Carotenoids, Selenium, and IL-6: Identifying Intervention Targets Using Epidemiological Data

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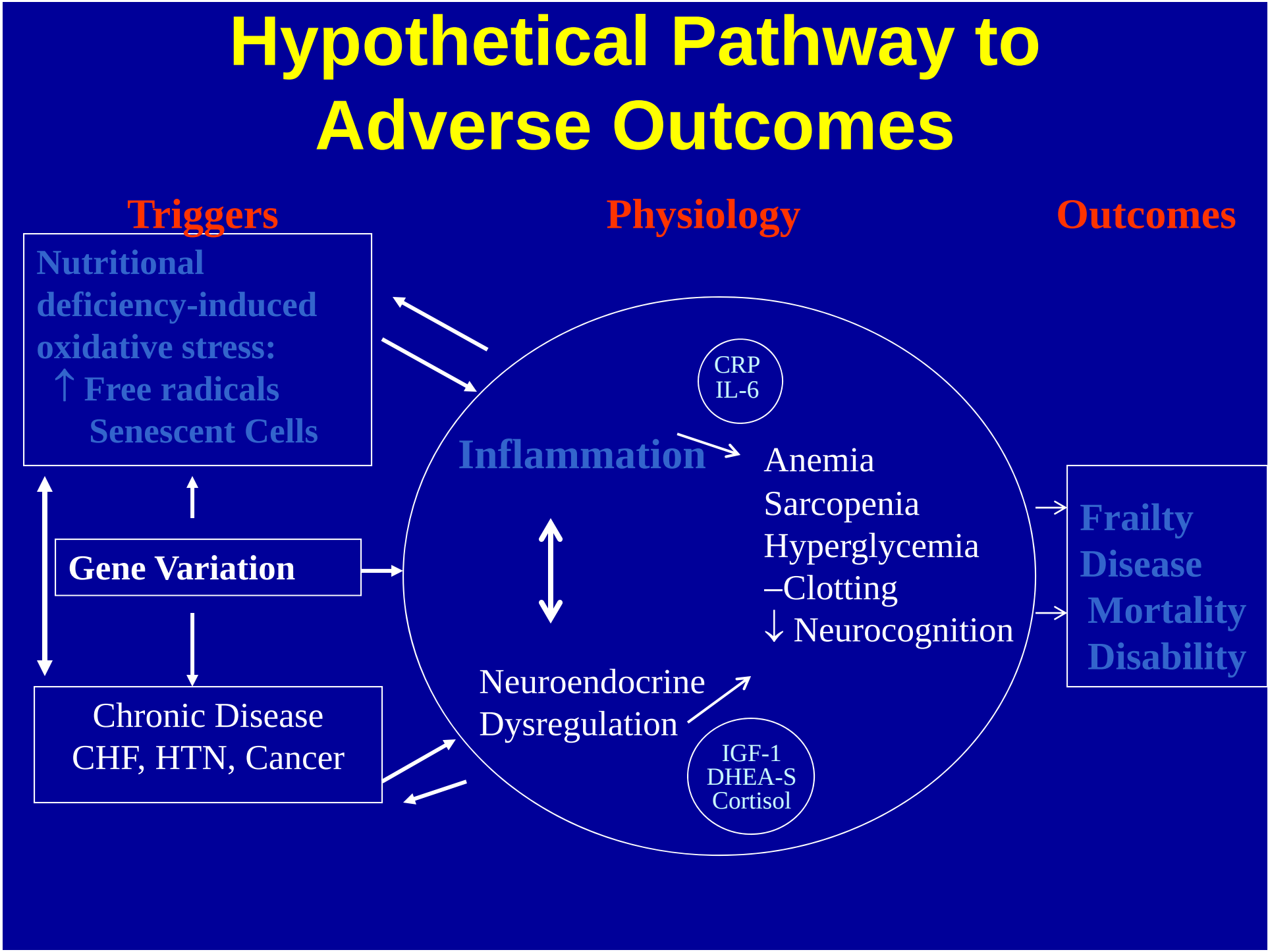
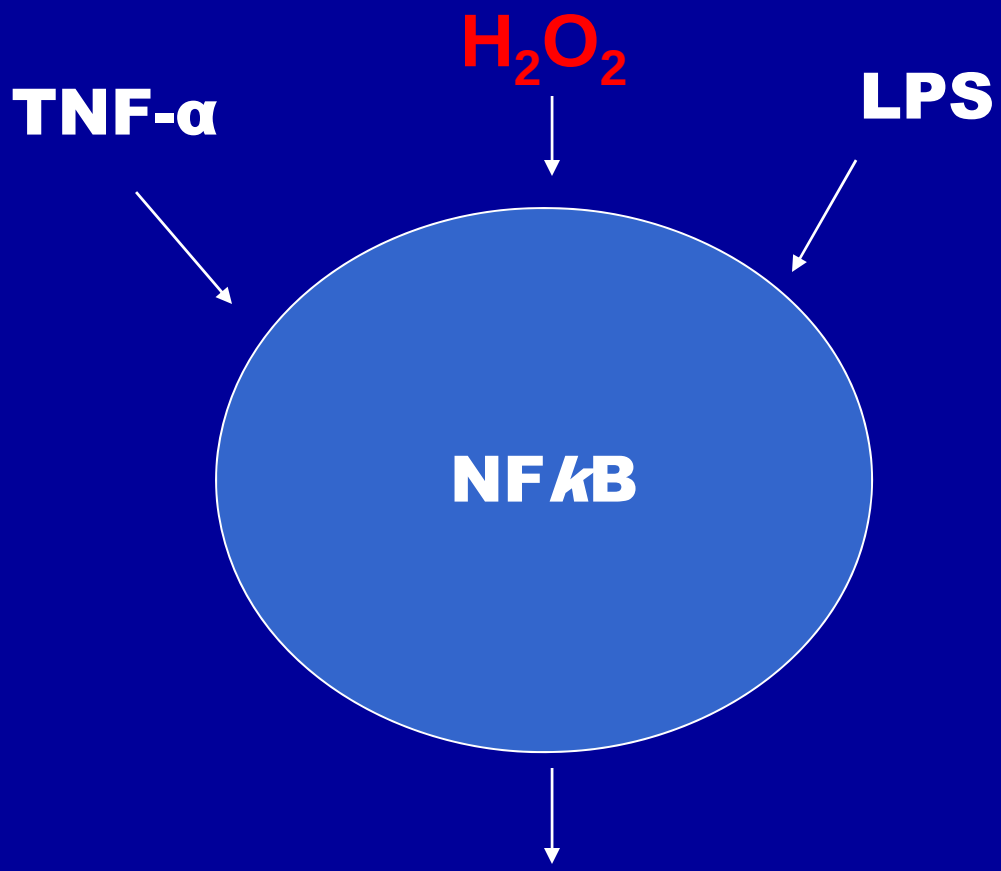
Introduction

- Biology that connects inflammation antioxidants, and late life decline
- Epidemiological evidence: The Good News and The Bad News
- Potential directions for intervention development

Hypothetical Pathway to Adverse Outcomes



Oxidative Stress & Inflammation



↑IL-6, Inflammatory & Coagulation Cascades

What Are Carotenoids?

- Yellow to red-pigmented plant-derived molecule
- Contains long conjoined units of hydrocarbon isoprene
- Isoprene units function to absorb and transfer electrons
- New or altered by-products of original molecule remain after interaction with oxidative products

Function of Carotenoids

- In plants, absorb energy from light and pass to chlorophyll
- Also protects chlorophyll from free radicals
- After ingestion by animals, stored in fat
- Absorbs free radicals in animal species as well
- Important precursor to vitamin A

Carotenoid Family

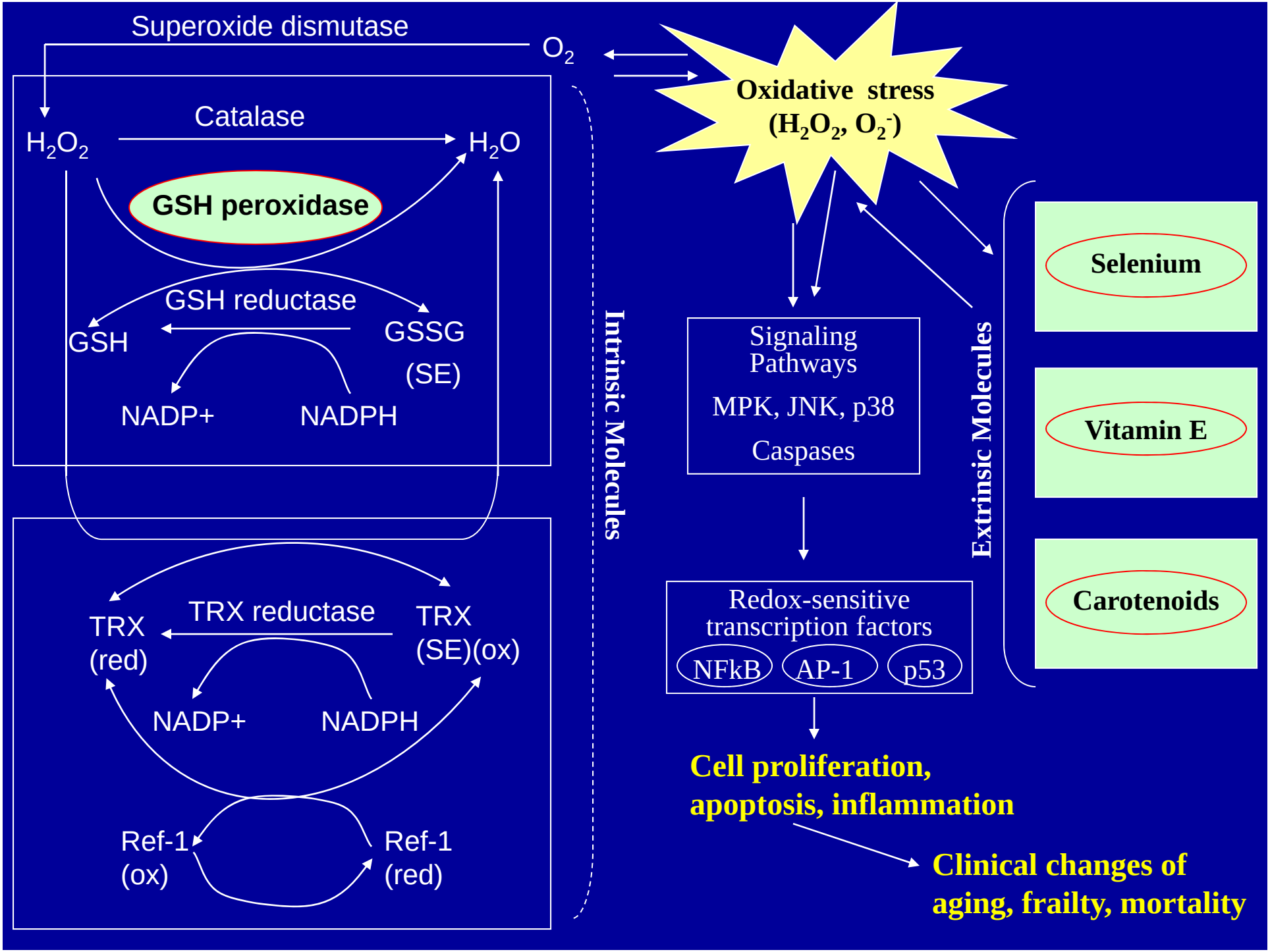
- α Carotene, yellow orange, dates, mangos
- β Carotene yellow, green leafy vegetables
- Lycopene, red tomatoes
- Lutein/Zeaxanthin, yellow corn
- β cryptoxanthin, green/yellow broccoli
- Total carotenoids

Selenium

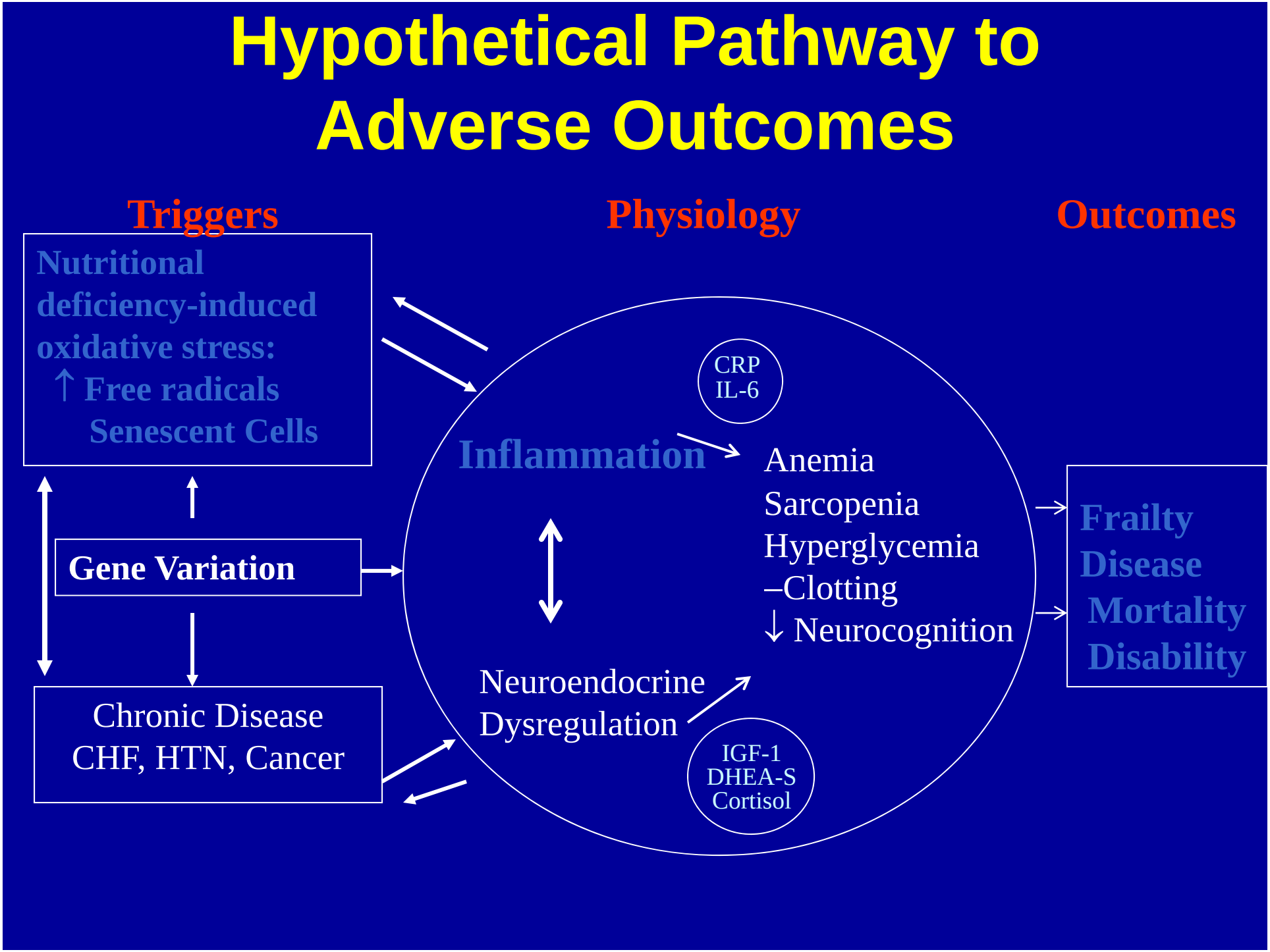
- Mineral taken into plants from soil
- Absorbed from plant or meat food sources
- Regional variation depending on soil levels
- Function in free radical quenching
- Incorporated into family of selenoproteins

Selenoproteins

- Glutathione peroxidases
- Thioredoxin reductase
- Selenoprotein P
- Iodothyronine diodinase


Superoxide dismutase
O_2
Catalase
H_2O_2
H_2O
GSH peroxidase
GSH reductase
GSH
GSSG
(SE)
NADP+
NADPH
TRX reductase
TRX
(red)
TRX
(SE)(ox)
NADP+
NADPH
Ref-1
(ox)
Ref-1
(red)
Intrinsic Molecules
Oxidative stress
(H_2O_2, O_2^-)
Signaling
Pathways
MPK, JNK, p38
Caspases
Redox-sensitive
transcription factors
NFkB
AP-1
p53
Extrinsic Molecules
Selenium
Vitamin E
Carotenoids
Cell proliferation,
apoptosis, inflammation
Clinical changes of
aging, frailty, mortality

Hypothetical Pathway to Adverse Outcomes



Disability and Carotenoid Levels

- IN CHIANTI population (N=928, age 65-102)
- Higher levels of total carotenoids significantly associated with better mobility measures after 6 years
  - Severe Walking Disability; OR 0.59, 95% CI 0.38-0.90 over 6 years
  - Significant lower decline in 4 meter walking speed
  - Lower incidence of not being able to complete 400 meter walk

Lauretani F et al, Rejuvenation Res., 2008

Frailty and Carotenoid Levels

- Women's Health and Aging Studies I and II (N=1436, age 65-101)
- Lower levels of beta-carotene is independent risk factor for the development of frailty
- Lower levels of total carotenoids predict the development of severe walking disability

Semba RD et al, Gerontology, 2006, and Age and Aging, 2007

Antioxidant levels, IL-6 and Mortality in Older Adults

In general, low levels predict higher levels of IL-6 over two years

Higher levels associated with fewer adverse outcomes, including mortality

Walston J et al, 2006 Am J Epi.

Population

Women's Health and Aging I (WHAS-1)

- Disability
  - ≥ 2 domains with difficulty
  - 1/3 most disabled community residents
- Age ≥ 65
- MMSE Score ≥ 18
- N=619 with complete blood draws

Odds Ratio of Being in the Highest IL-6 Tertile by Micronutrient

Micronutrient	OR	95%CI	P-value
α Carotene (μmol/L)	0.65	0.53,0.80	0.0001
β carotene (μmol/L)	0.72	0.59,0.87	0.001
Lycopene (μmol/L)	0.75	0.63,0.91	0.003
Lutein/Zeaxanthin (μmol/L)	0.72	0.59,0.89	0.004
β cryptoxanthin (μmol/L)	0.77	0.63,0.94	0.016
Total carotenoids (μmol/L)	0.65	0.53,0.79	<0.0001

*N=619 for all analyses except alpha-tocopherol/cholesterol ratio (n=605), zinc (n=615), and selenium (n=591)

Odds Ratio of Being in the Highest IL-6 Tertile by Micronutrient

Micronutrient	OR	95%CI	P-value
Retinol (μmol/L)	0.87	0.72,1.05	0.038
α tocopherol (μmol/L)	0.91	0.74,1.11	0.05
α tocopherol /cholesterol ratio (mg/g)	1.01	0.82,1.24	0.777
Zinc (μg/L	0.99	0.82,1.20	0.948
Selenium (μg/L)	**0.65**	**0.52,0.80**	**<0.0001**

*N=619 for all analyses except alpha-tocopherol/cholesterol ratio (n=605), zinc (n=615), and selenium (n=591)

Odds Ratio of Having IL-6 Increase by 3.21 pg/ml in One Year

Alpha-carotene

Baseline alpha carotene (μmol/L)	N	Year 1				
		OR	CI			
<=0.039	146	2.48*	1.05, 5.88			
>0.039, <=0.094	126	1.49	0.60, 3.72			
>0.94	155	1				

Walston J et al, Am J Epi 2006

Odds Ratio of having IL-6 increase by >3.21 pg/ml over 2 Years

Alpha-carotene

Baseline alpha carotene (μmol/L)	N	Year 1		N	Year 2	
		OR	CI		OR#	CI
<=0.039	146	2.48*	1.05, 5.88	112	7.99**	2.27, 28.21
>0.039, <=0.094	126	1.49	0.60, 3.72	111	7.12**	2.08, 24.38
>0.94	155	1		119	1	

Walston J et al, Am J Epi 2006

Odds Ratio of having IL-6 increase by 3.21 pg/ml in one year

Beta-carotene

Beta-carotene (μmol/L)	N	Year 1				
		OR	CI			
<=0.23	138	1.68	0.74, 3.84			
>0.23, <=0.45	141	0.96	0.42, 2.21			
>0.45	148	1				

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by >3.21 pg/ml over 2 Years

Beta-carotene

Beta-carotene (μmol/L)	N	Year 1		N	Year 2	
		OR	CI		OR	CI
<=0.23	138	1.68	0.74, 3.84	115	4.09*	1.38, 12.11
>0.23, <=0.45	141	0.96	0.42, 2.21	108	3.52*	1.19, 10.39
>0.45	148	1		119	1	

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by 3.21 pg/ml in One Year

Lutein/Zeaxanthin

Lutein Zeaxanthin (μmol/L)	N	Year 1				
		OR	CI			
<=0.27	132	1.12	0.46, 2.74			
>0.27, <=0.41	144	1.34	0.61, 2.94			
>0.41	151	1				

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by > 3.21 pg/ml over 2 Years

Lutein/Zeaxanthin

Lutein Zeaxanthin (μmol/L)	N	Year 1		N	Year 2	
		OR	CI		OR	CI
<=0.27	132	1.12	0.46, 2.74	105	5.57**	1.74, 17.80
>0.27, <=0.41	144	1.34	0.61, 2.94	114	3.18*	1.08, 9.39
>0.41	151	1		123	1	

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by 3.21 pg/ml in One Year

Total Carotenoids

Total carotenoids (μmol/L)	N	Year 1				
		OR	CI			
<=1.17	132	2.05	0.86, 4.91			
>1.17, <=1.80	142	1.94	0.83, 4.52			
>1.80	153	1				

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by 3.21pg/ml over 2 Years

Total Carotenoids

Total carotenoids (μmol/L)	N	Year 1		N	Year 2	
		OR	CI		OR	CI
<=1.17	132	2.05	0.86, 4.91	113	3.98**	1.51, 10.49
>1.17, <=1.80	142	1.94	0.83, 4.52	103	1.40	0.47, 4.14
>1.80	153	1		126	1	

Walston J et al, Am J Epi 2006

Odds Ratio of Having IL-6 Increase by 3.21pg/ml over 2 Years

Selenium

Selenium (μmol/L)	N	Year 1		N	Year 2	
		OR	CI		OR	CI
<=110.0	**131**	0.53	0.23, 1.27	**99**	0.94	0.36, 2.45
>110.00, <=122.90	**138**	0.76	0.34, 1.68	**115**	0.81	0.32, 2.03
>122.90	**140**	1		**122**	1	

Walston et al, Am J Epi 2006

Antioxidants & Mortality

Micronutrients	# of Deaths in 5 yrs	Unadjusted		Age, Race, Adjusted		Fully Adjusted	
		HR	95% C.I.	HR	95% C.I	HR	95% C.I
Alpha Carotene:							
<=0.040 μmol/L	71	1.19	0.85,1.68	1.44	1.02,2.04	1.06	0.70,1.59
>0.040, <=0.094 μmol/L	73	1.21	0.86,1.69	1.30	0.92,1.82	1.19	0.81,1.74
>0.094 μmol/L	62	1		1		1	
Total Carotenoids:							
<=1.167 μmol/L	75	1.23	0.88,1.72	1.32	0.95,1.85	1.07	0.72,1.58
>1.167, <=1.806 μmol/L	67	1.03	0.73,1.45	1.09	0.78,1.54	1.02	0.69,1.50
>1.806 μmol/L	64	1		1		1	
Selenium:							
<=109.9 μg/L	78	1.66	1.17,2.37	1.48	1.03,2.13	1.54	1.03,2.32
>109.9, <=122.8 μg/L	68	1.40	0.98,2.02	1.24	0.86,1.79	1.30	0.86,1.96
>122.8 μg/L	51	1		1		1	

Walston J, et al., Am J Epi, 2006

Mortality and Antioxidants

- 47 Low-biased randomized clinical trials (n=180,938)
- Supplementation significantly associated with all cause mortality
  - B-carotene (RR, 1.05: 95% CI, 1.02-1.08)
  - Vitamin A (RR 1.16; 95% CI, 1.10-1.24)
  - Vitamin E (RR, 1.04; 95% CI, 1.01-1.07)

Bjelakovic G et al. JAMA, 2007

Mortality and Antioxidants

- Vitamin C and Selenium supplementation not associated with mortality
- Many of individual or combination intervention with selenium close to significant reduction of mortality
- Authors suggest further study of selenium and Vitamin C warranted

Bjelakovic G et al. JAMA, 2007

Mortality and Carotenoid Supplementation

- Increased mortality first identified smokers in lung cancer study
- Subsequent analyses reveal significant increased risk of all cause mortality with antioxidant supplements
- May be related to conversion of extra molecules to free radicals

Mortality and Carotenoid Supplementation

- Vitamins and Lifestyle cohort (VITAL Study)
- Observational study of 77,126 individuals who reported on 10 years of supplement use
- Lung Cancer Registry used to identify 521 subjects who developed lung cancer through December 2005

Satia JA, et al., Am J Epi, 2009

Mortality and Carotenoid Supplementation

- Longer duration of use associated with increased risk of lung cancer
  - Lutein: HR 2.02, (95% CI, 1.28-3.17) for total lung CA risk
  - Beta-carotene: HR 3.22, 95% CI 1.29-8.07) for small cell lung CA with 4 years vs. no use.

Satia JA, et al., Am J Epi, 2009

Summary of Data

- Low levels of carotenoids predict IL-6 increase in older populations
- Low levels of carotenoids are associated with adverse outcomes in older adults
- Carotenoid supplementation is associated with adverse outcomes in many studies

Summary of Data

- Low levels of selenium predicts mortality in populations of older adults (close in general populations)
- Selenium supplementation not associated with increased mortality

Missing Evidence

- No studies in older adults that target those with deficits
- Inflammation itself may drive levels of antioxidants lower
- No clear evidence if this is related to diet or to innate biology that uses up antioxidants at increased rate

Missing Evidence

- Vast areas of biochemistry left to explore
- Poor understanding of selenoproteins and of toxic byproducts of carotenoids
- Does inflammation chew up molecules, or alter selenoprotein make-up?

Potential Study Design

- Identify at risk older adults with low antioxidants and high IL-6
- Randomize to placebo and intervention and follow inflammatory markers, health status, and evolution of frailty and functional decline