Systemic metabolic alterations (paraneoplastic syndromes)

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Interest or importance?

- 75,000 cancer deaths per year in Canada; increased months of survival with metastatic disease
- Pain /symptoms are or become the dominating feature of the disease for patients

*Cancer patients in Canada see a physician on average 35 times during their last 12 months of life with cancer

*20,500 lung cancer deaths in Canada, median survival 10 months = 6,150,000 person-days of life with an incurable malignancy

Conceptual model of cancer cachexia trajectory

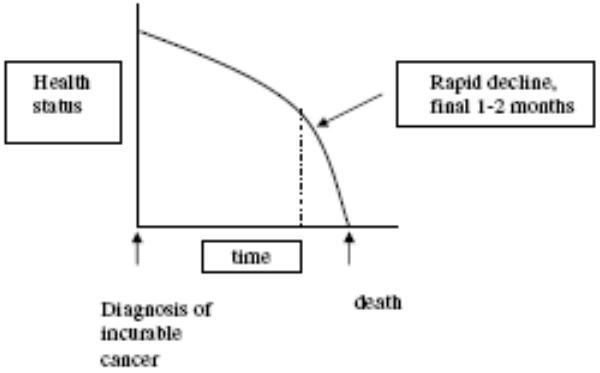
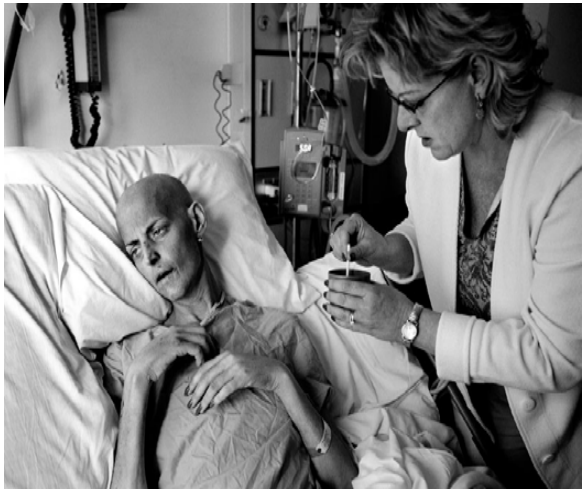


Fig. 1 – Conceptual model of cancer death trajectory.[122,123]



Barb Tarbox 1961 - 2003

Tumor direct effects

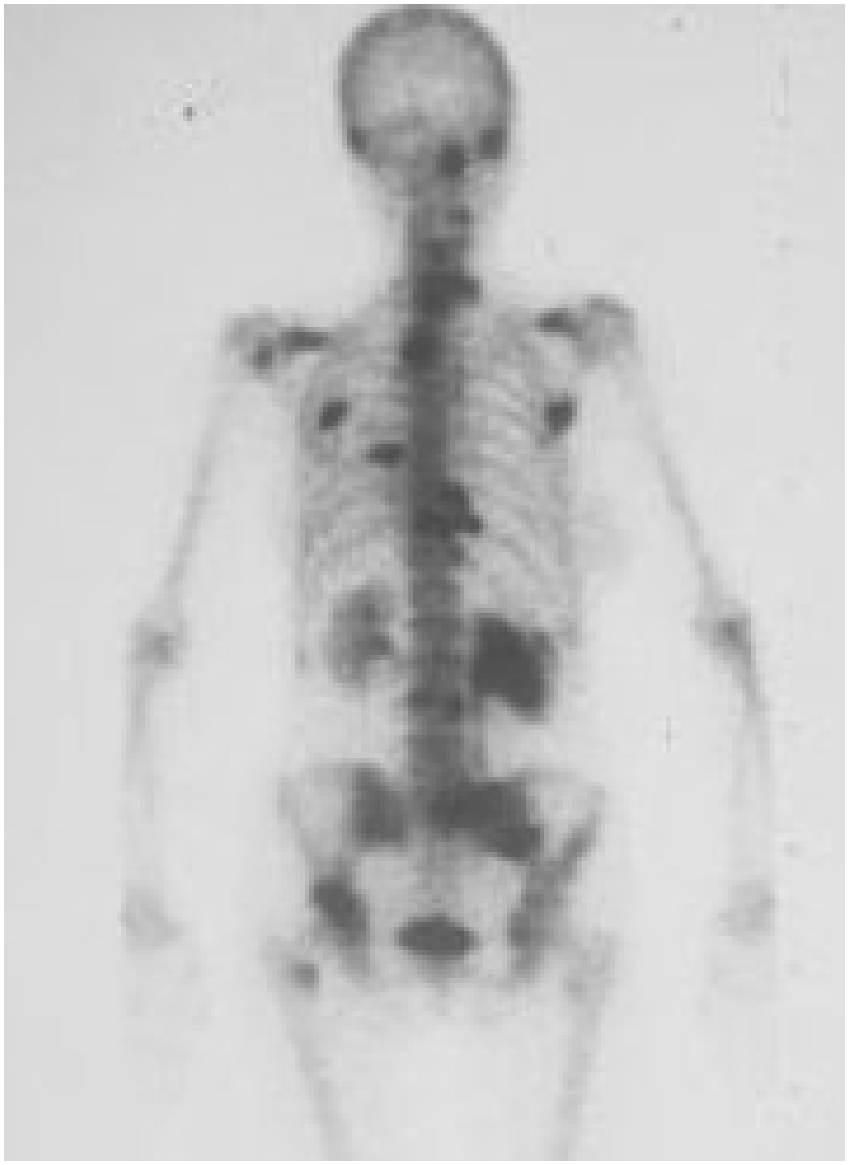
Cancers produce locally appearing symptoms by growing into and thus irritating or destroying other tissues and putting pressure on other tissues.

Brain tumor : seizures

Colorectal cancer: bowel obstruction

Breast /prostate: sequelae of bone metastases

Pain



Clinical features of bony metastases

Most common cause of intractable pain

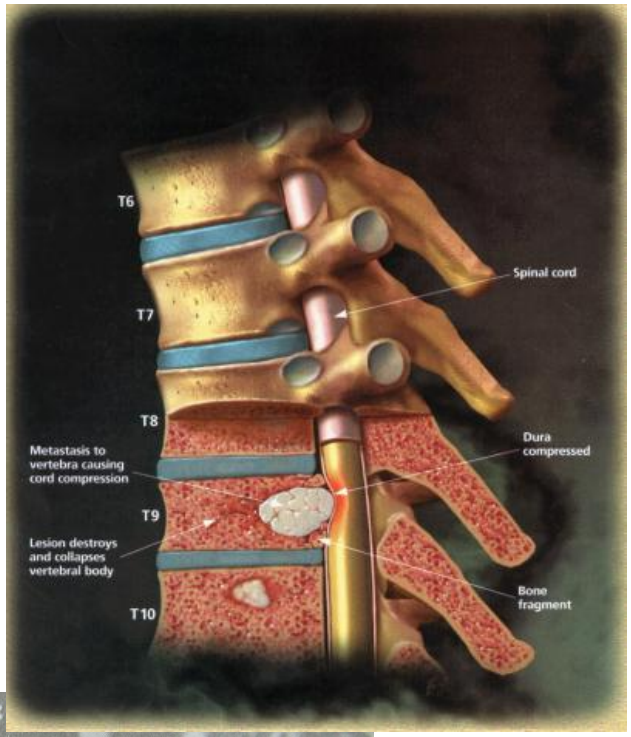
Pathological fracture

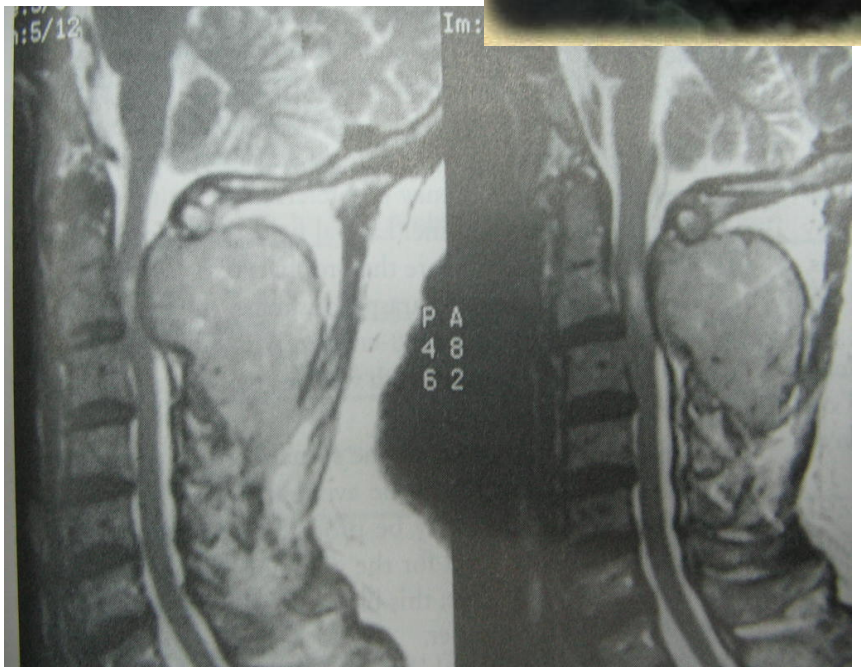
Hyper-calcemia

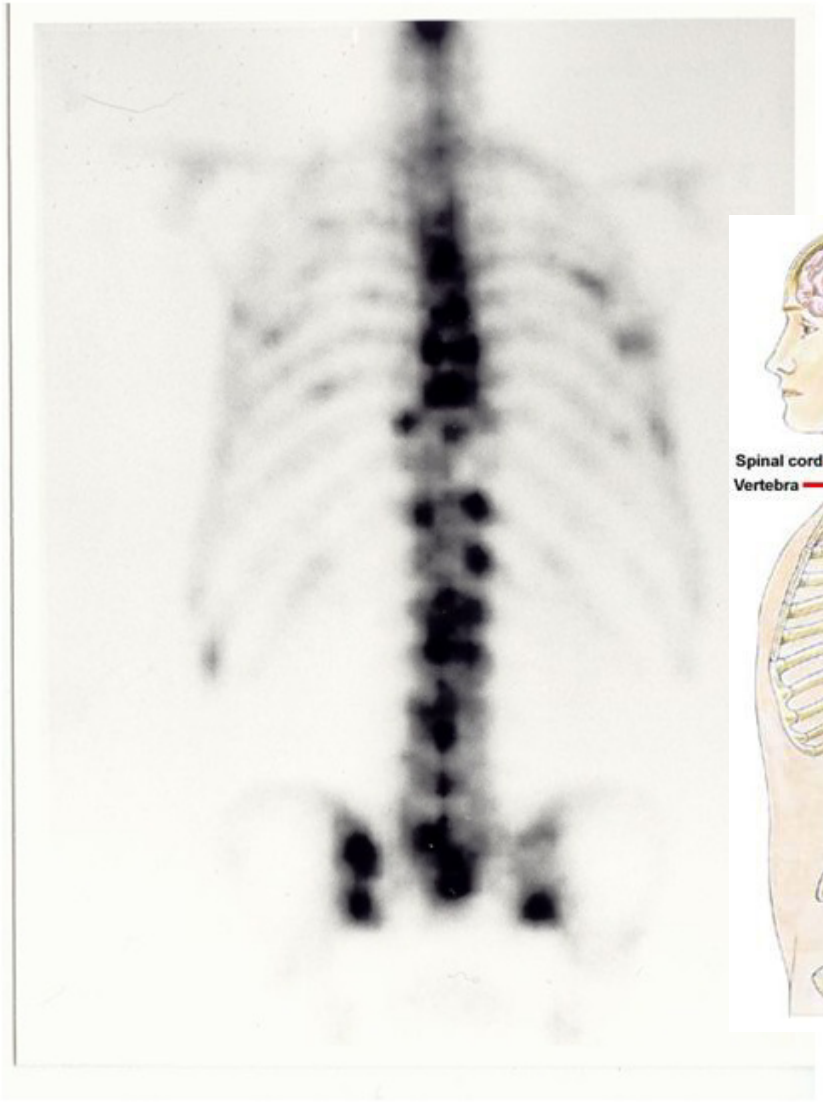
Spinal cord compression / fracture

*the patient is injected with 600 MBq of technetium-99 and then scanned with a gamma camera.

- A saggital view of cervical spine showing a huge mass compressing the spinal canal mainly at the level of the 2nd cervical vertebra.



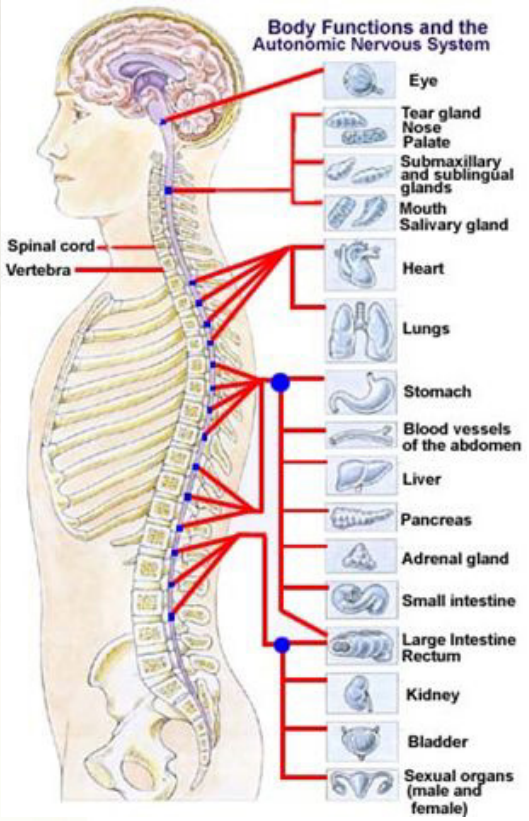




Pain

Motor functions

Autonomic functions

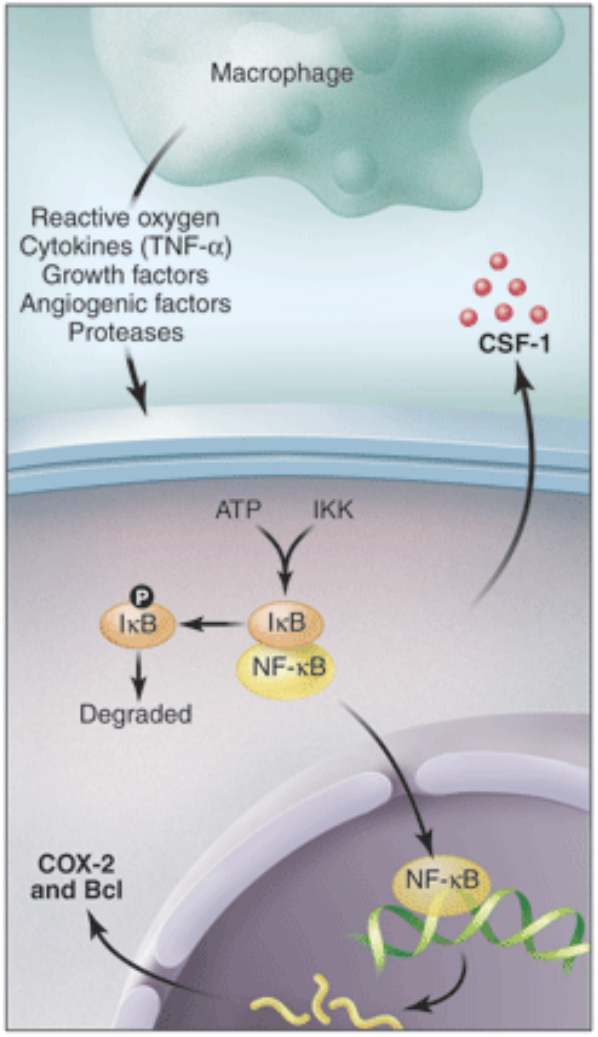


Spinal cord compression

- Severe pain
- Numbness in limbs
- Paralysis
- Loss of nerve function serving the organs
- Bedridden – total dependent care

- Corticosteroids to reduce edema and inflammation
- Surgery, only if some function could be anticipated
- Palliative radiotherapy “fast track”
- Rehabilitation / mobilization

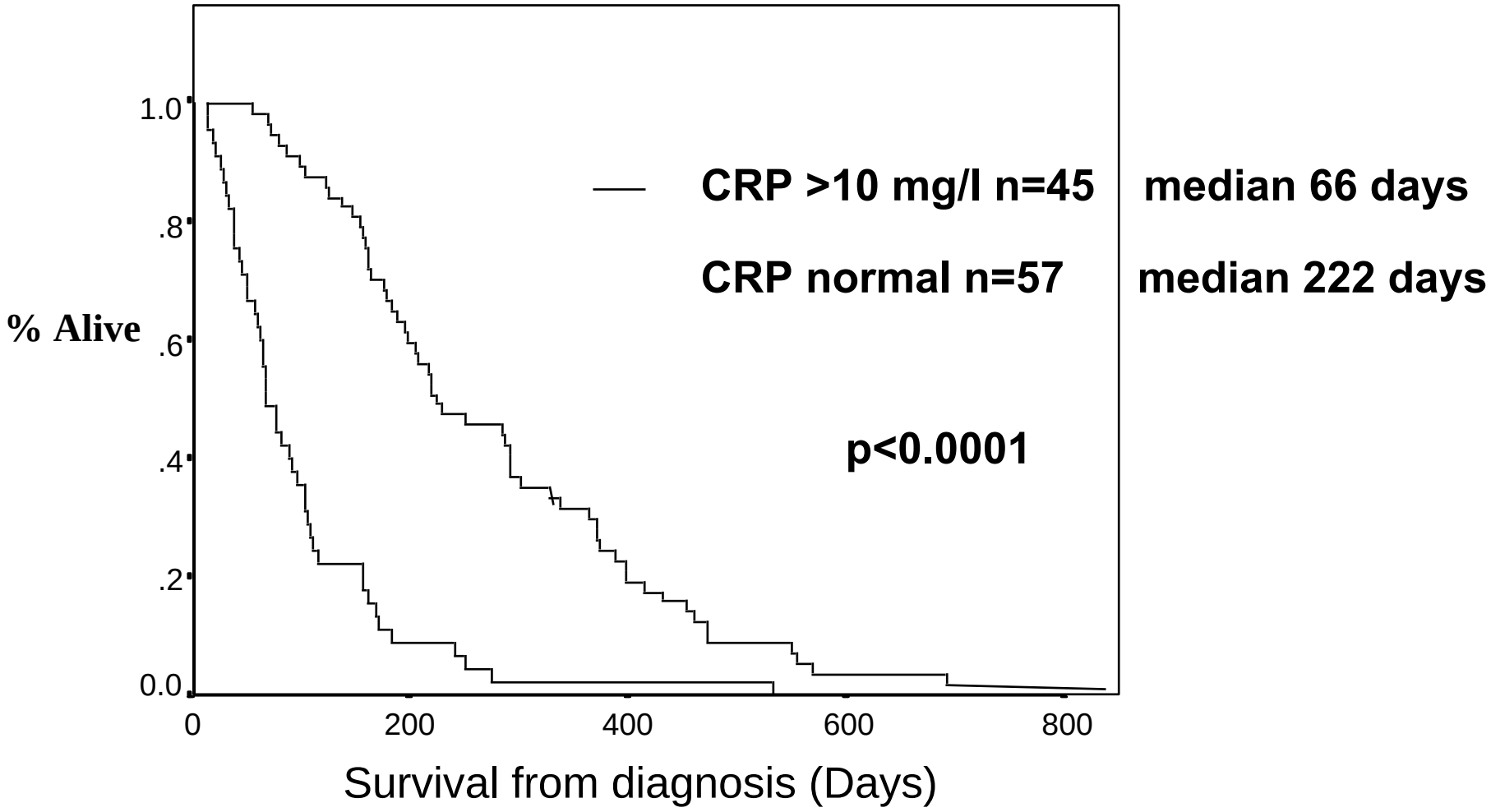
Inflammation, a unifying theme in cancer progression , prognosis and the development of paraneoplastic pain, anorexia, wasting and altered sleep behaviour



<u>Vicious cycle</u>. Macrophages produce several substances that can enhance tumor growth, including TNF-α , which can turn up NF- kB activity in both target tissue cells and in macrophages themselves. Tumor cells produce substances such as colony stimulating factors CSF-1 and COX-2 that give a further boost to inflammatory processes, as well as proteins such as Bcl that inhibit apoptosis.

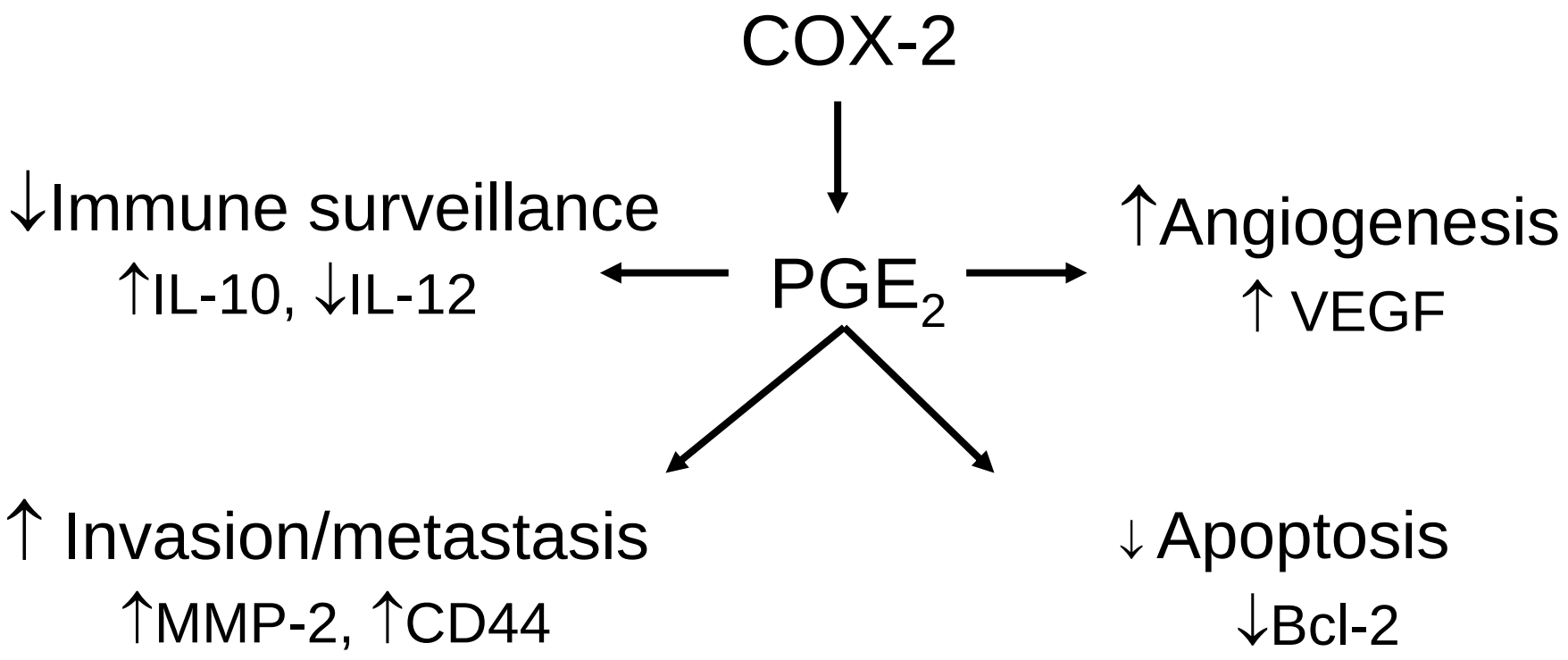
- *Science 5 November 2004: Vol. 306. no. 5698, pp. 966 - 968 Inflammation and Cancer: The Link Grows Stronger, Jean Marx*

Pancreatic Cancer, C reactive protein, a marker of systemic inflammation and survival



Falconer et al, 1995

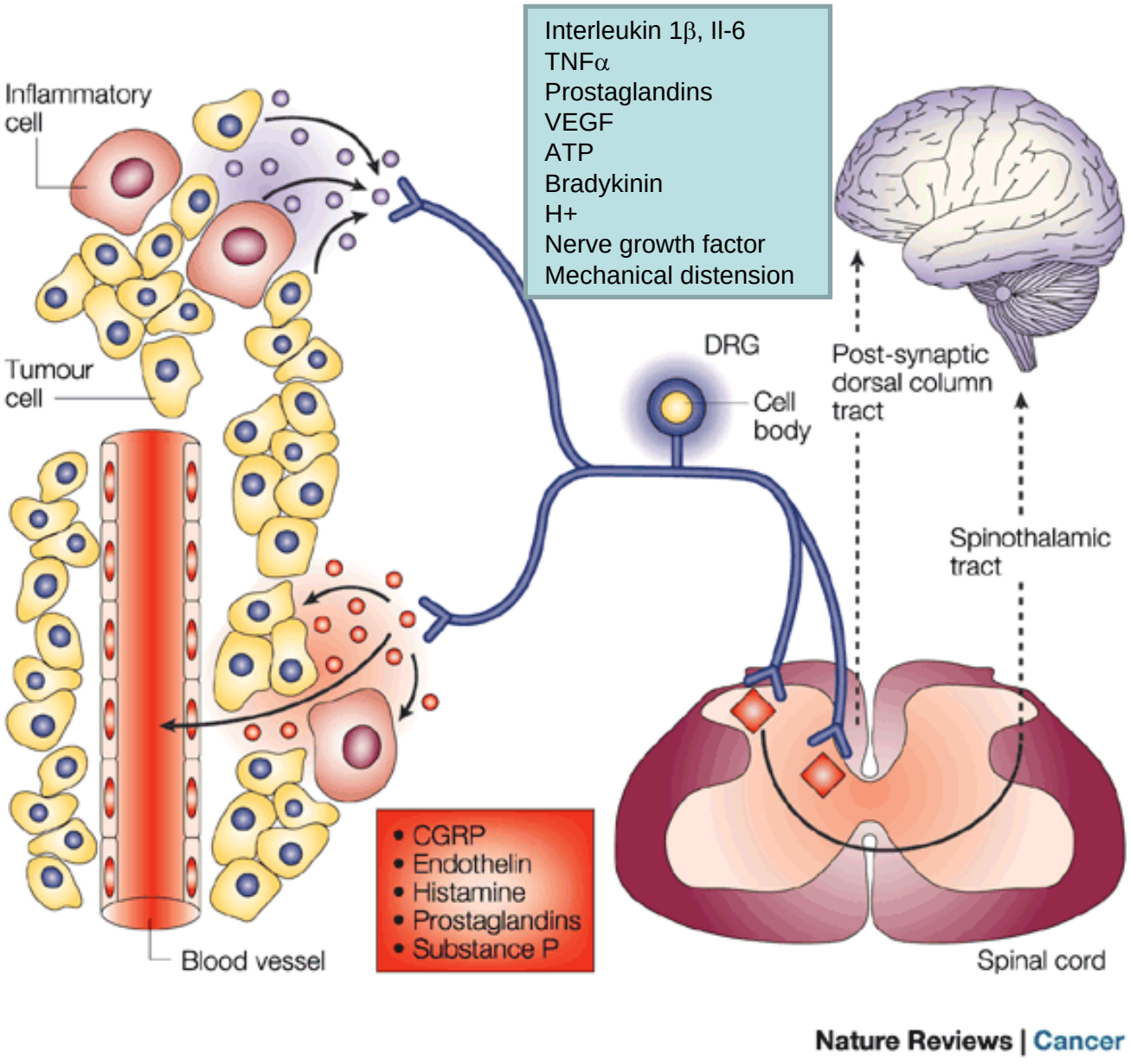
Proposed COX-2/PGE_2 Pathways in Cancer



Dannenberg AJ. *Lancet.* 2001;2:544-551; Tsujii M. *Cell*. 1995;83:493-501; Tsujii M. *Proc Nat Acad Sci*. 1997;94:3336-3340. Tsujii M. *Cell*. 1998;93:705-716; Masferrer JL. *Cancer Res*. 2000;60:1306-1311;Gately S. *Cancer Met* Rev. 2000; 19:19-27. Gallo O. *Nature*. 2001;3:53-61; Stolina M. *J Immunol*. 2000;164:361-370. Huang M. *Cancer Res*. 1999;58:1208. Nzeako UC. *Hepatology*. 2002;35:552-559.

Inflammation and cancer pain

- hyperalgesia, in which there is pain after a stimulus that is normally non-painful, a frequent accompaniment of inflammation and cancer
- Inflammation locally around tumor may be intense, with local activity of macrophages and neutrophils which produce multiple hyperalgesic ligands : eicosanoids, cytokines, bradykinin, adenosine, 5-hydroxytryptamine

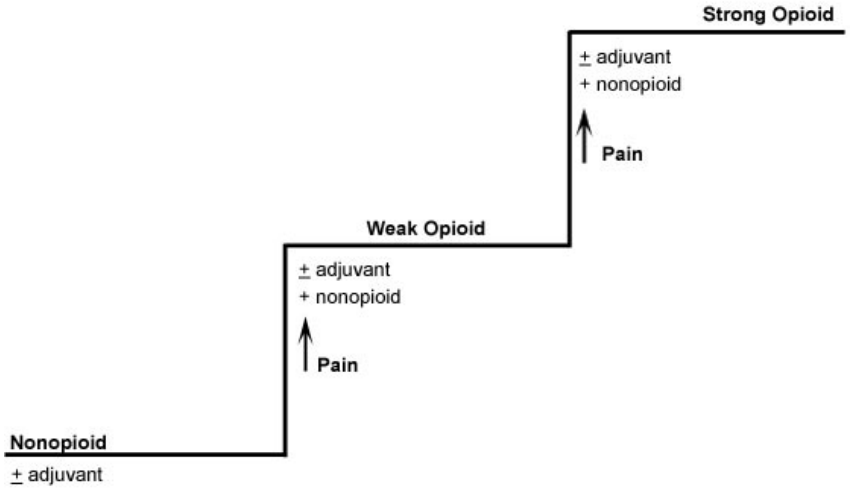


Cancer cells and inflammatory cells release a variety of products that either excite or sensitize the nociceptor. Painful stimuli are detected by the nociceptors, the cell bodies of which lie in the dorsal root ganglion (DRG), and are transmitted to neurons in the spinal cord.

Inflammation and cancer pain

- Interleukin-1β induces hyperalgesia
- PGE_2, 15(S)-dihydroxy eicosatrienoic acid (HETE), leukotriene B : all are sensitizing agent for nociceptors (pain receptors)
- Numerous inflammatory mediators present at sites of malignancy can lower nociceptor threshold and, consequently, substantially increase nociceptor input to the CNS after trivial stimuli, such as a movement or light touch.

Successes in treatment of paraneoplastic syndromes

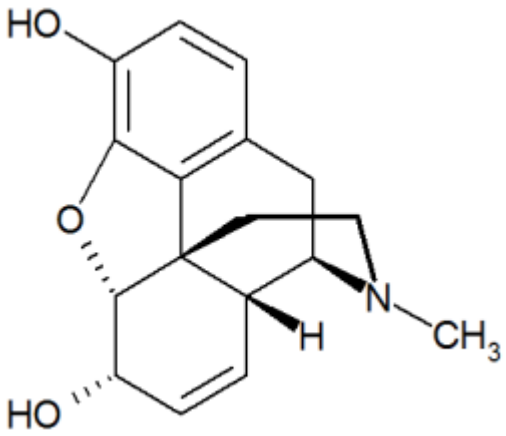


Biology of nociception relatively well understood..

Cancer pain can be relieved in 80-90% of patients using an opioid-based analgesic regimen.

WHO pain treatment ladder

Papaver somniferum
(opium poppy)



Morphine, principal active agent

Tumor indirect / systemic effects

- Paraneoplastic syndromes are defined as clinical syndromes involving non-metastatic systemic effects that accompany malignant disease. In a broad sense, these syndromes are collections of symptoms that result from substances produced by the tumor, and they occur remotely from the tumor itself.

A cluster of “nonspecific” paraneoplastic features, also called “sickness behavior” and constituting a well known cluster of symptoms experienced by cancer patients.

Fever
Dysgeusia (altered taste sensation)
Anorexia
Wasting and muscle atrophy
Fatigue/loss of energy
Headaches
Muscle stiffness
Pain- hyperalgesia
Sleep disturbance

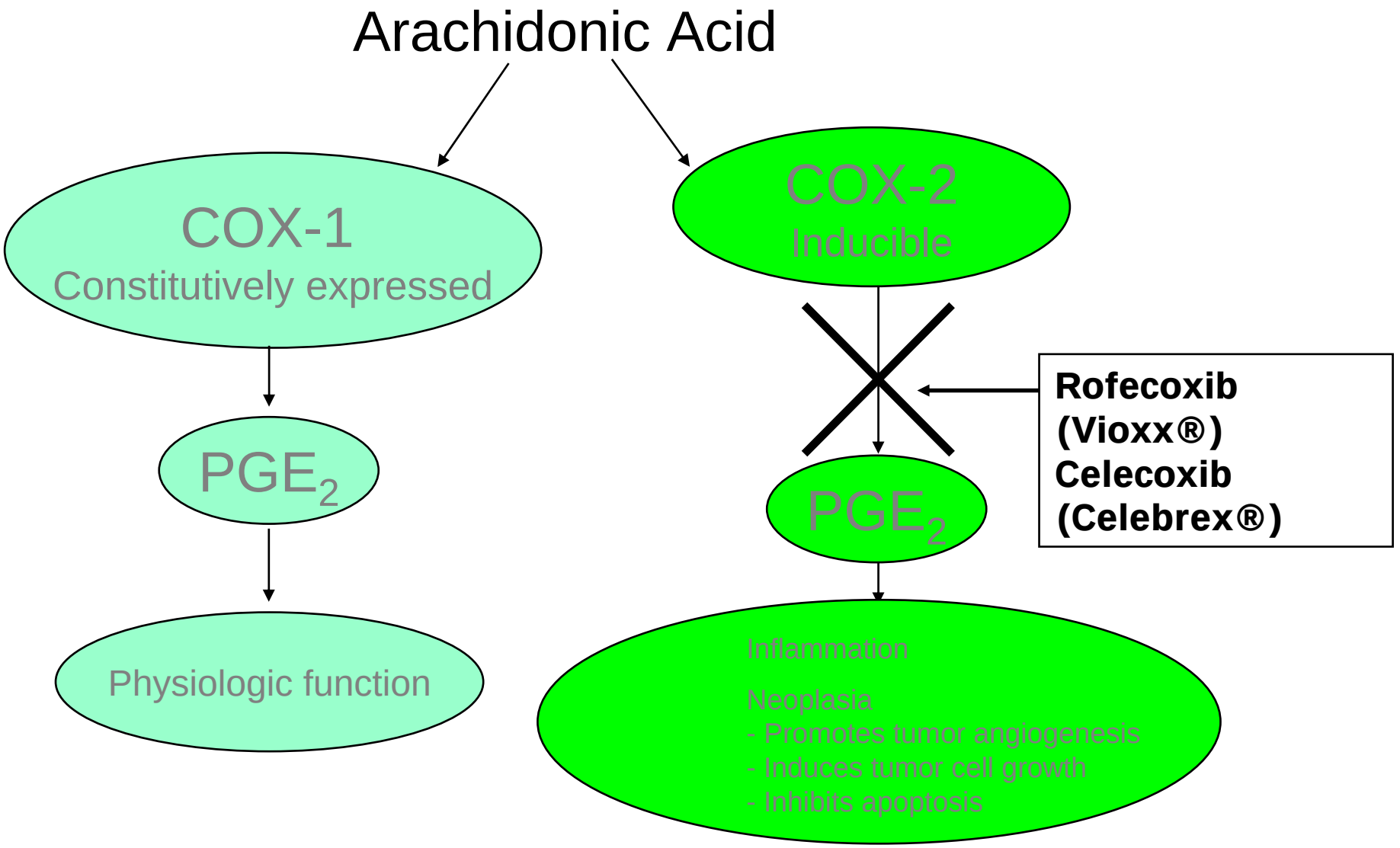
Therapeutic use of cytokines: side effects

- IFN γ most frequent side-effects are flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain, and convulsion.
- TNFα anorexia, fever, fatigue
- Il-1,6 fever, anorexia, flu-like symptoms, fatigue

Treating Inflammation

- **Steroids** glucocorticoids: cortisol, dexamethasone, prednisone
- **NonSteroidal Anti-Inflammatory Drugs (NSAIDs)** aspirin, ibuprofen, indomethacin, celecoxib,
- **Cytokine targetted agents** ie infliximab (Remicade®). A monoclonal antibody that binds to TNF-α
-

Specificity of COX-2 Inhibition



Dannenberg AJ. *Lancet Oncol*. 2001;2:544-551; Masferrer JL et al. *Cancer Res*. 2000;60:1306-1311; Turini et al. *Annu Rev Med*.2002;53:35-57.

Inflammation and cancer fatigue and sleep disturbance

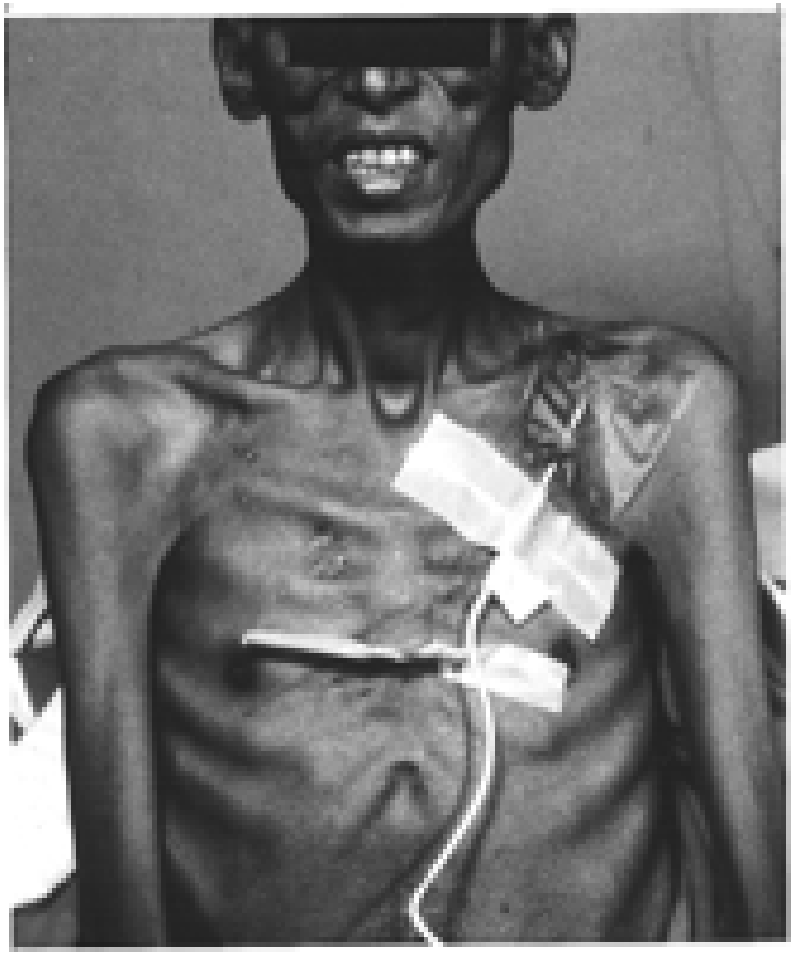
- Several cytokines are somnogenic whether given systemically or centrally (ie hypothalamic centres of sleep regulation)
- Il-1β and TNFα individually and synergistically increase the duration of slow wave sleep (non-rapid eye movement sleep).
- The intensity of Slow Wave Sleep is also increased as evidenced by enhanced amplitudes of EEG slow-waves; similar supranormal slow-waves occur after sleep deprivation.
- Changes in alertness, drowsiness/lethargy, dreaming in addition to sleep

Systemic inflammation: central inducer of catabolic processes

Inflammation and cancer –associated cachexia (wasting)

- The role of pro-inflammatory cytokines as catabolic factors , discovered in the early 1980's has subsequently evolved and these are now believed to be key factors underlying various forms of wasting.
- *Cachectin* was one of the early names used for Tumor Necrosis Factor a, due to its ability to induce anorexia and wasting.

The *cachexias* : wasting diseases



Chronic

Cancer

AIDS

Chronic obstructive pulmonary disease

Chronic heart failure

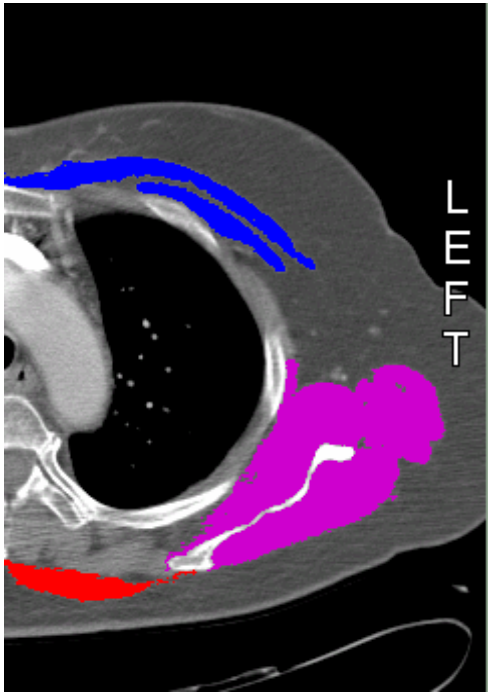
Old age

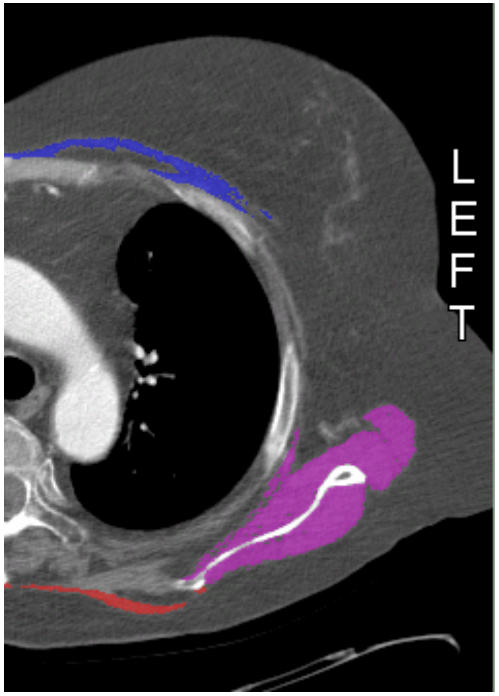
Acute

Sepsis

Trauma

Burns



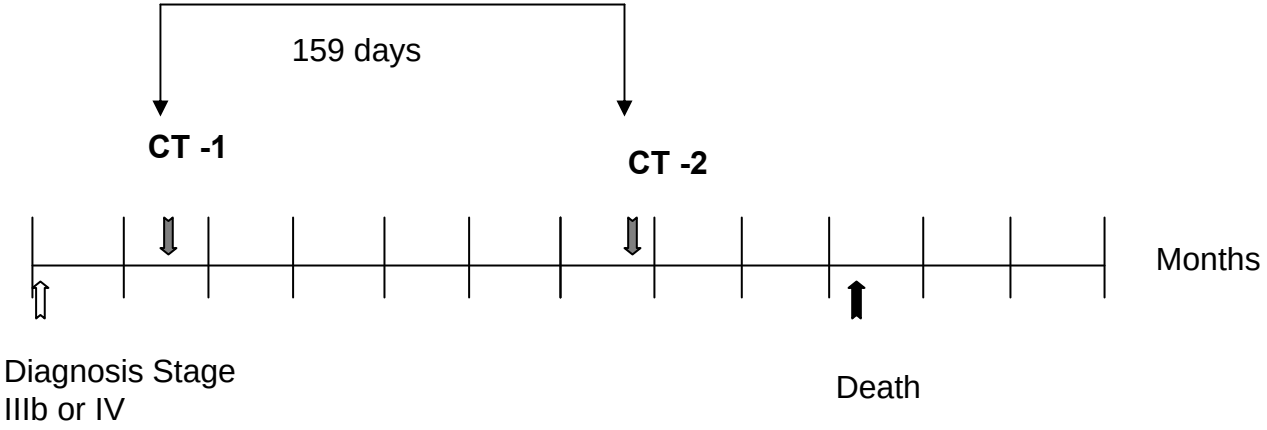


Scapular

Trapezius

Pectoral

T4 skeletal muscles



Review

Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2010.02218.x

Energy regulation and neuroendocrine–immune control in chronic inflammatory diseases

R. H. Straub[1], M. Cutolo[2], F. Buttgereit[3] & G. Pongratz[1]

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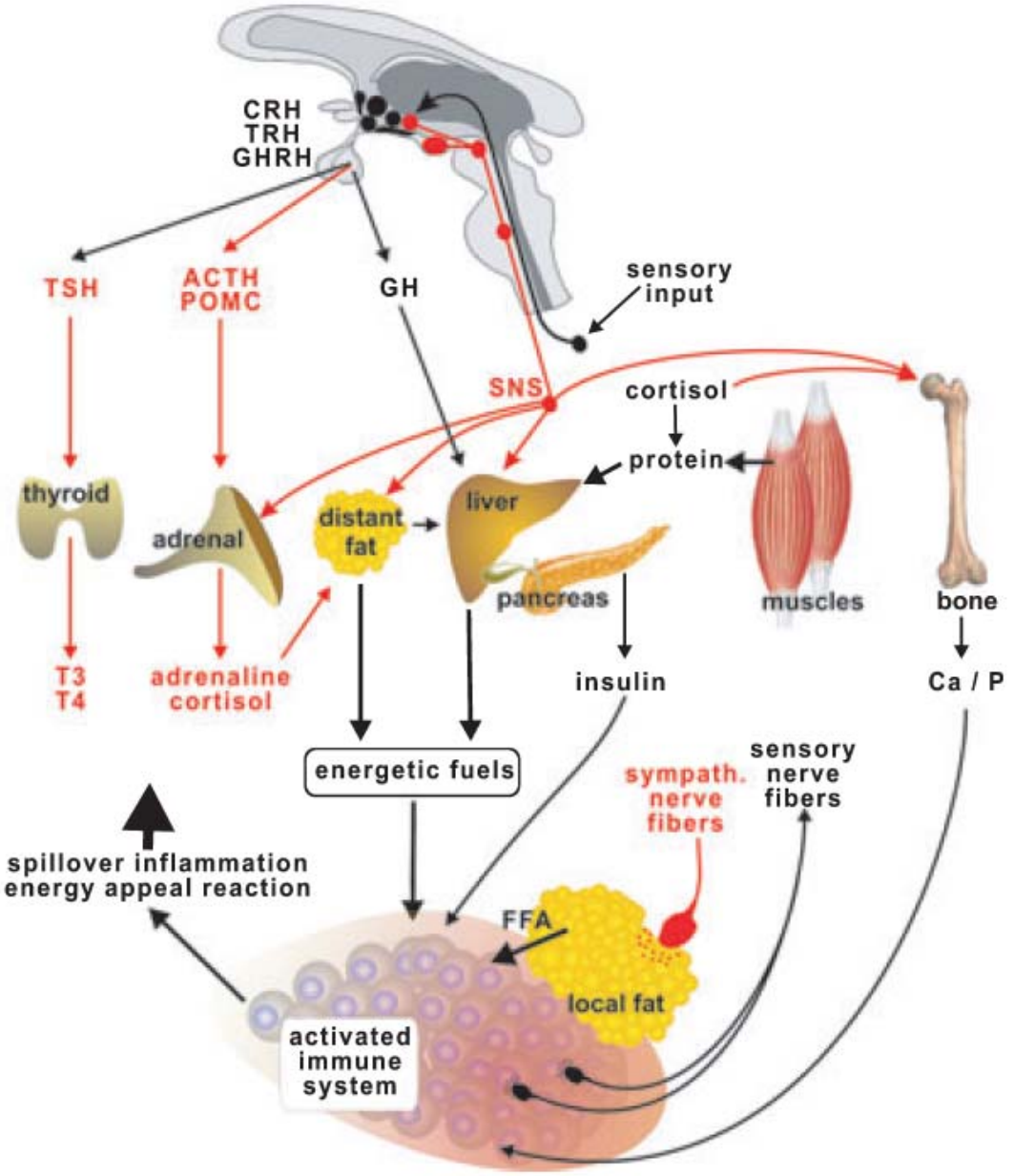
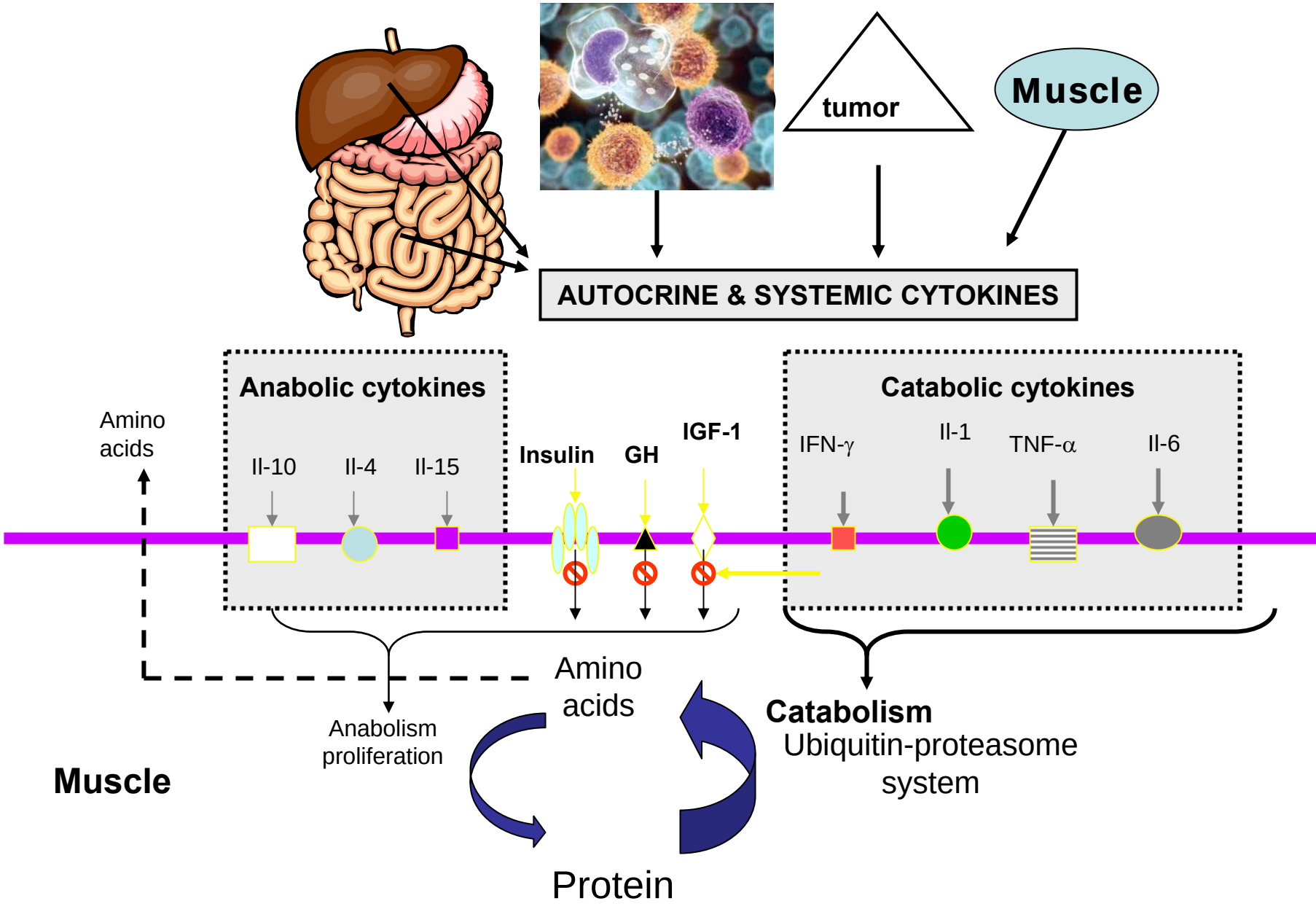


Skeletal muscle is part of an elegant choreographed response with the purpose of providing energetic fuels and amino acids to an activated immune system.

This response is paralleled by in energy storage response during periods without inflammation when nutrients are available .


tumor
Muscle
AUTOCRINE & SYSTEMIC CYTOKINES
Anabolic cytokines
Il-10
Il-4
Il-15
Amino acids
Insulin
GH
IGF-1
Catabolic cytokines
IFN-γ
Il-1
TNF-α
Il-6
Amino acids
Anabolism proliferation
Catabolism
Ubiquitin-proteasome system
Muscle
Protein

Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic–pituitary–adrenal axis

Theodore P. Braun,[1,2] Xinxia Zhu,[1] Marek Szumowski,[1] Gregory D. Scott,[2,3] Aaron J. Grossberg,[1,2] Peter R. Levasseur,[1] Kathryn Graham,[4] Sheehan Khan,[5] Sambasivarao Damaraju,[6] William F. Colmers,[7] Vickie E. Baracos,[4] and Daniel L. Marks[1]

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[4]Department of Oncology, [5]Department of Computer Science, [6]Department of Laboratory Medicine and Pathology, and [7]Department of Pharmacology, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

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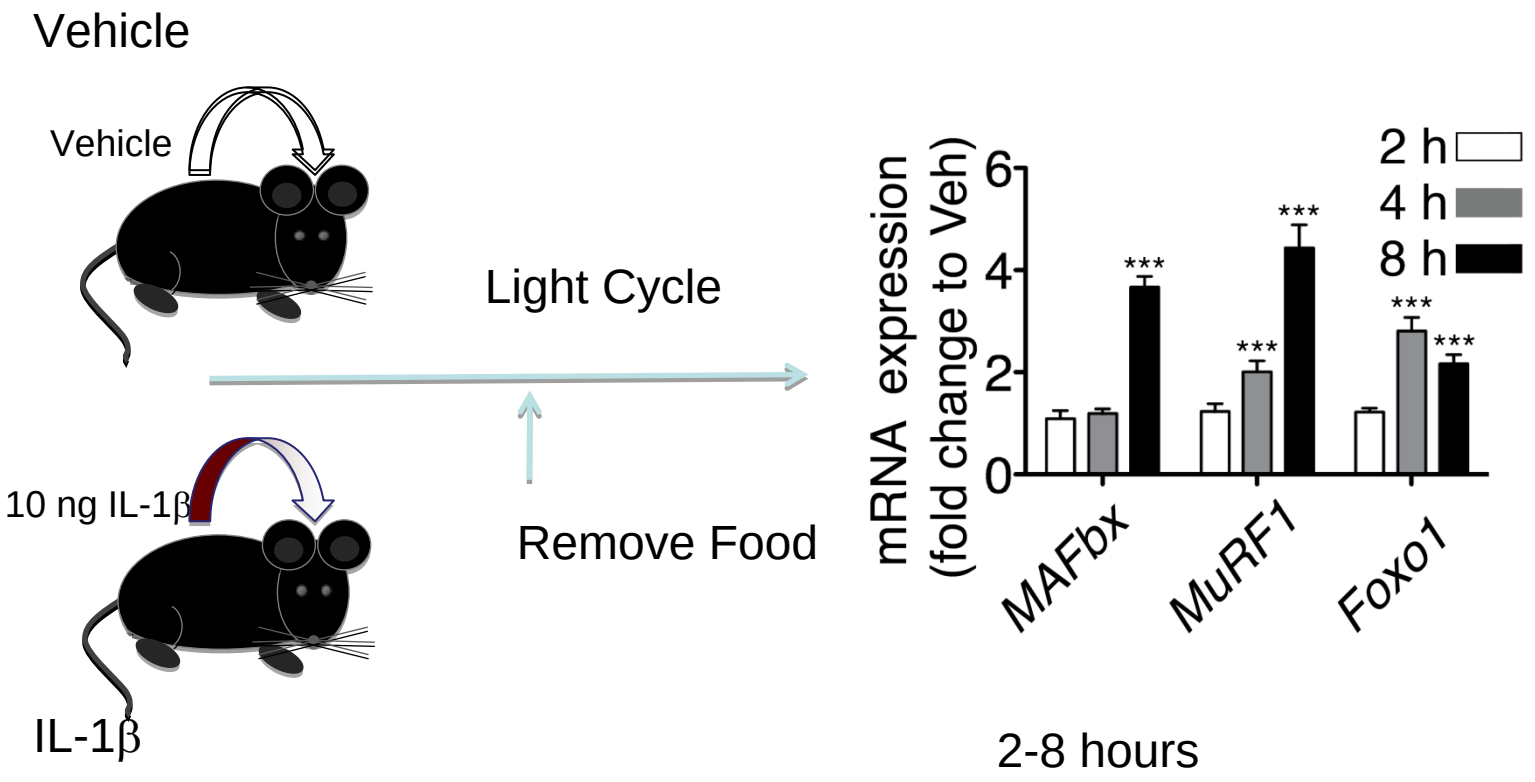
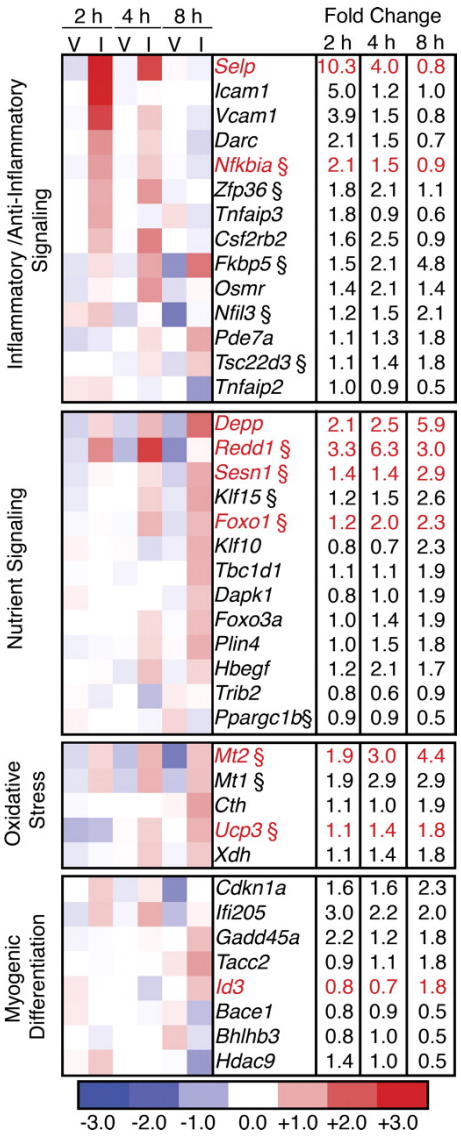
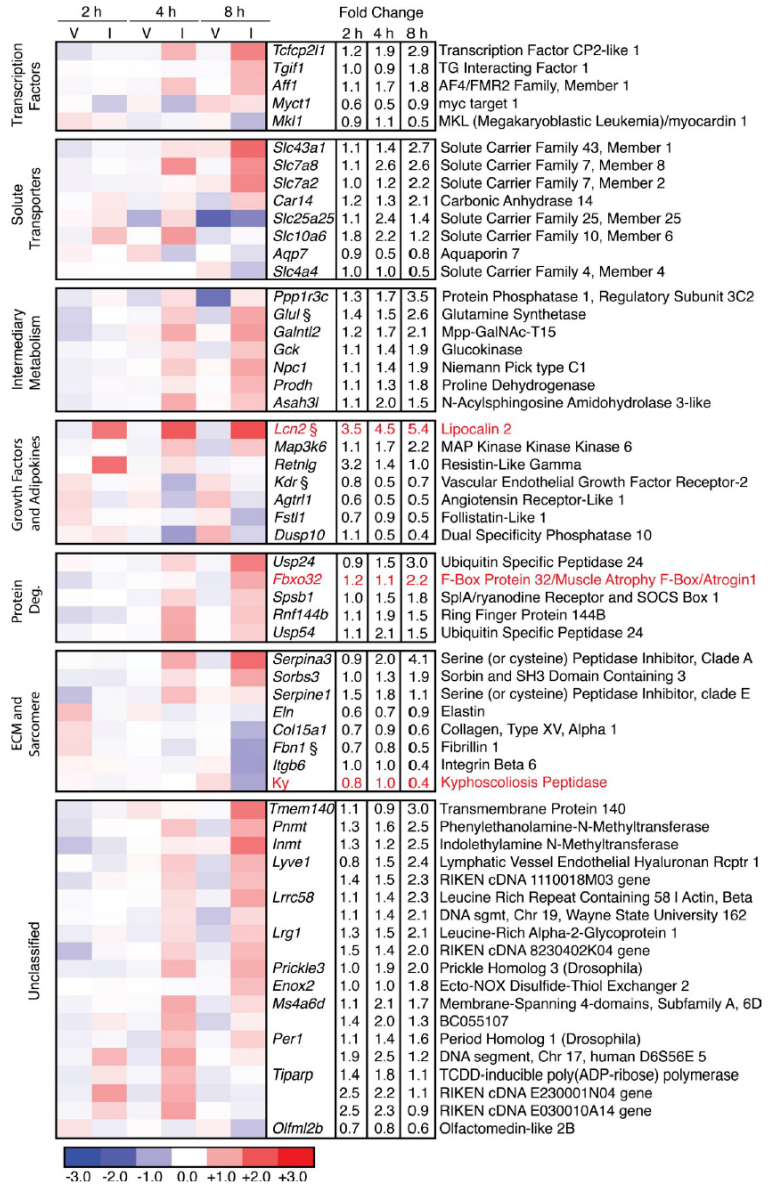
www.jem.org/cgi/doi/10.1084/jem.20111020

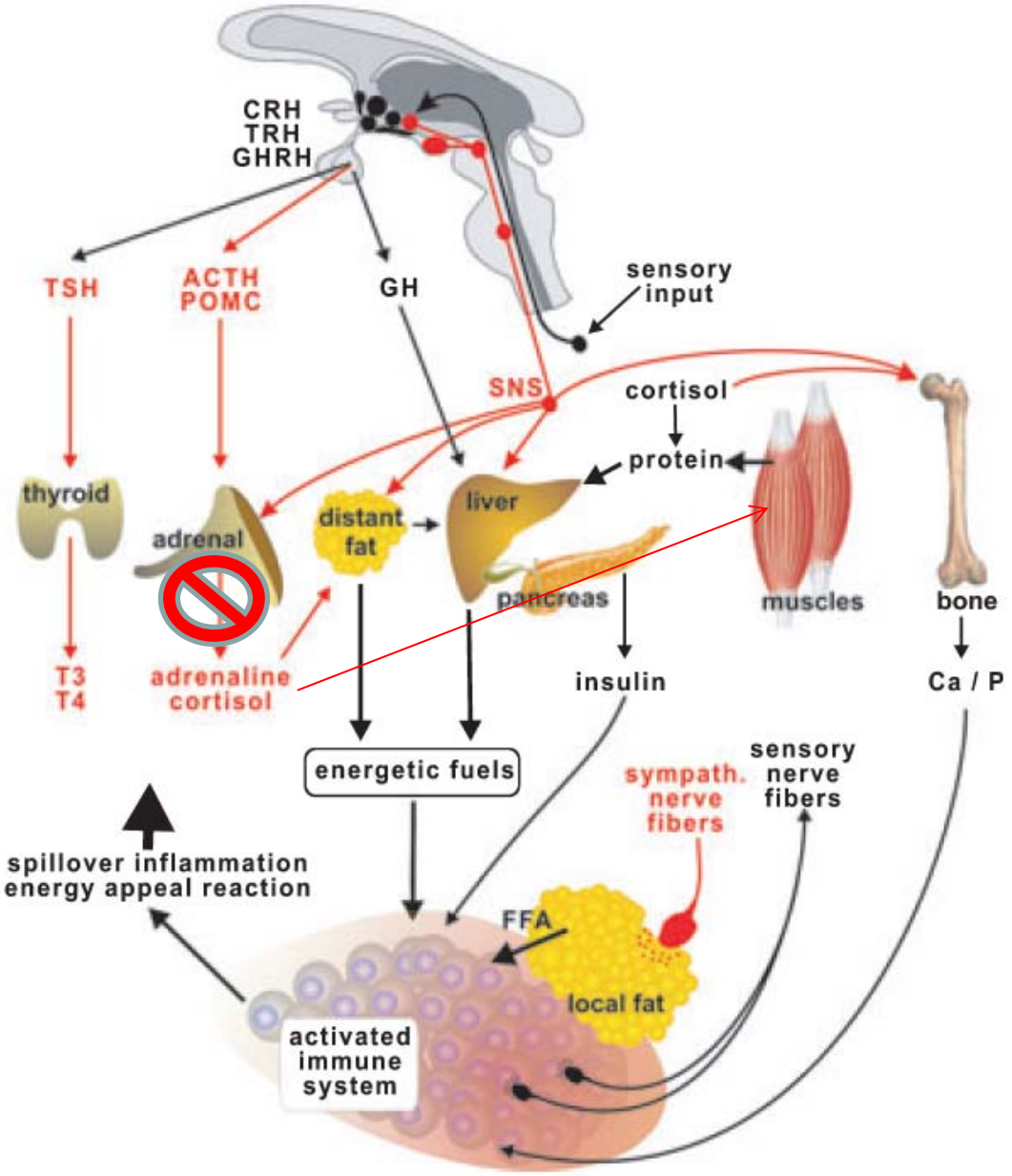
Central inflammation results in transcriptional changes of ubiquitin ligases consistent with atrophy



Central IL-1β treatment induces rapid and dynamic changes in skeletal muscle gene expression.







So brain does talk to muscle, but since adrenalectomy blocked the response, this is an HPA-mediated effect. There were many glucocorticoid responsive genes in the transcriptional profile.

Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression

STEWART H. LECKER,[1] R. THOMAS JAGOE,*,[1] ALEXANDER GILBERT, MARCELO GOMES,[††] VICKIE BARACOS,[†] JAMES BAILEY,[‡] S. RUSS PRICE,[‡] WILLIAM E. MITCH,[§] AND ALFRED L. GOLDBERG[††,2]

FASEB J. 18, 39–51 (2004)

Venn diagram of the microarray studies

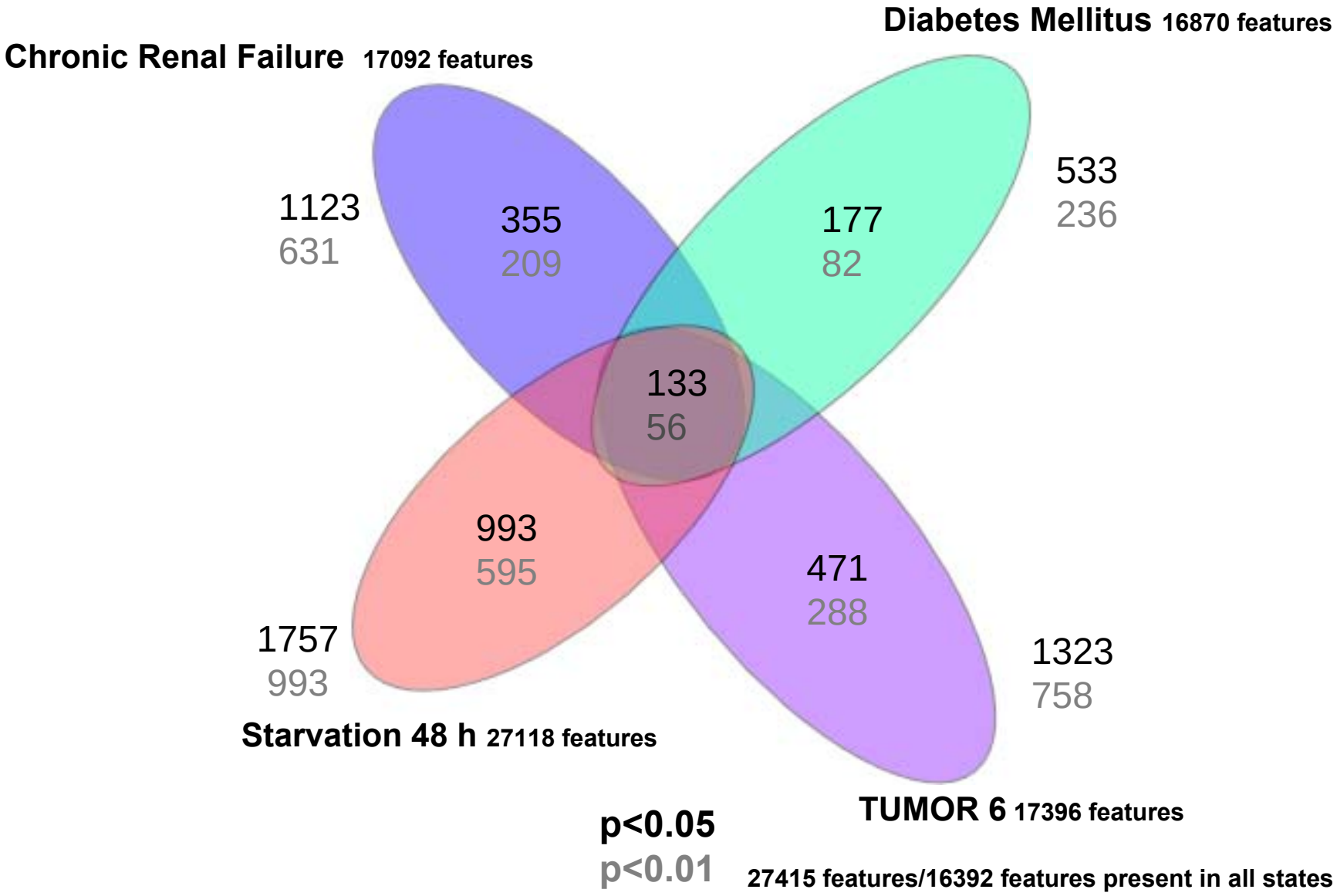


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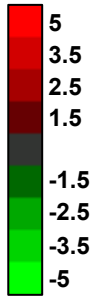
TABLE 1. *Loss of muscle weight and increases in muscle protein degradation in the catabolic states studied*

		Muscle weight		Protein degradation	
Condition	Sample	(mg)	% loss	(pmol Tyr mg^{-1} $2h^{-1}$)	% increase
Fasting[a]	Control	137.3 ± 1.8		230 ± 11	
	Fasting	118.4 ± 1.7	14	342 ± 13	49
Tumor implantation[b]	Control	45.0 ± 0.6		251 ± 13	
(Yoshida hepatoma)	Tumor	38.6 ± 0.7	14	410 ± 17	63
Chronic renal failure[c]	Control	28.6 ± 1.4		150 ± 13	
(7/8 nephrectomy)	CRF	20.3 ± 1.5	29	236 ± 32	57
Diabetes[c]	Control	39.4 ± 1.0		149 ± 5	
(streptozotocin)	Diabetes	31.6 ± 1.1	20	208 ± 8	40

[a] Differences in muscle weights refer to changes in mouse gastrocnemius after a 48 h fast, as reported previously (20). Protein degradation rates taken from ref 3 refer to EDL muscle in rat after 24 h fasting. [b] Muscle weights and degradation rates measured in epitrochlearis muscle in rats 5 days after implantation of Yoshida ascites hepatoma and taken from ref 5. Similar weight changes were described for gastrocnemius (5). Even greater weight loss (22%) occurred in the lateral gastrocnemius muscles used in the present study. [c] Representative values for muscle weights and protein degradation rates measured in rat epitrochlearis muscle used in the present study and similar to published results for chronic renal failure (23) and diabetes (4).

Transcriptional activation of ubiquitin, ubiquitin ligases, proteasome subunits and lysosomal cathepsins: atrophy genes

Clone	Unigene	Primary Sequence Name		F T U D
3137251	Hs.183842	UBB	ubiquitin B	
2730250	Hs.183704	UBC	ubiquitin C	
2132619	Hs.3297	RPS27A	ribosomal protein S27a	
4157922	Hs.5308	UBA52	ubiquitin A-ribosomal protein fusion product	
1723142	Hs.61661	FBXO32	Atrogin-1/MAFbx	
751477	Mm.32920	Ncube1	non-canonical Ub-conjugating enzyme 1	
747318	Mm.21634	Ube4b	ubiquitination factor E4B	
2195309	Hs.82159	PSMA1	proteasome 20S subunit, alpha 1	
723267	Mm.30097	Psma1		
466041	Mm.30097			
572285	Mm.2287	Psma5	proteasome 20S subunit, alpha 5	
1737833	Hs.82793	PSMB3	proteasome 20S subunit, beta 3	
571569	Mm.21874	Psmb3		
901317	Hs.89545	PSMB4	proteasome 20S subunit, beta 4	
466254	Mm.29582	Psmc4	proteasome 19S subunit, ATPase, 4	
2123183	Hs.78466	PSMD8	proteasome 19S subunit, non-ATPase, 8	
113452	Hs.90744	PSMD11	proteasome 19S subunit, non-ATPase, 11	
833508	Mm.28571	Psmd11		
448976	Hs.112396	PA200	KIAA0077 protein	
1707220	Hs.75981	USP14	Ub-specific protease 14	
315082	Mm.930	Ctsl	cathepsin L	
2935790	Hs.87417	CTSL2		



FASEB J 2004

Is inflammation good or bad?

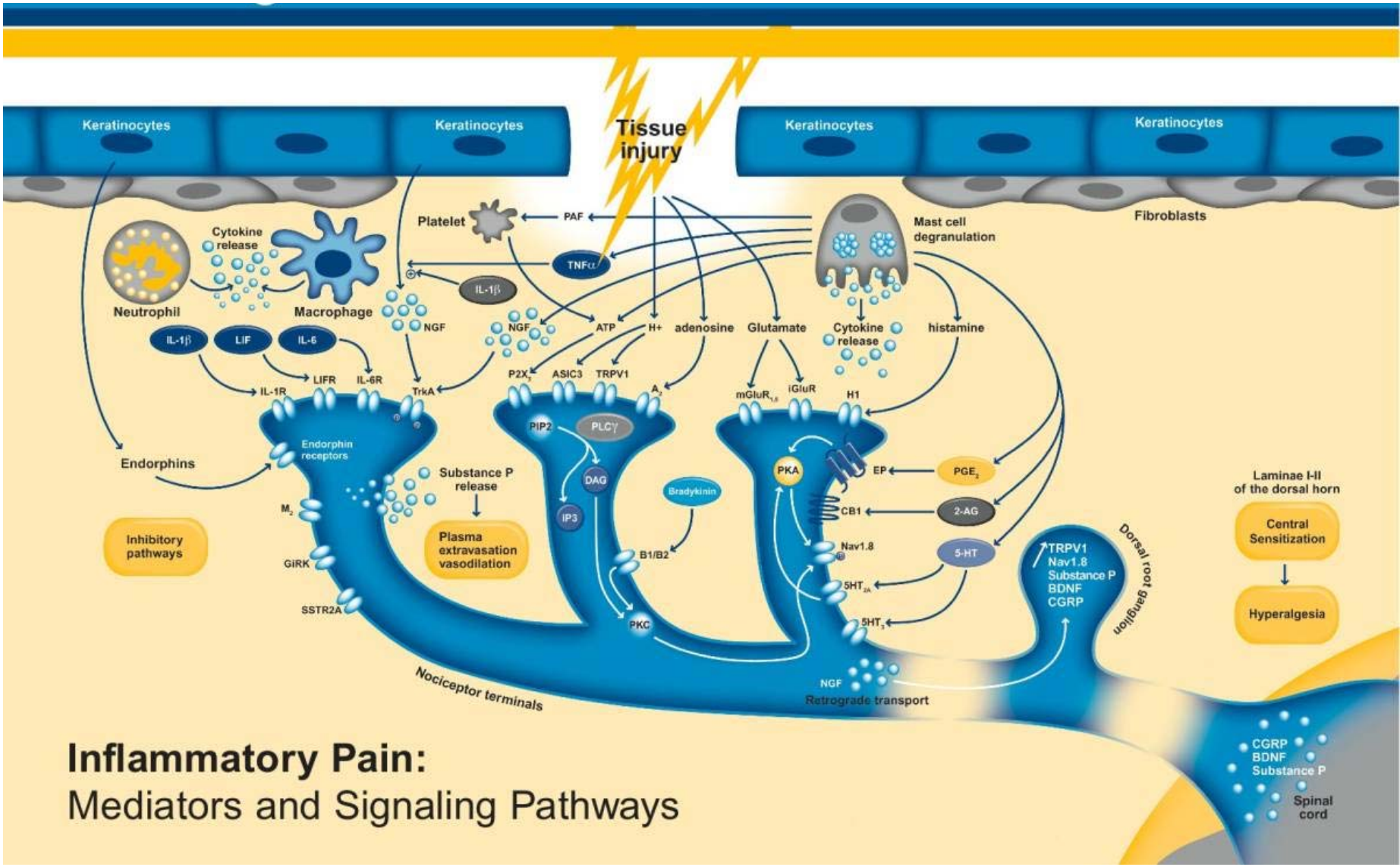
- Acute inflammation is essential to body defense; promotes repair processes at the expense of body reserves.
- **Chronic inflammation**, however, can result in **considerable tissue damage** (ie arthritis, Chron's disease).
- Excess inflammation : ie tumor secreting quantities of inflammatory mediators

Inflammation

Paraneoplasia

Neoplasia

Nociceptors are primary sensory neurons activated by stimuli capable of causing tissue damage

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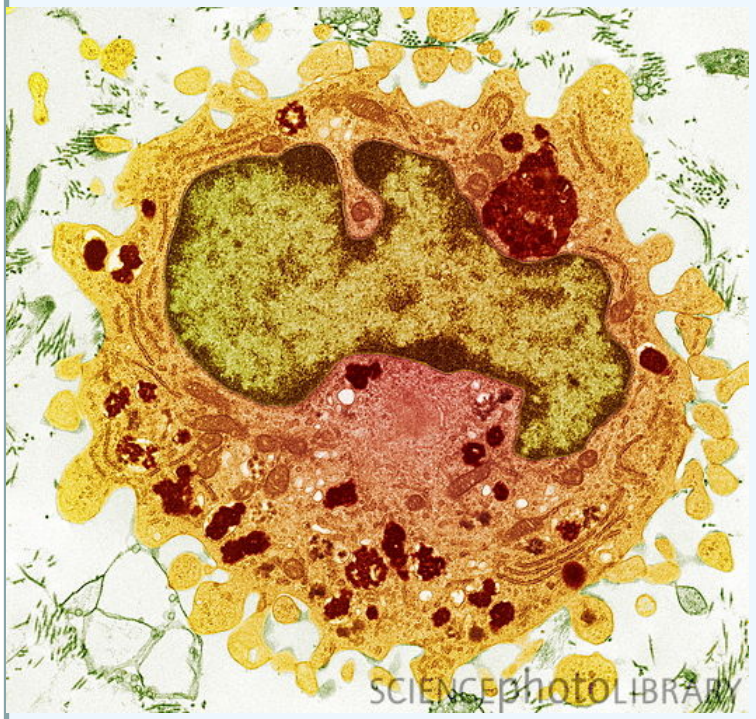
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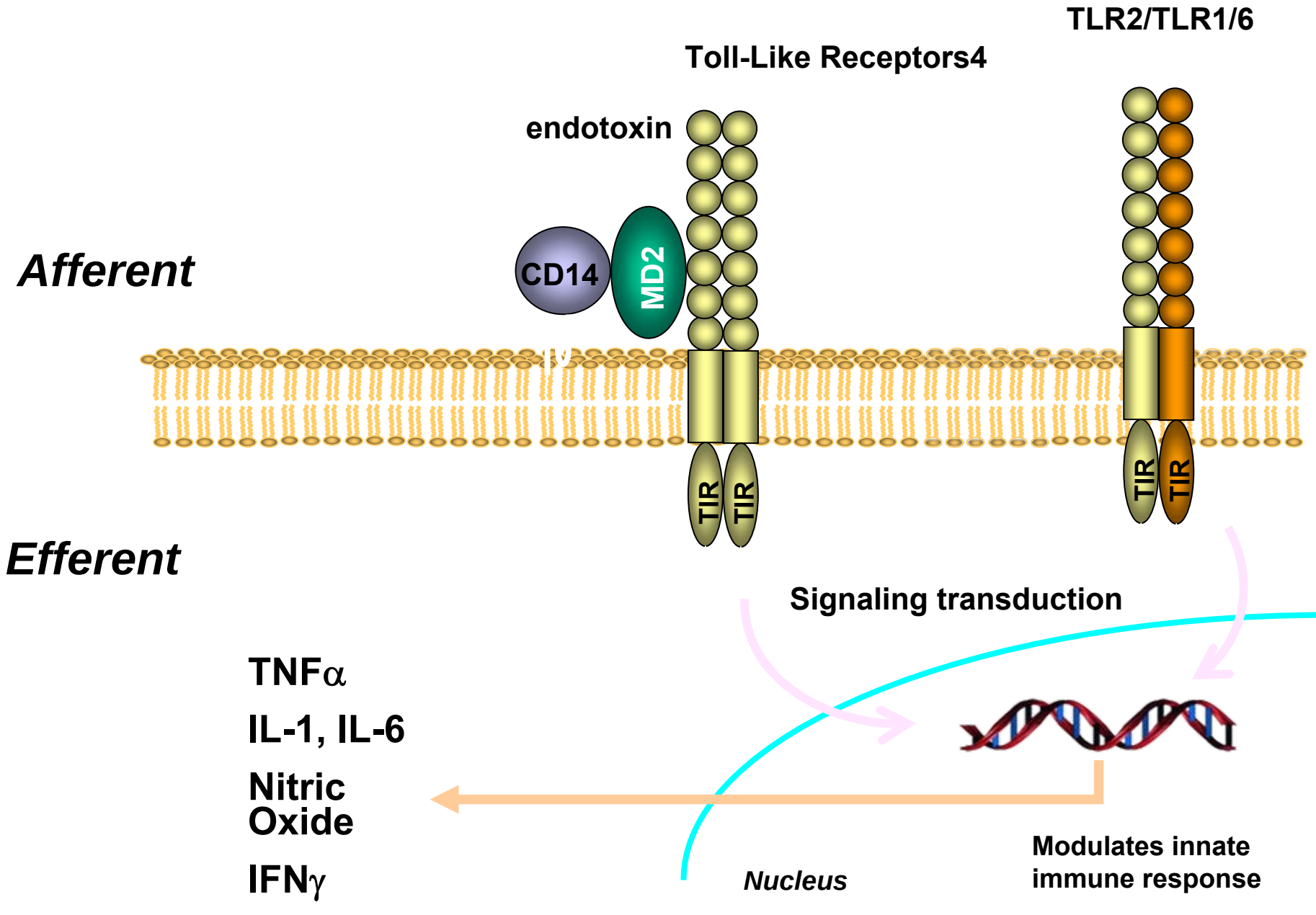
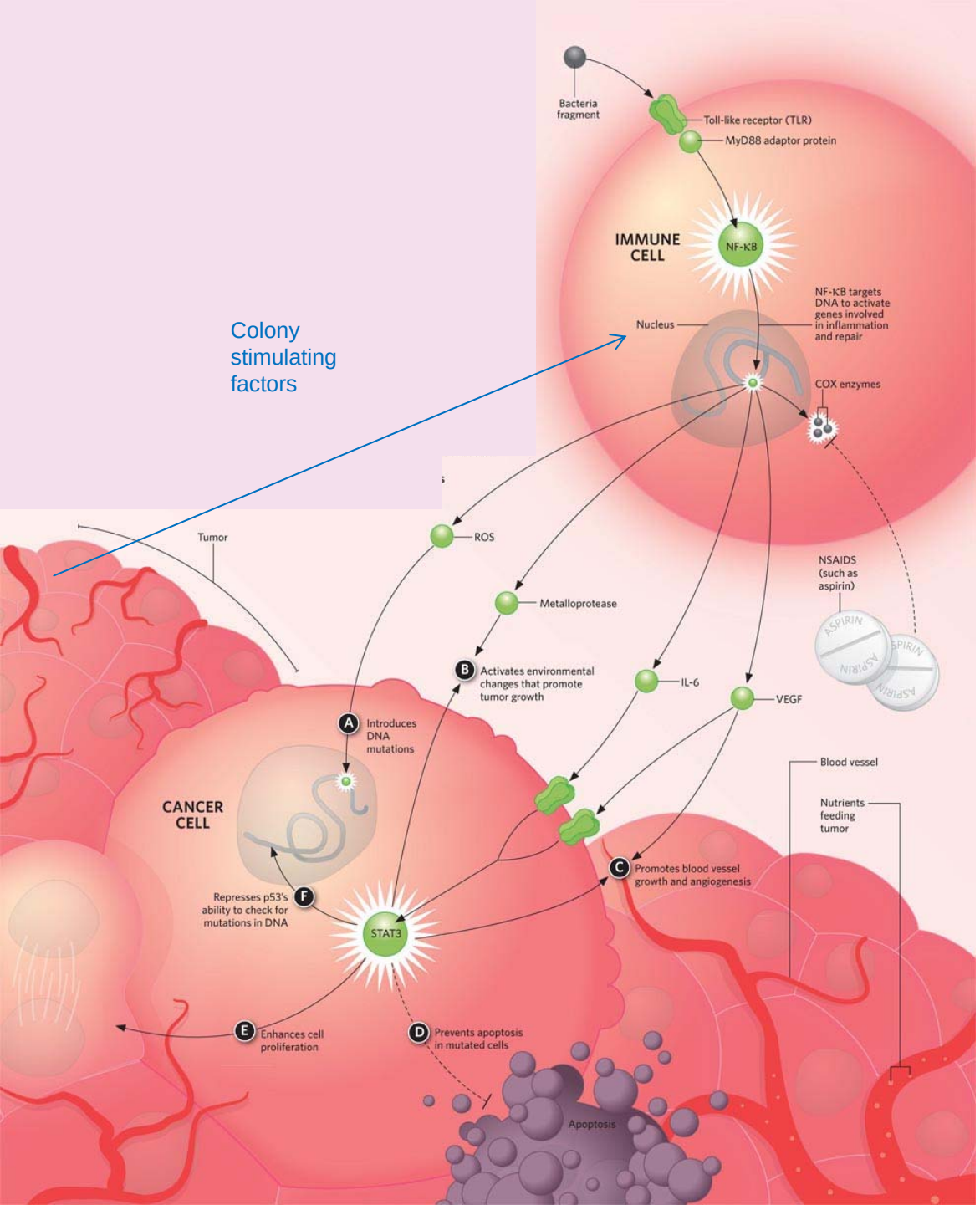
Activation of cytokine production by macrophages




Colony stimulating factors
Bacteria fragment
Toll-like receptor (TLR)
MyD88 adaptor protein
IMMUNE CELL
NF-κB
NF-κB targets DNA to activate genes involved in inflammation and repair
Nucleus
COX enzymes
Tumor
ROS
NSAIDS (such as aspirin)
Metalloprotease
B Activates environmental changes that promote tumor growth
IL-6
VEGF
A Introduces DNA mutations
CANCER CELL
Blood vessel
Nutrients feeding tumor
C Promotes blood vessel growth and angiogenesis
Represses p53's ability to check for mutations in DNA
F
STAT3
E Enhances cell proliferation
D Prevents apoptosis in mutated cells
Apoptosis