06	2.16±0.08	4.56±0.15
	Pearson's r	-0.04	-0.10	0.21
	P-value	0.26	0.013	<0.001
Overt hypothyroidism (N = 113)	Slope (A)	-0.23±0.02	-0.56±0.09	0.18±0.02 ↑↑
	Intercept (B)	4.84±0.11	5.40±0.29	2.17±0.12
	Pearson's r	-0.75	-0.51	0.66
	P-value	<0.001	0.06	<0.001
Subclinical hyperthyroidism (N = 175)	Slope (A)	-0.05±0.02	-0.46±0.08	0.03±0.02
	Intercept (B)	-1.79±0.46	0.21±0.52	5.53±0.38
	Pearson's r	-0.13	-0.38	0.10
	P-value	0.07	<0.001	0.17
Overt hyperthyroidism (N = 75)	Slope (A)	0.002±0.003	0.003±0.007	0.41±0.02 ↑↑↑
	Intercept (B)	-4.44±0.19	-4.40±0.16	-1.79±1.25
	Pearson's r	0.07	0.04	0.91
	P-value	0.56	0.72	<0.001

(From Lamichhane et al (Thyroid Hormones-Thyrotropin Interrelationships 2020) https://www.biorxiv.org/content/10.1101/2020.06.26.173252v1

The FT3:FT4 ratio in 3,875 healthy euthyroid controls across 5 segments of the normal TSH reference range

TSH levels (mU/L)	n.	TSH (mU/L)	FT4 (pmol/L)	FT3 (pmol/L)	FT3/FT4 ratio
0.40–1.00	1306	0.7	14.2	4.47	0.31
	IQR range	(0.57–0.90)	(12.5–15.7)	(3.85–5.00)	(0.27–0.36)
1.01–1.50	878	1.3	13.9	4.34	0.31
	IQR range	(1.16–1.40)	(12.1–15.4)	(3.85–4.93)	(0.27–0.37)
1.51–2.00	625	1.79	13.8	4.47	0.31
	IQR range	(1.62–1.90)	(12.0–15.4)	(3.85–4.93)	(0.27–0.37)
2.01–2.50	402	2.26	13.4	4.47	0.32
	IQR range	(2.11–2.40)	(11.6–15.4)	(3.85–4.94)	(0.27–0.37)
2.51–4.00	664	3.1	12.9	4.47	0.33
	IQR range	(2.70–3.70)	(11.6–15.0)	(3.85–5.00)	(0.28–0.39)

IQR = interquartile range.

Source: Gullo et al, 2011, PLoS ONE 6(8): e22552 doi:10.1371/journal.pone.0022552.g001

(From Normal FT3:FT4 Thyroid Hormone Ratios in Large Populations – Thyroid Patients Canada https://www.biorxiv.org/content/10.1101/2020.06.26.173252v1

There is no one Thyroid assay that can ensure Euthyroidism. Recent work with Free Thyroid Assays show that the Ratio of Free T3 to Free T4 may be a more useful clinical paramter. The above from indicate the distinct ratio differents in the major Thyroid Classifications, that Euthyroid and SC Hyperthroid have similar ratio. The ratio is noted stable across ^TSH in SC.

XXX. FreeT3 TRIAD PLUS FreeT4 ACTIONS

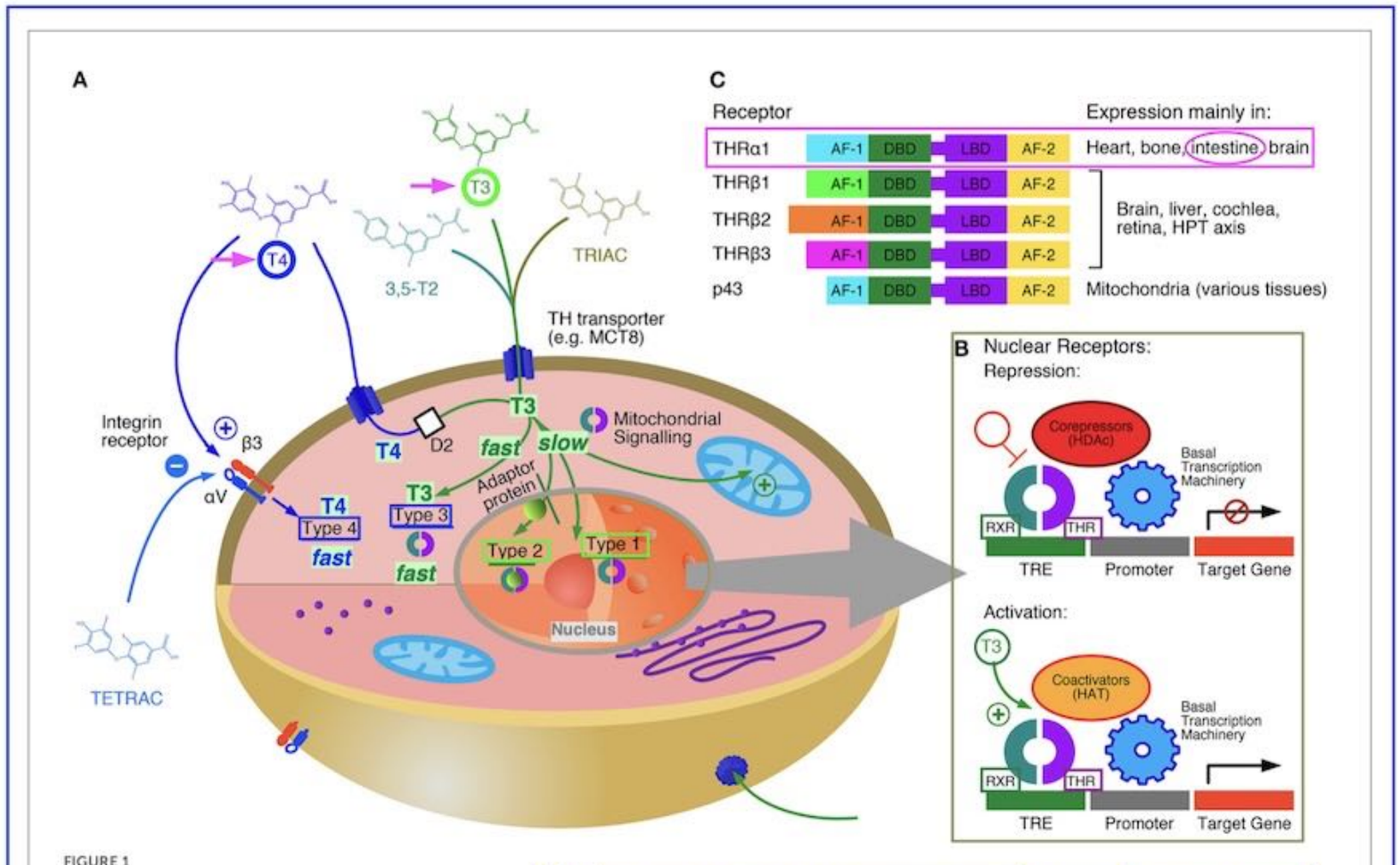


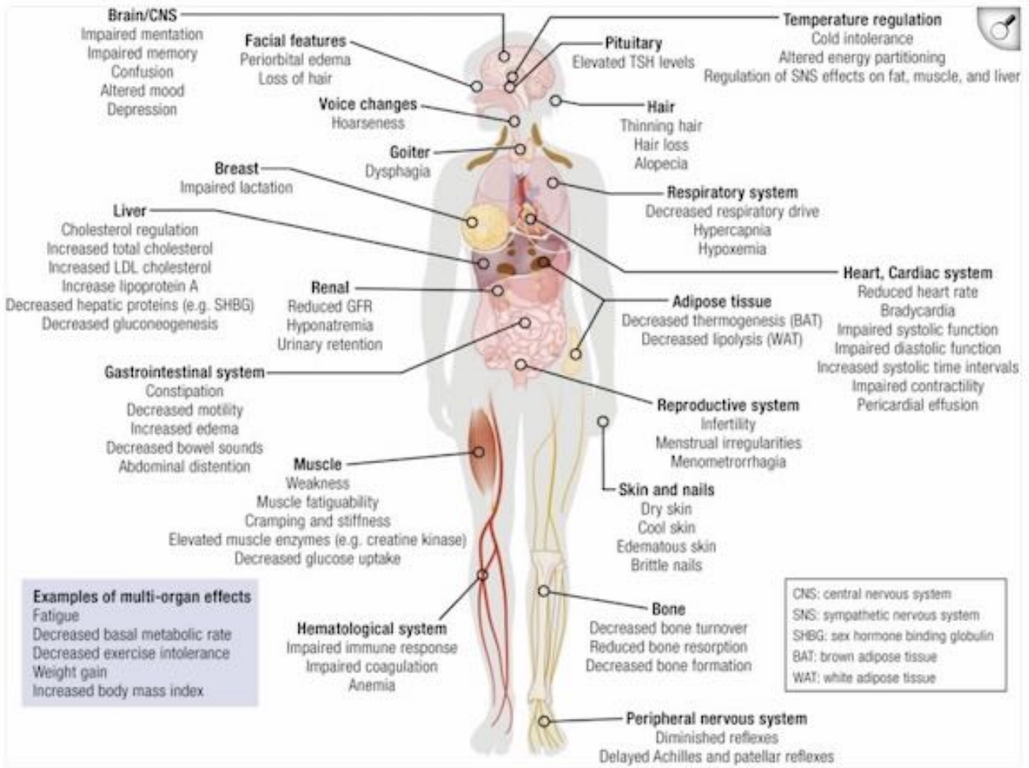
FIGURE 1
Types and mechanisms of thyroid hormone signaling. T4 is a prohormone with respect to genomic signaling but a true fast-acting hormone regarding type 4 action, which is inhibited by the iodothyroacetate TETRAC). Genomic action (type 1, type 2 and mitochondrial signaling) occurs on a slow time scale, whereas non-genomic effects (type 3 and type 4 signaling) represent a fast response (A). Thyroid hormone receptors (THR) usually act as heterodimers. Without thyroid hormone bound they block the transcription together with corepressors. Iodothyronines displace the corepressors and stimulate gene expression together with coactivators (B). Tissue specific distributions of THRs further contribute to the diversity of signaling patterns in the organism (C) (48, 65–69). AF-1, activation function 1; AF-2, activation function 2; D2, type 2 deiodinase; DBD, DNA-binding domain; HAT, histone acetyl-transferase; HDAc, histone deacetylase; LBD, ligand-binding domain; RXR, retinoid X receptor; TRE, thyroid-hormone response element.

Adapted from Müller P, Leow MK-S and Dietrich JW, Front. Cardiovasc. Med. 9:942971 (2022)

T3 and T4 have
compartmentalized
effects in the cell and varied onset:
Nuclear/Mitochondrial *Genomic*
Type1,2 (T3, T4>T3) SLOW
Cellular *Non-Genomic*
Type3 (T3,T4>T3) *FAST*
Membrane Integrin *Non-Genomic*
Type4 (T4) *FAST*

XVIII. THYROID, THYROID EVERYWHERE A NOT A DROP TO DRINK

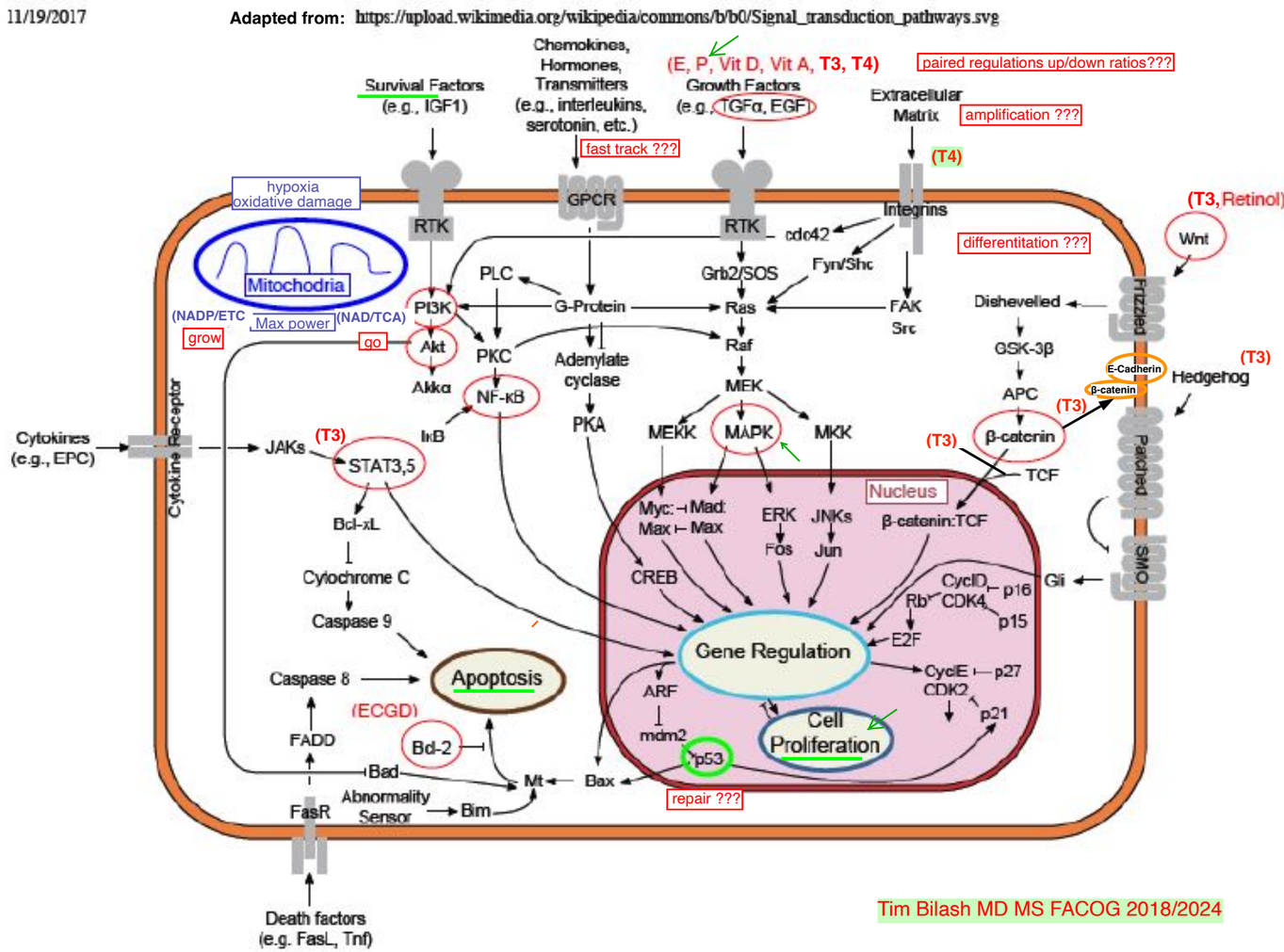
From Optimal Thyroid Hormone Replacement - Jonklaas
Endocr Rev. 2021 Sep 20;43(2):366–404. doi: 10.1210/endrev/bnab031
https://pmc.ncbi.nlm.nih.gov/articles/PMC8905334/figure/F1/
https://pmc.ncbi.nlm.nih.gov/articles/PMC8905334/



One issue with Thyroid metabolism is its ubiquity and compartmentalization. *“The clinical manifestations of hypothyroidism are diverse and potentially emanate from the effects of thyroid hormone deficiency in any organ system of the body. Both signs and symptoms exhibit a wide spectrum of severity, ranging from subtle to profound.”*

XIX. SUMMARY - ENDOCRINE BALANCE

ATP is the primary energy currency in cells for function. NADH primarily uses energy for catabolic pathways like cellular respiration, while NADPH uses energy for anabolic processes like fatty acid synthesis and maintaining cellular redox balance.



Tim Bilash MD MS FACOG 2018/2024

All cell metabolism appears to be modulated by Thyroid Hormones in Ratio FreeT3/FreeT4 balancing. There is a need to include other basic Hormones (Estradiol, Progesterone, Vitamin D, Vitamin A,Thyroxine, Triiodothyronine).