Cancer cachexia in the age of obesity

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Albert Cancer Foundation Chair in Palliative Medicine
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2010 November 9

Conceptual model of cancer and cancer cachexia trajectory?

Barb Tarbox 1961 - 2003

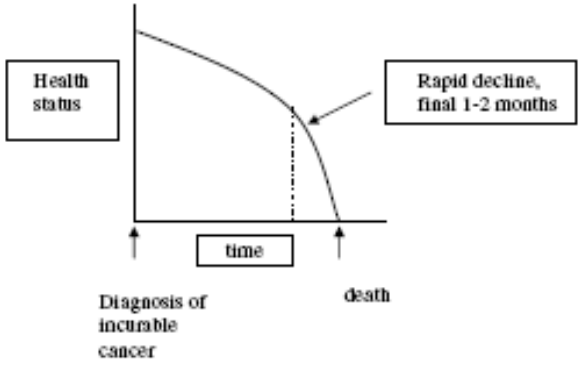
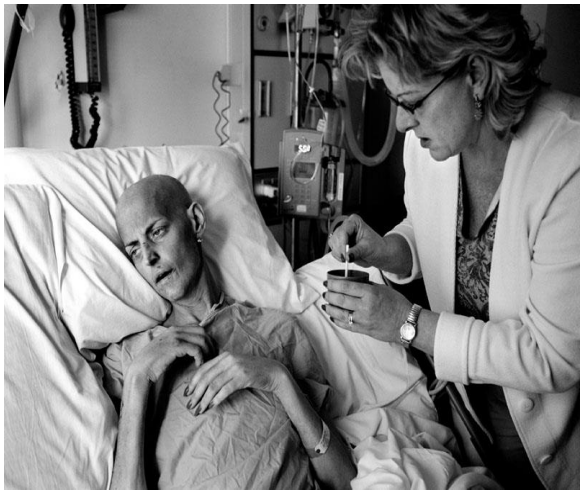
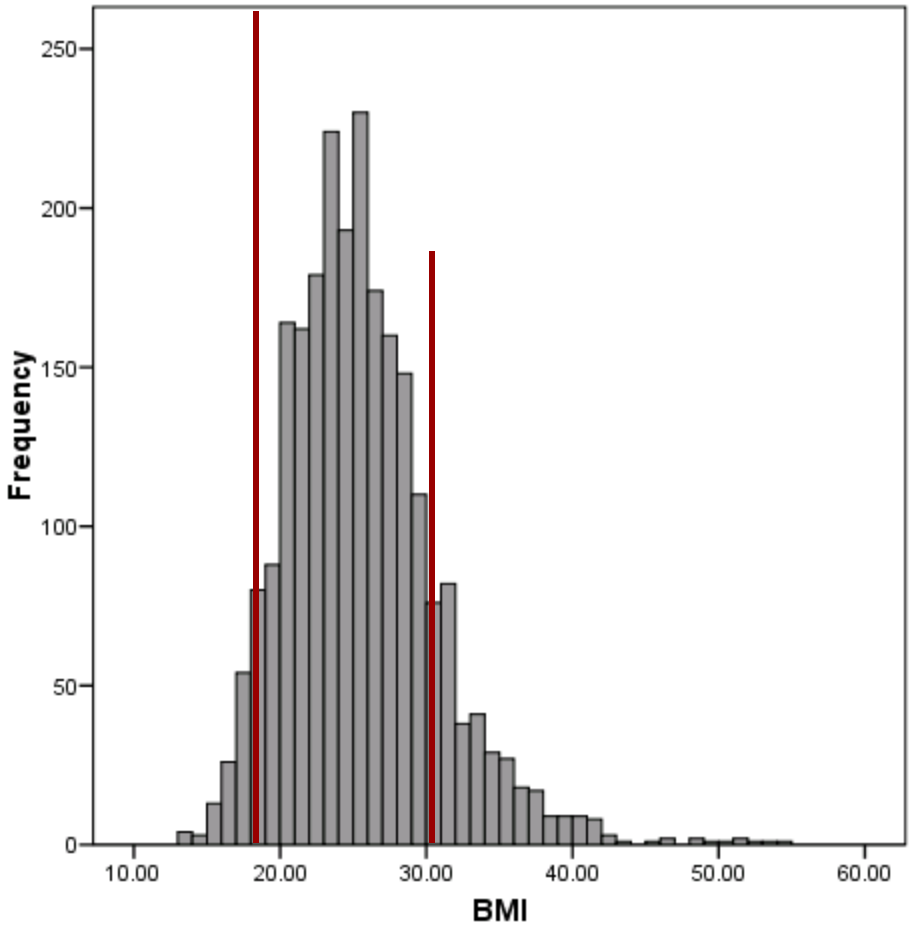


Fig. 1 – Conceptual model of cancer death trajectory.[122,123]



BMI Distribution for Cross Cancer Institute (n=2391 patients newly referred to Medical Oncology clinics with advanced lung or GI malignancies

Almost nobody is malnourished according to conventional criteria i.e. under weight – BMI <18.5 kg/m^2



Cancer patients are increasingly likely to be simultaneously :

Overweight or Obese

Obesity a risk factor for cancer, Age is a risk factor for weight gain

and

Sarcopenic
(depleted of skeletal muscle and overall lean body mass)

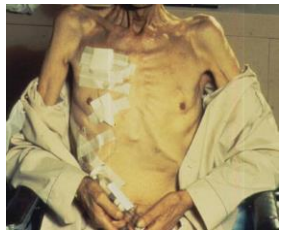
Old age, inflammation, illness and anti-cancer therapy contribute to muscle loss

Table 2 Weight and muscle wasting in a population-based cohort of patients with non–small cell lung and colorectal cancers[a]

Time to death, days	*N*	Prevalence of sarcopenia[b] (%)	% Weight loss (6 months)	Mean body mass index (kg/m^2)
Non-small cell lung cancer				
<55	51	55	–11.8	23.9
56–112	51	48	–8.4	23.5
113–184	52	50	–6.8	24.6
185–249	52	50	–6.1	25.1
250–390	51	48	–6.3	25.2
391–515	51	42	–5.4	24.5
516–755	52	42	–3.4	25.5
>755	81	42	–2.9	26.1
Colorectal cancer				
≤245	93	55	–7.8	25.5
246–512	92	59	–9.8	24.8
513–774	95	46	–6.5	25.9
775–916	90	51	–7.8	25.6
917–1089	92	47	–7.2	25.9
1090–1288	95	39	–7.6	26.6
1289–1545	90	34	–6.4	27.4
>1545	92	34	–4.2	26.3

[a]Data represent all deaths due to indicated diagnoses in northern Alberta, Canada (37).
[b]Classification based on sex-specific cutoffs for L3 skeletal muscle index (men, <52.4 cm^2/m^2; women, <38.5 cm^2/m^2) (35).

A continuum of muscularity



+3SD

+2SD

Mean for healthy young adults

-2SD Sarcopenia

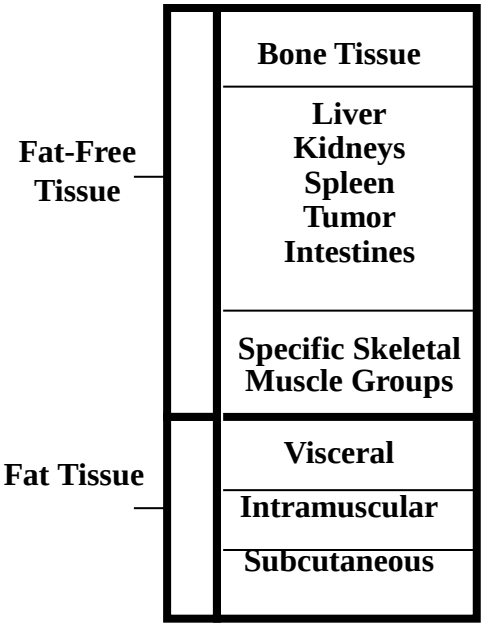
-3SD

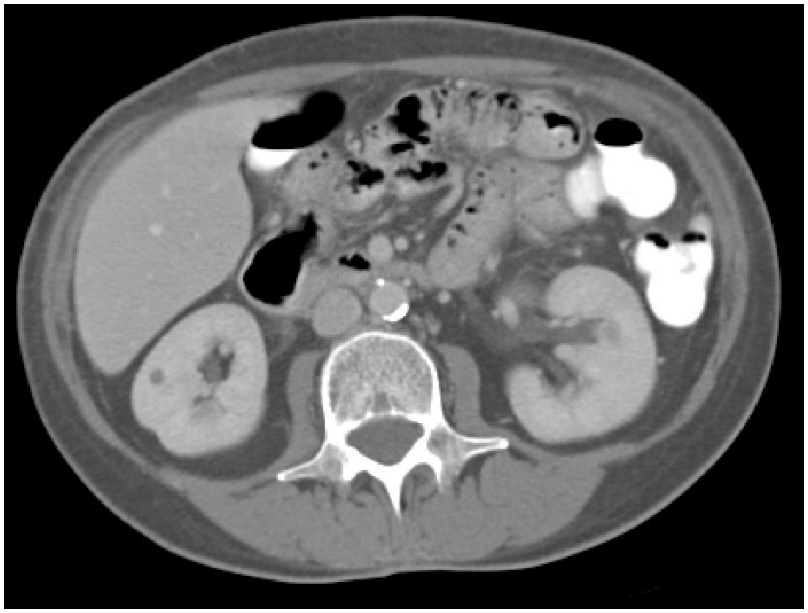
Elite physical function

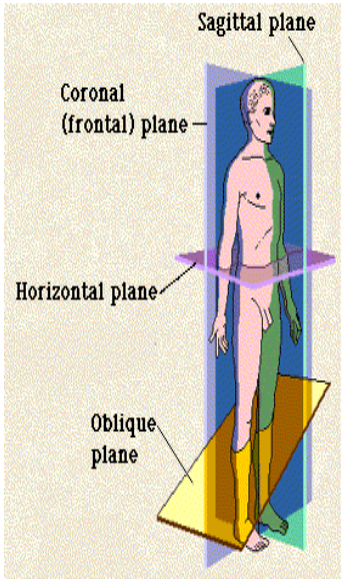
No physical function

Cancer patients

Computed tomography: an apt approach for assessment of body condition in oncology

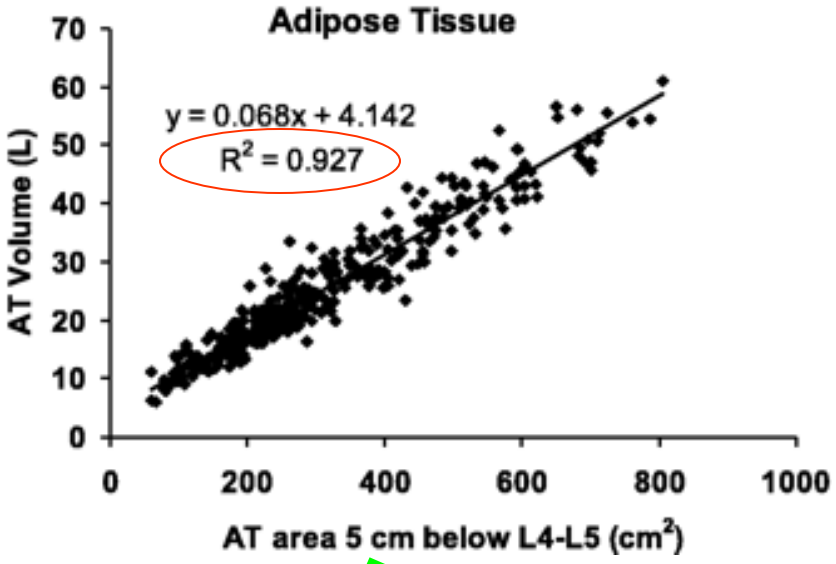


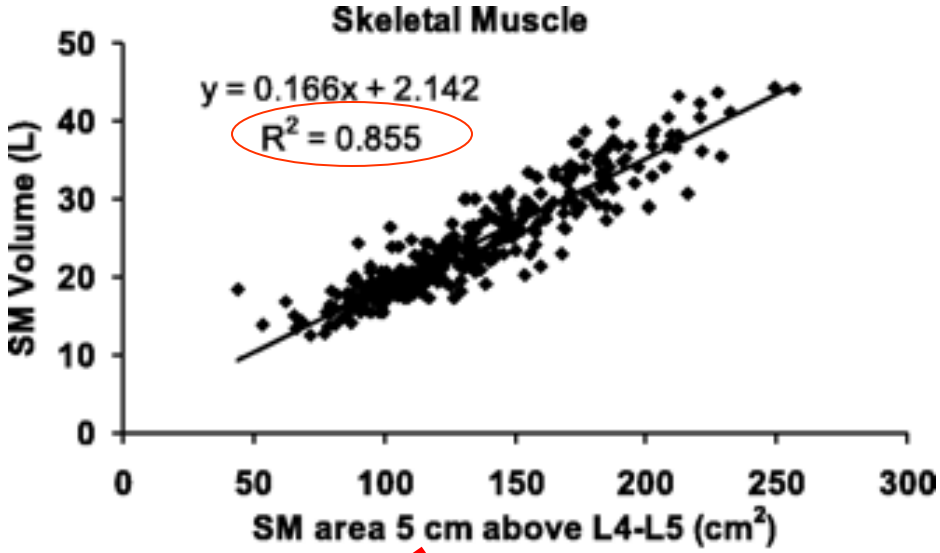


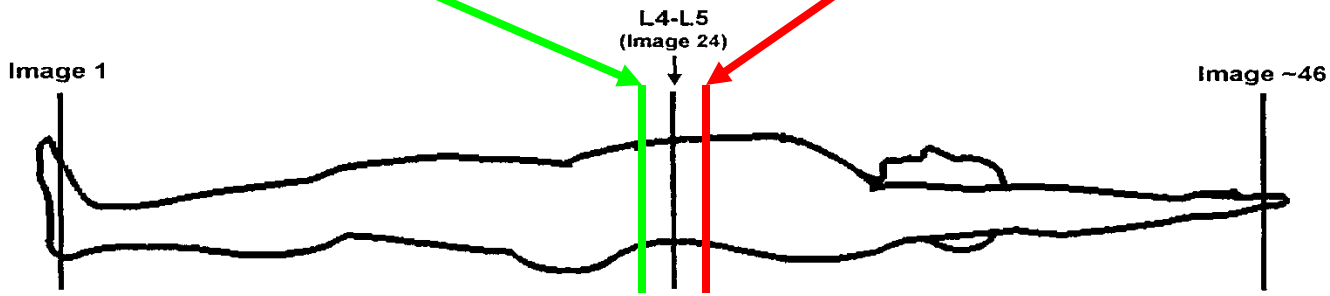


Association Between Whole Body Tissue Volume (L) and Single Abdominal Surface Area (cm^2)

Shen, W. et al. J Appl Physiol 97:2333-2338 2004







Methods

The emerging role of computerized tomography in assessing cancer cachexia

Carla M.M. Prado, Laura A. Birdsell and Vickie E. Baracos

Current Opinion in Supportive and Palliative Care 2009, 3:269–275

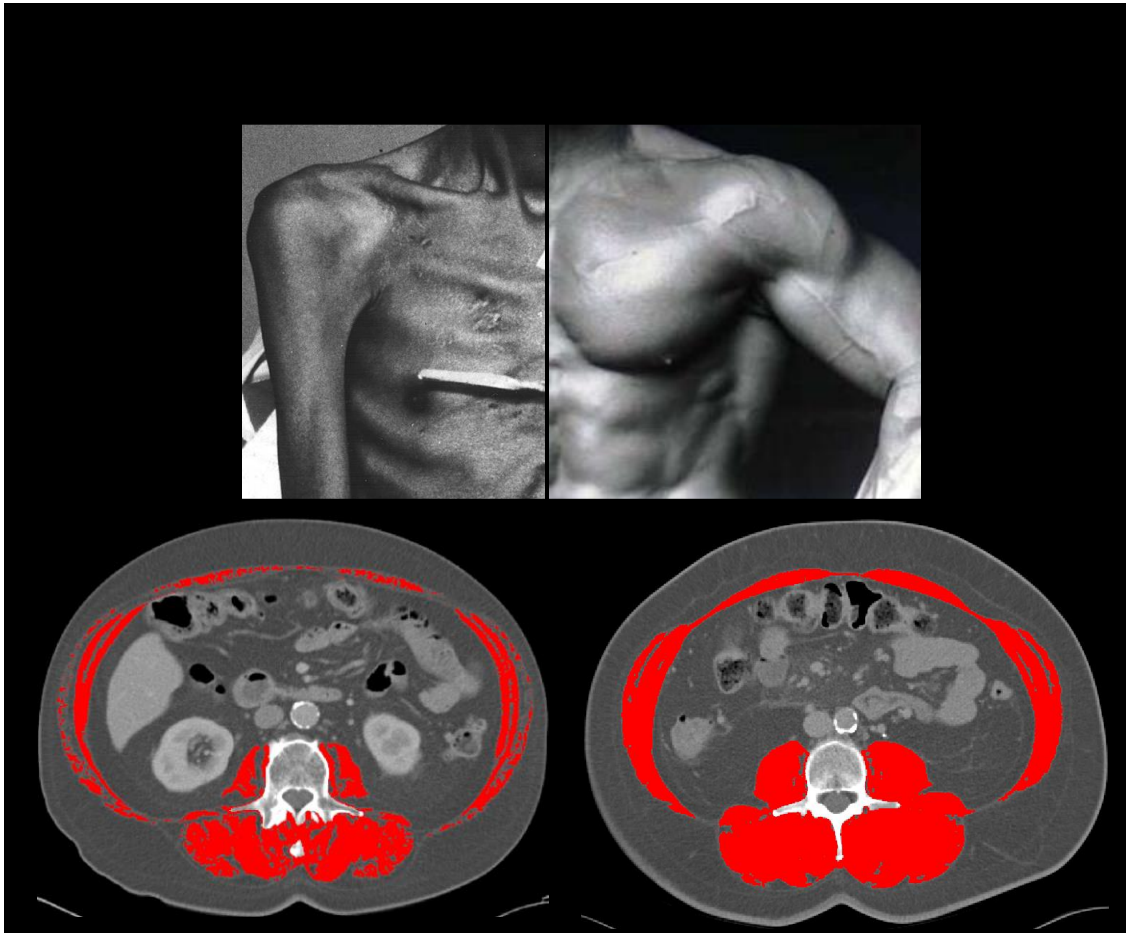
A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care.

Mourtzakis M, Prado C, Lieffers JR, et al.

Appl Physiol Nutr Metab. 2008;33(5):997-1006**.**

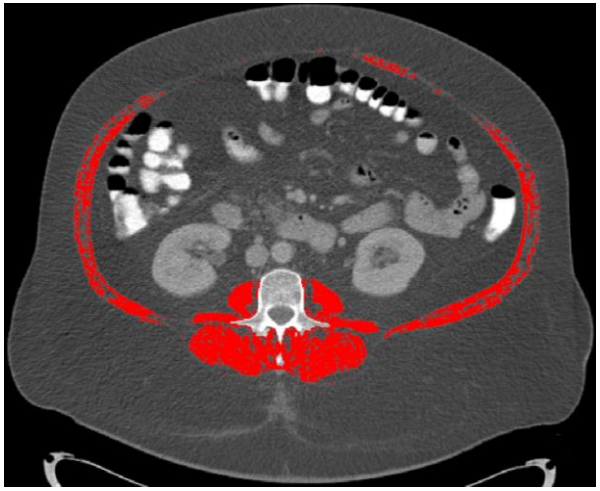
Variation in skeletal muscle : comparison of two cancer patients with identical body mass index

Abdominal computed tomography images in horizontal plane. Images taken at 3rd lumbar vertebra. Red color indicates skeletal muscles: *rectus abdominus,* oblique and lateral abdominal muscles, *psoas,* paraspinal muscles. Patient at left shows sarcopenia (severe muscle depletion); both patients have identical height, weight, body mass index (30.0) and body surface area.



New terms and new definitions : *Sarcopenic obesity*

- The “confluence of 2 epidemics” (R. Rubenoff)
- Entails the sum of health risks of both conditions



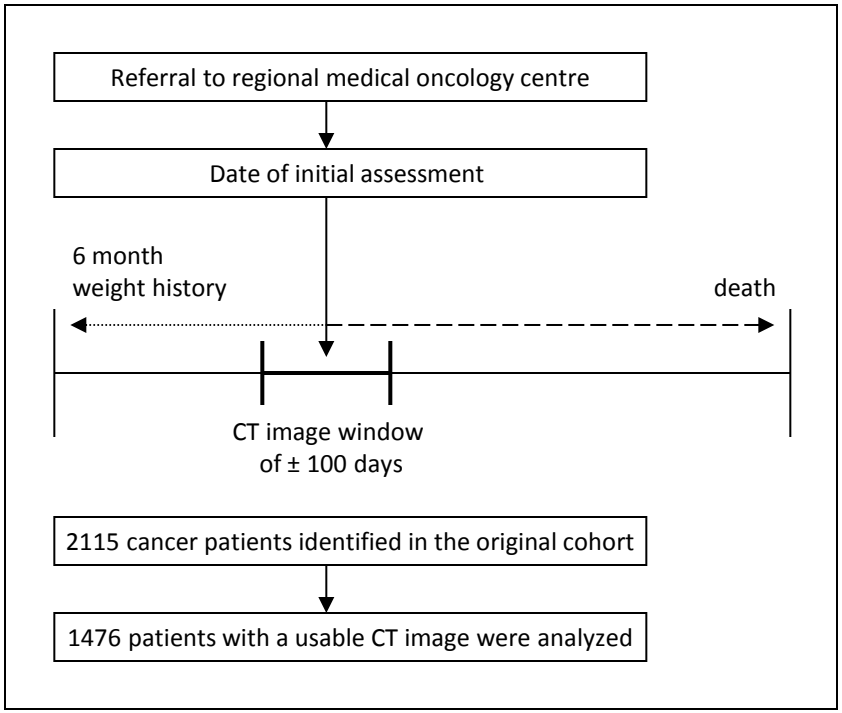
Cachexia: A new definition

William J. Evans*, John E. Morley [1], Josep Argilés [1], Connie Bales [1], Vickie Baracos [1], Denis Guttridge [1], Aminah Jatoi [1], Kamyar Kalantar-Zadeh [1], Herbert Lochs [1], Giovanni Mantovani [1], Daniel Marks [1], William E. Mitch [1], Maurizio Muscaritoli [1], Armine Najand [1], Piotr Ponikowski [1], Filippo Rossi Fanelli [1], Morrie Schambelan [1], Annemie Schols [1], Michael Schuster [1], David Thomas [1], Robert Wolfe [1], Stefan D. Anker [1]

Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat.

Clin Nutr. 2008 Dec;27(6):793-9.

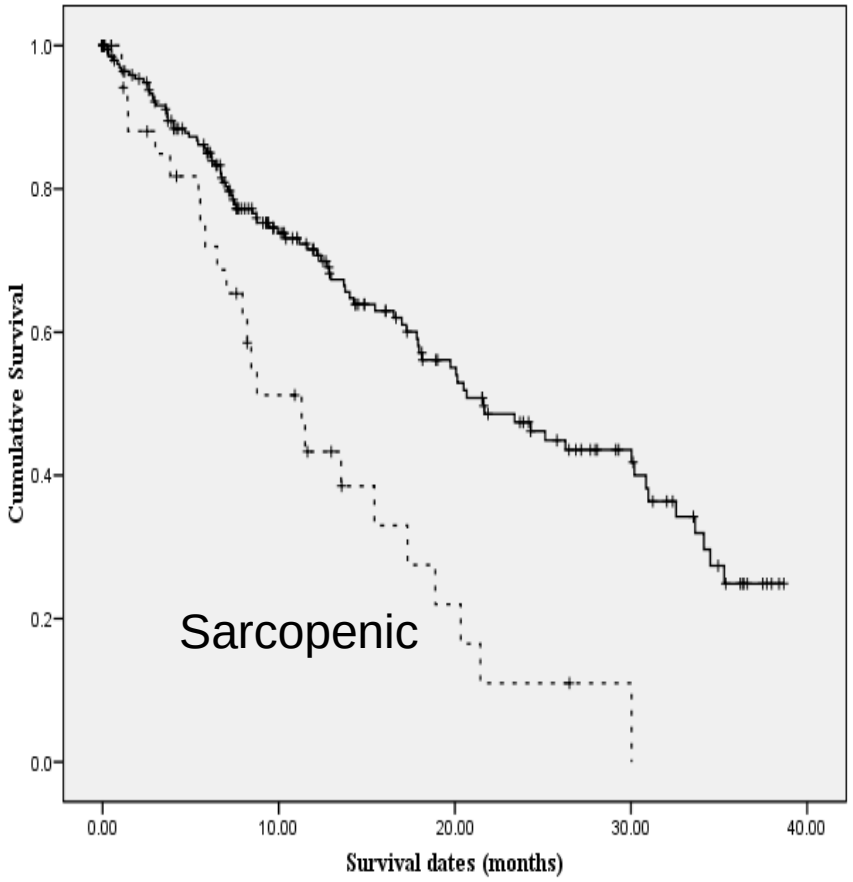
Population – based study of 2115 consecutively referred patients with solid tumors of the respiratory or gastrointestinal tracts



Study timeline and patient selection.

Survival is related to sarcopenia in obese patients with solid tumors

- **independent of age, disease stage and performance status**
- **11 months vs 21 months median survival**



Results from 250 obese cancer patients with solid tumors of the respiratory or gastrointestinal tract

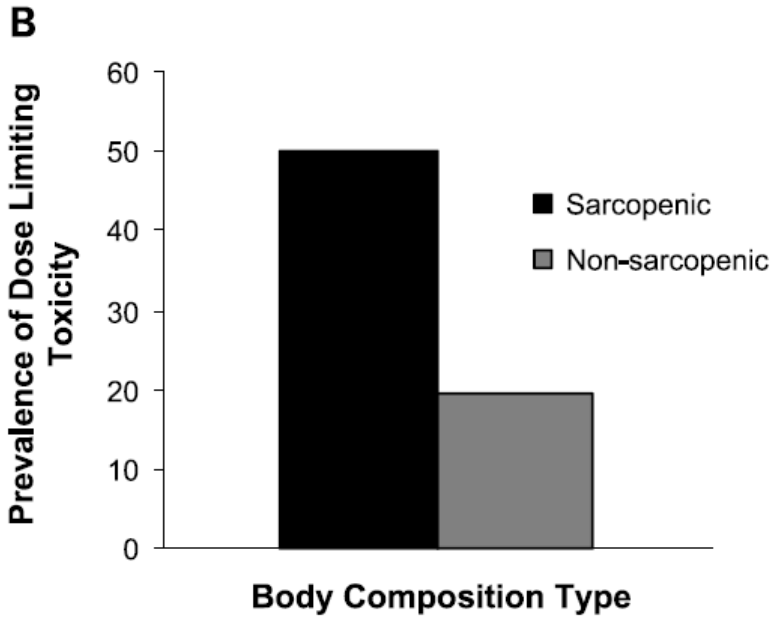
Sarcopenic obesity was shown to be a significant independent predictor of survival (HR 4.2 [2.4 – 7.2],p<0,0001) in a model which included age, stage, functional status

Prado et al, Lancet Oncol 2008

Sarcopenia as a Determinant of Chemotherapy Toxicity and Time to Tumor Progression in Metastatic Breast Cancer Patients Receiving Capecitabine Treatment

Carla M.M. Prado,[2] Vickie E. Baracos,[1,2] Linda J. McCargar,[2] Tony Reiman,[1] Marina Mourtzakis,[1] Katia Tonkin,[1] John R. Mackey,[1] Sheryl Koski,[1] Edith Pituskin,[1] and Michael B. Sawyer[1]

Clin Cancer Res 2009;15(8) April 15, 2009



Metastatic breast ca, taxane – or anthracycline resistant.

1250 mg/m^2 capecitabine BID

Dose – limiting toxicity defined as ≥ grade 2 and resulting in interruption of treatment (dose reduction or dose delay)

P=0.039

Sarcopenia predicts infections and convalescent care in elderly patients undergoing colorectal cancer resection, Lieffers et al.

Multivariate logistic regression

	Infectious complications			
	Unadjusted OR [95% CI]	**P value**	**Adjusted OR [95% CI]**	**P value**
Sarcopenia **No** **Yes**	**ref** **4.4 [1.5, 13.0]**	**0.008**	**ref** **4.6 [1.5, 13.9]**	**0.007**
Sex Female Male	ref 1.1 [0.43, 2.8]	0.84	ref 0.99 [0.36, 2.7]	0.98
Cancer stage II III IV	ref 0.63 [0.21, 1.9] 0.45 [0.14, 1.5]	0.42	ref 0.63 [0.20, 2.0] 0.42 [0.12, 1.5]	0.40
Primary tumor site Colon/RSJ Rectum	ref 1.2 [0.43, 3.6]	0.67	ref 1.1 [0.37, 3.5]	0.82

Major categories of infection:

A41.X: Septicemia

J15.X, J18.X: Pneumonia

K65.0, K65.9: Acute and unspecified peritonitis

N39.0: Urinary tract infection, site not specified

T81.4: Infection following a procedure not elsewhere classified (includes: abscess: intra-abdominal, stitch, subphrenic, wound or septicemia))

A04.7: Enterocolitis due to *C difficile*

A09: Diarrhea and gastroenteritis of presumed infectious origin

What about specific effector molecules which induce wasting?

- Signals and signal transduction to muscle cells
  - Proinflammatory cytokines
  - Myostatin and the activin receptor
  - Androgen receptor

- Pathways of induction of protein degradation
- Therapeutic targets

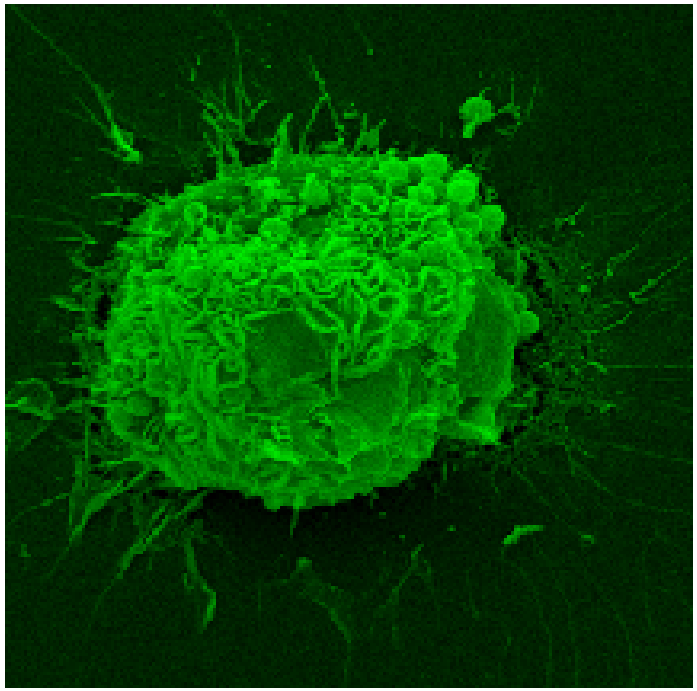
Baracos VE et al. New England Journal of Medicine 1983 :308(10):553-8.

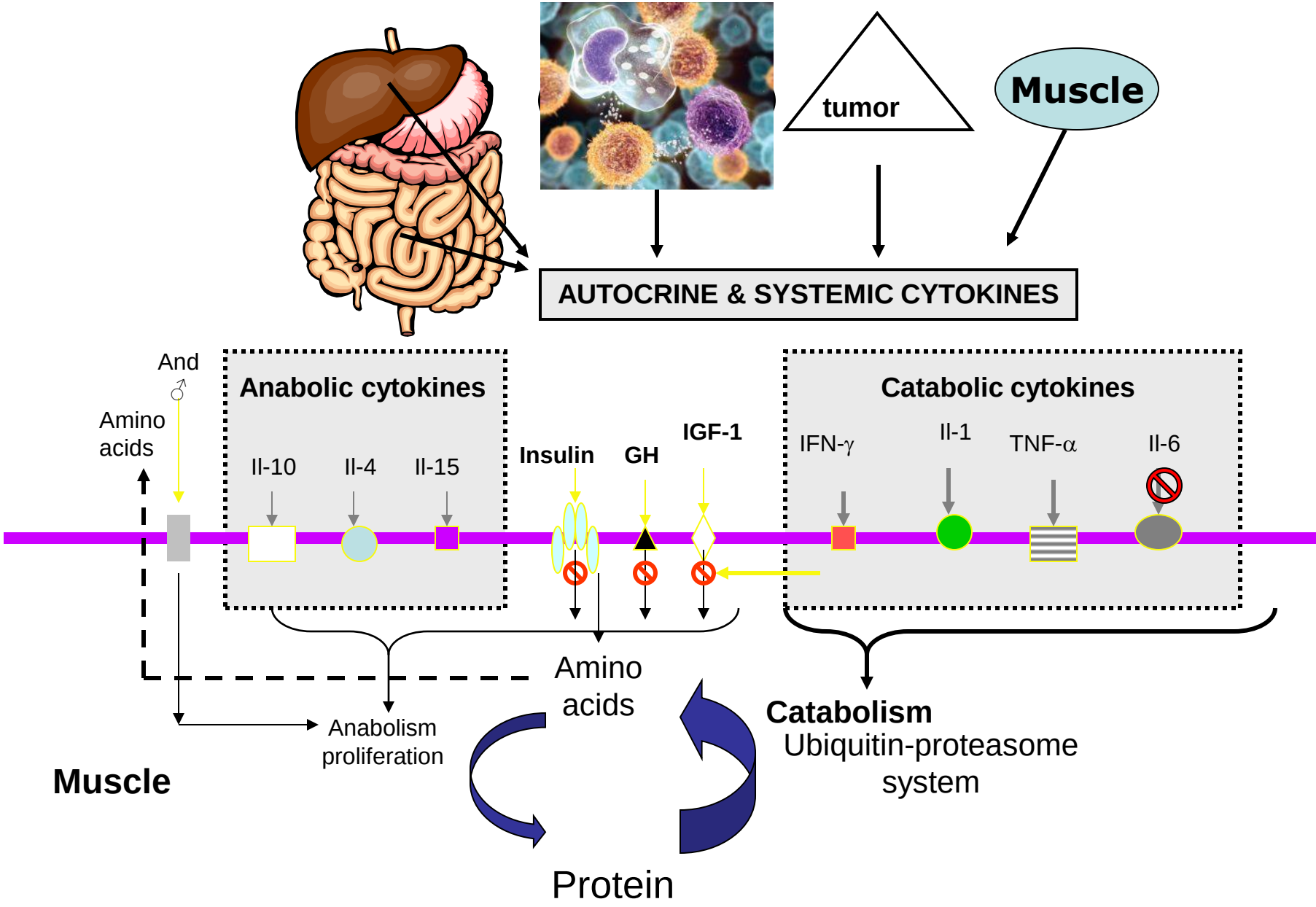
Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever.

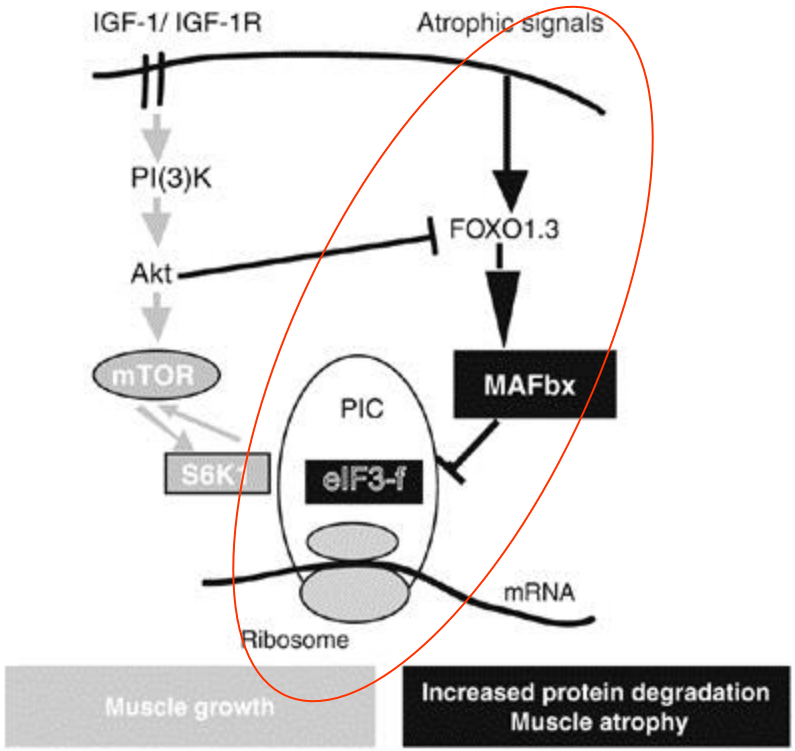
- a cytokine, Interleukin-1, from mononuclear phagocytes, had a direct action to increase protein catabolism in skeletal muscle in vitro.

- The link between fever, inflammation, infection, injury , cancer and muscle wasting.

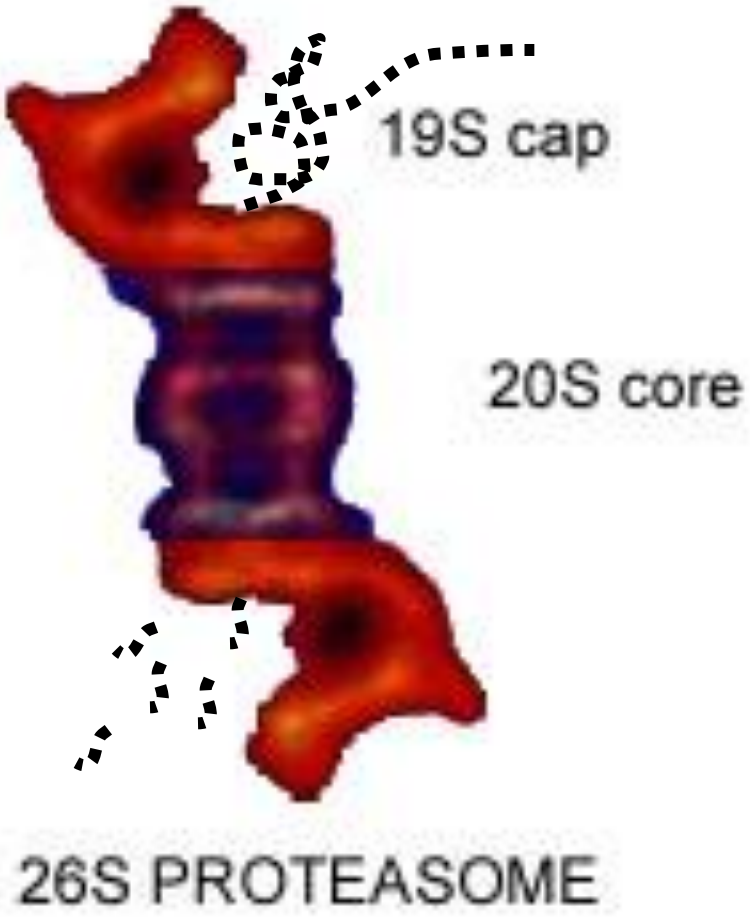
- The role of pro-inflammatory cytokines as “*cachectins*” has subsequently evolved and these are now believed to be key factors underlying various forms of wasting.




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


IGF-1/ IGF-1R
Atrophic signals
PI(3)K
Akt
FOXO1.3
mTOR
MAFbx
PIC
S6K
eIF3-f
mRNA
Ribosome
Muscle growth
Increased protein degradation
Muscle atrophy

What's doing the degrading?

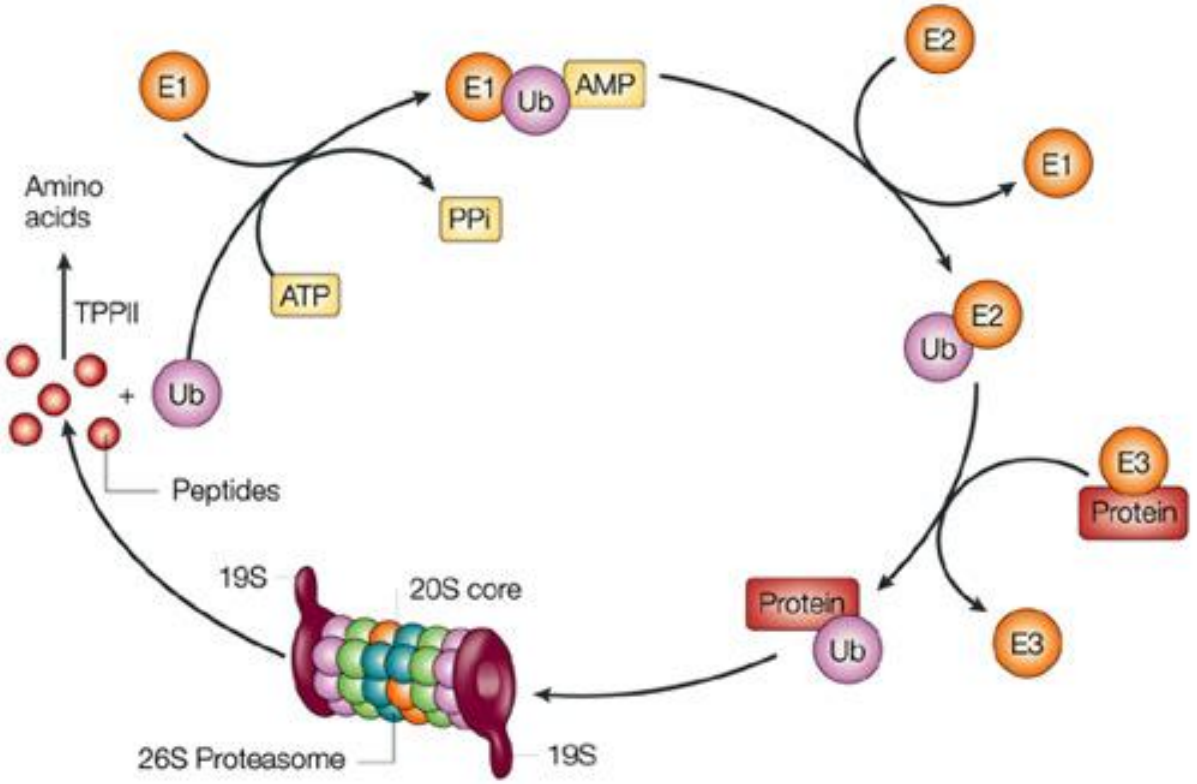


PROTEASOMES

Proteolytic core module and two regulatory cap complexes.

Cylindrical structure consisting of 4 stacked rings, protease active sites in the central cavity

Response elements in skeletal muscle: ATP-Ubiquitin-dependent proteolysis seems to be the ultimate downstream effector of humoral catabolic factors in general – is it a target for anti-catabolic therapy?

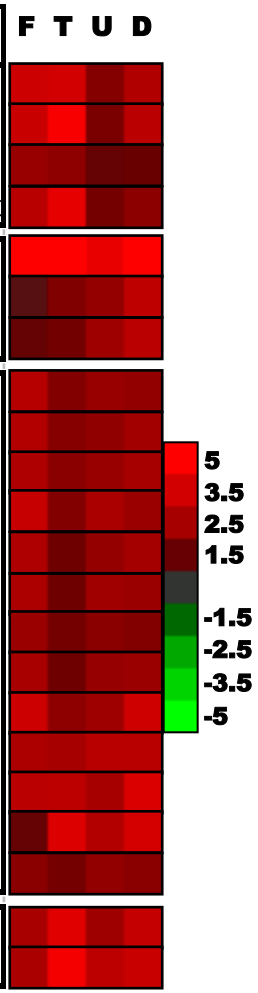


Nature Reviews | Cancer

Gene expression events common to muscle wasting

Lecker SH, Jagoe RT, Gilbert A, Gomes M, Baracos VE, Bailey J, Price SR, Mitch WE, Goldberg AL Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. FASEB J 18:39-51 2004

Clone	Unigene	Primary Sequence Name	
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	



Fasting

Tumor

Uremia

Diabetes

Lecker SH et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. FASEB J. 2004 Jan;18(1):39-51

Identification of the most – expressed gene (12-17 - fold) of the common gene expression events associated with all of the muscle atrophies.

A novel protein with an F-box motif = a new, muscle – specific ubiquitin ligase:

“ATROGIN-1” or “MAFbox”

Science 23 November 2001:
Vol. 294. no. 5547, pp. 1704 - 1708

Identification of Ubiquitin Ligases Required for Skeletal Muscle Atrophy
David J. Glass et al

Of a small subset was universal in muscle atrophy models. Two of these genes encode ubiquitin ligases: *Muscle RING Finger 1* (*MuRF1*), and a gene we designate *Muscle Atrophy F-box* (*MAFbx*), the latter being a member of the SCF family of E3 ubiquitin ligases.

Overexpression of *MAFbx* in myotubes produced atrophy, whereas mice deficient in either *MAFbx* or *MuRF1* were found to be resistant to atrophy. These proteins are potential drug targets for the treatment of muscle atrophy.

Reversal of Cancer Cachexia and Muscle Wasting by ActRIIB Antagonism Leads to Prolonged Survival

Cell

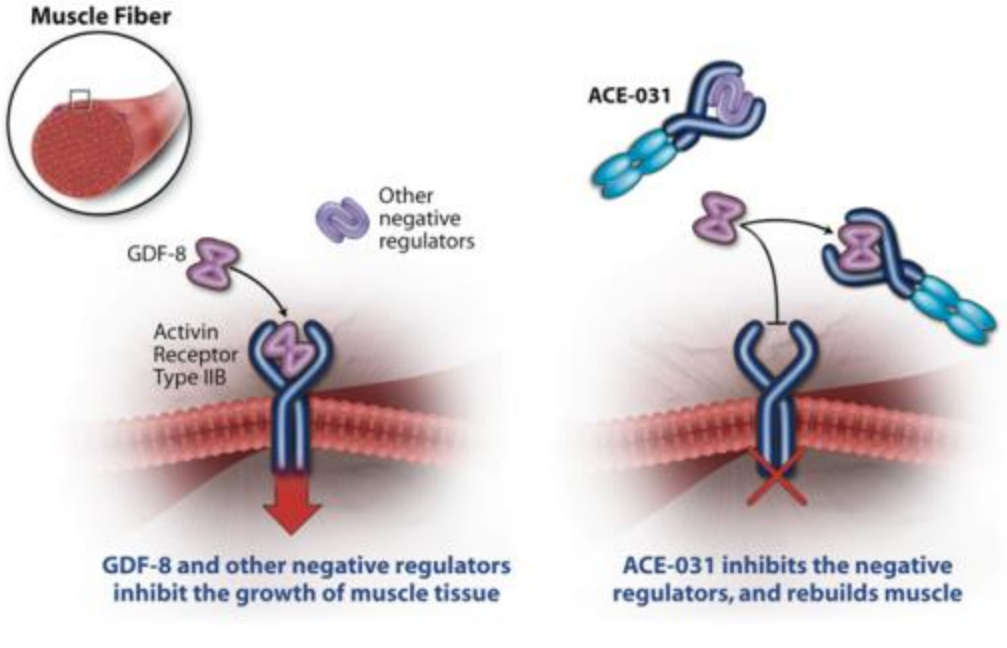
Xiaolan Zhou,[1] Jin Lin Wang,[1] John Lu,[1] Yanping Song,[1] Keith S. Kwak,[1] Qingsheng Jiao,[1] Robert Rosenfeld,[1] Qing Chen,[1] Thomas Boone,[1] W. Scott Simonet,[1] David L. Lacey,[1] Alfred L. Goldberg,[2] and H.Q. Han[1,*]

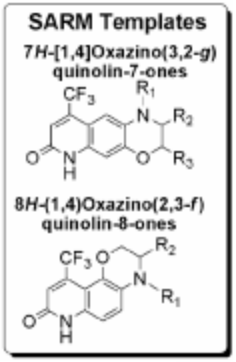
[1]Departments of Metabolic Disorders and Protein Science, Amgen Research, Thousand Oaks, CA 91320, USA

[2]Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA

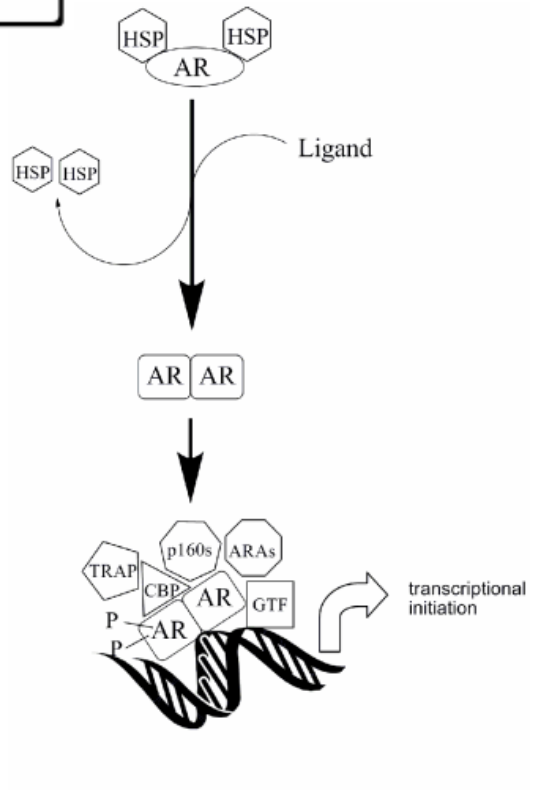
*Correspondence: hqhan@amgen.com

DOI 10.1016/j.cell.2010.07.011





Selective Androgen Receptor Modulators (SARMs) a unique class of molecules currently under development for treatment of a variety of diseases that were previously treated with anabolic steroids .

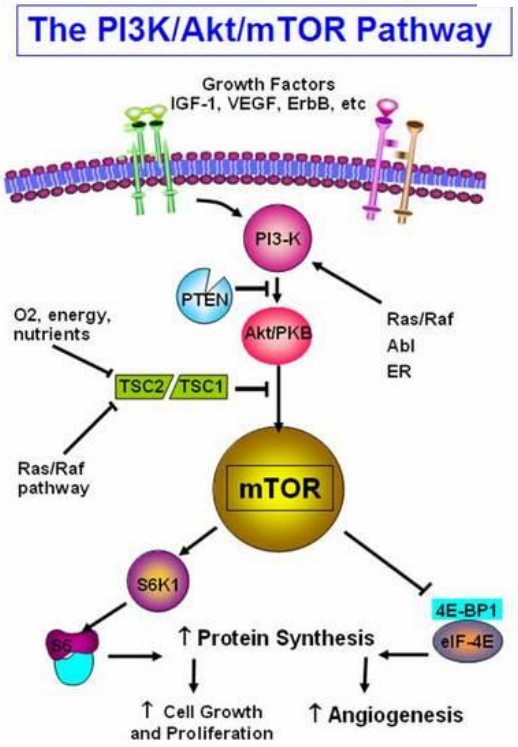


ANDROGEN RECEPTOR is maintained in an inactive complex by HSPs 70 and 90 and corepressors. On ligand binding, the receptor homodimerizes and enters the nucleus. Hormone binding increases the phosphorylation status of the receptor. The AR binds to the ARE on the promoter of androgen responsive genes, leading to the recruitment of coactivators and general transcription factors, leading to gene transcription

Association of Skeletal Muscle Wasting With Treatment With Sorafenib in Patients With Advanced Renal Cell Carcinoma: Results From a Placebo-Controlled Study

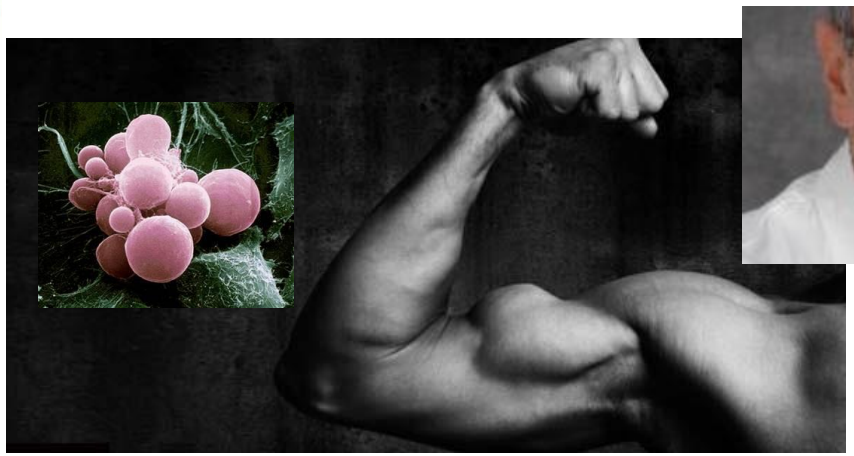
Sami Antoun, Laura Birdsell, Michael B. Sawyer, Peter Venner, Bernard Escudier, and Vickie E. Baracos

J Clin Oncol 28. © 2010 by American Society of Clinical Oncology



Sorafenib causes muscle wasting independent of disease progression

Mean loss ~ 2.1 kg muscle during 1 y on sorafenib



Sarcopenia, signals, cancer cachexia

- Diagnostic images provide an expedient way to identify patients with depletion of muscle

- Sarcopenia is a predictor of poor outcome: mortality, toxicity, infection
- Muscle wasting is effected by the ubiquitin-proteasome pathway

- Muscle wasting may be a side effect of drugs targeting AKT, mTOR and related pathways, which regulate tumor cell proliferation as well as muscle anabolism

- Muscle wasting may be prevented by alteration of a number of specific signal transduction events involving cytokine/cytokineR, myostatin/activinR, androgen/androgenR, ubquitin proteasome pathway or muscle –specific signals leading to its activation.

Questions?