Metabolické aspekty monitorovaného umírání

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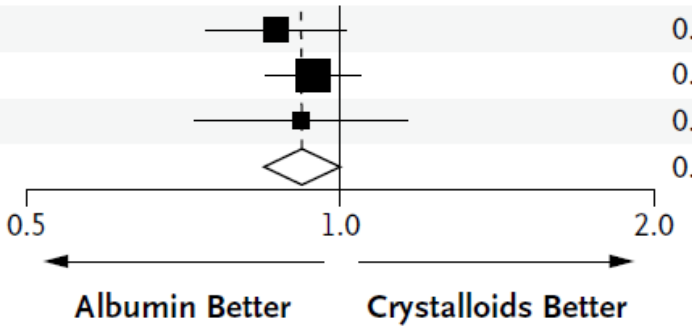
Je to jen problém čím a kolik?

Trial	Albumin	Crystalloids	Relative Weight	Relative Risk (95% CI)	P Value
	no. of patients who died/total no.		%		
SAFE[2]	185/603	217/615	30.41	0.87 (0.74–1.02)	
ALBIOS[1]	365/888	389/893	54.90	0.94 (0.85–1.05)	
EARSS[3]	96/399	103/393	14.69	0.92 (0.72–1.17)	
All trials	646/1890	709/1901	100.00	0.92 (0.84–1.00)	0.046



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Sepse v centru pozornosti intenzivní péče – smrtnost 20 – 50%, ale až 70%

- Monitorované umírání
- Časně na vysokých dávkách katecholaminů
- Typicky však po několika týdnech v důsledku multiorgánového selhání a terminální pneumonie přehodnocením intenzity léčebného přístupu nebo v následné péči
- Arteficiálně ventilovaný, něco noradrenalinu, mírně prosáklý, bez svalové hmoty, enterálně podvyživený, kontinuálně či spíše již intermitentně dialyzovaný
- Dávno pesimistický personál a později i smířená rodina čekající na vysvobozující konec
- Velké sebevědomí, že to opravdu nešlo, vždyť jsme ti nejlepší


Evolution

Selected Best Practices and Suggestions for Improvement

PSI 13: Postoperative Sepsis

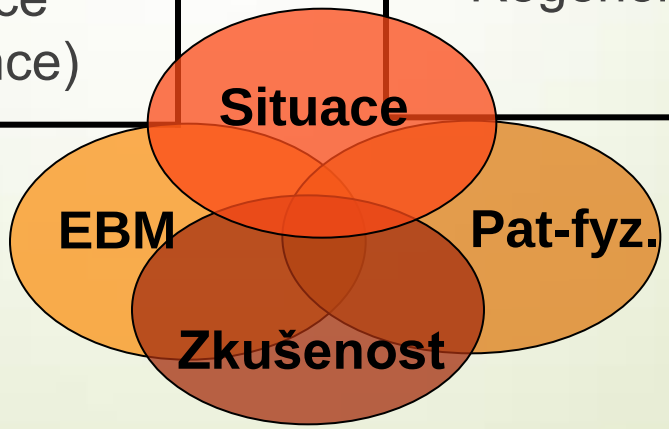
Why Focus on Sepsis?

- More than 750,000 cases of sepsis are reported in the United States each year. Between 11 percent and 27 percent of ICU admissions have severe sepsis, with mortality rates ranging from 20 percent to more than 50 percent.[1]
- Implementation of the entire Surviving Sepsis Campaign bundle has been associated with documentation of a decrease in mortality.[2]
- Not only does postoperative sepsis cause patient harm, it also significantly increases the cost of patient care. The cost of sepsis care in the United States has been estimated at $400 billion annually.[3]
- Starting in 2015, the postoperative sepsis rate PSI will be one of the measures used for Medicare's Hospital Value-Based Purchasing (as part of a composite indicator) that links quality to payment.[4]

Nedbalost a neznalost

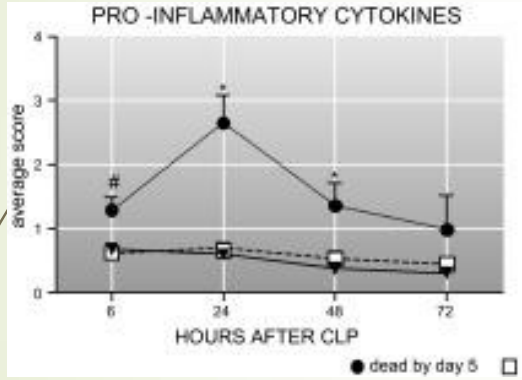
- Pozdní dg. - ↓SpO_2, delirium
- Nedůsledná a pomalá aplikace balíčků
- Protrahovaná hypovolemie s noradrenalinem
- Pozdní neadekvátní ATB terapie
- Časování invazivní intervence
- Organizace zdravotní péče (dlouhodobá rekonvalescence)

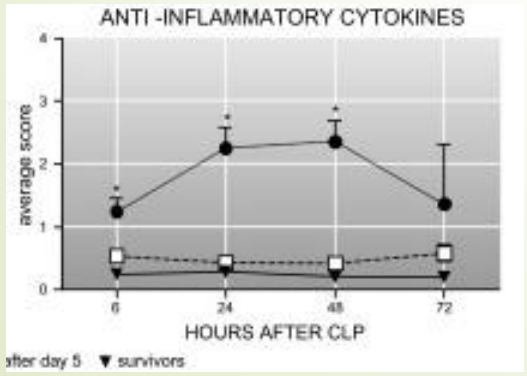
- Poměr tekutinové rsuscitace a katecholaminů
- Přeceněný význam vyrovnané bilance tekutin
- Vedllejší účinky katecholaminů
- Cytoprotektivní aktivity
- Modulace zánětu
- Regenerační postupy

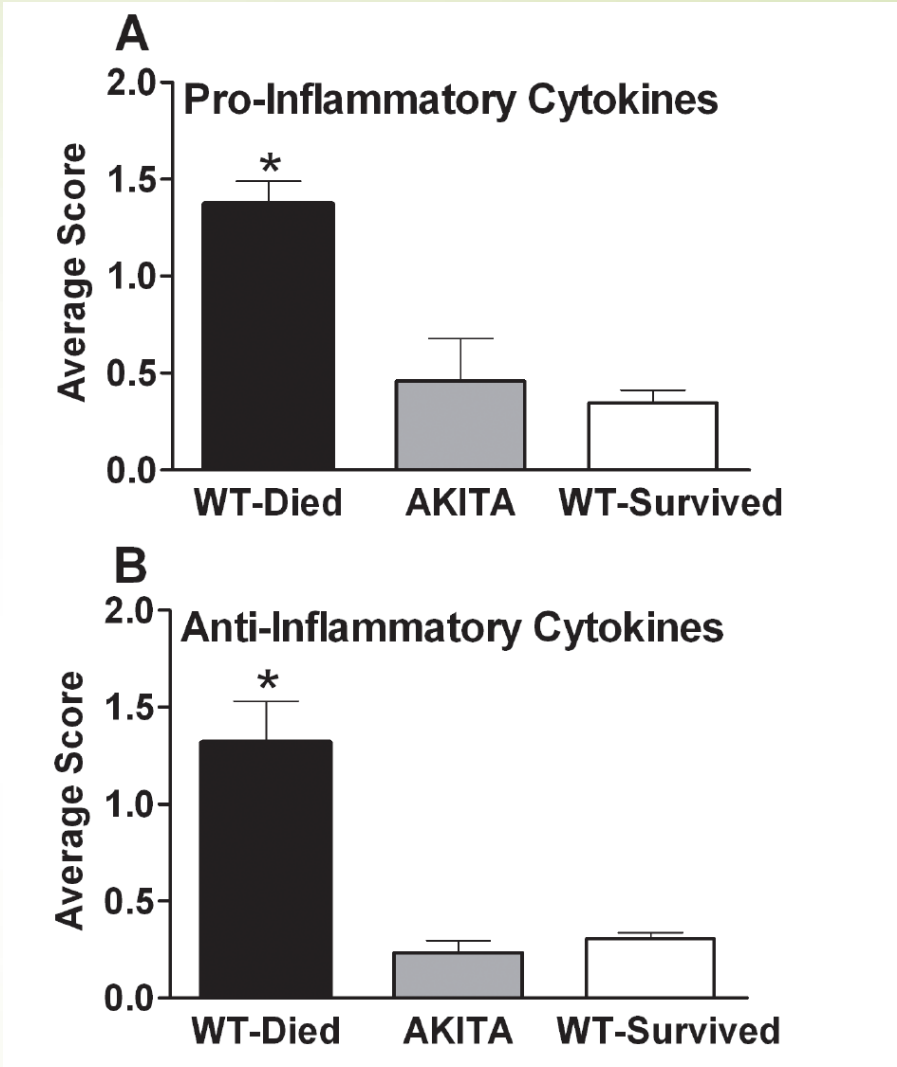


Akutní buněčné poškození v sepsi

- Infekce, toxin
- Ischemie, hypoxie
- Reaktivní formy kyslíku a dusíku
- Cytokinová bouře







UNTREATED TYPE 1 DIABETES INCREASES SEPSIS-INDUCED MORTALITY WITHOUT INDUCING A PRE-LETHAL CYTOKINE RESPONSE

Marcin F. Osuchowski[*,†], **Florin L. Craciun**[*], **Elizabeth Schuller**[*], **Corneliu Sima**[‡], **Robert Gyurko**[‡], and **Daniel G. Remick**[*]

Shock. 2010 October ; 34(4): 369–376. doi:10.1097/SHK.0b013e3181dc40a8.

Decoding cell death signals in liver inflammation

Catherine Brenner[1,2,†], Lorenzo Galluzzi[3,4,5,†], Oliver Kepp[3,6], Guido Kroemer[4,5,6,7,8,*]

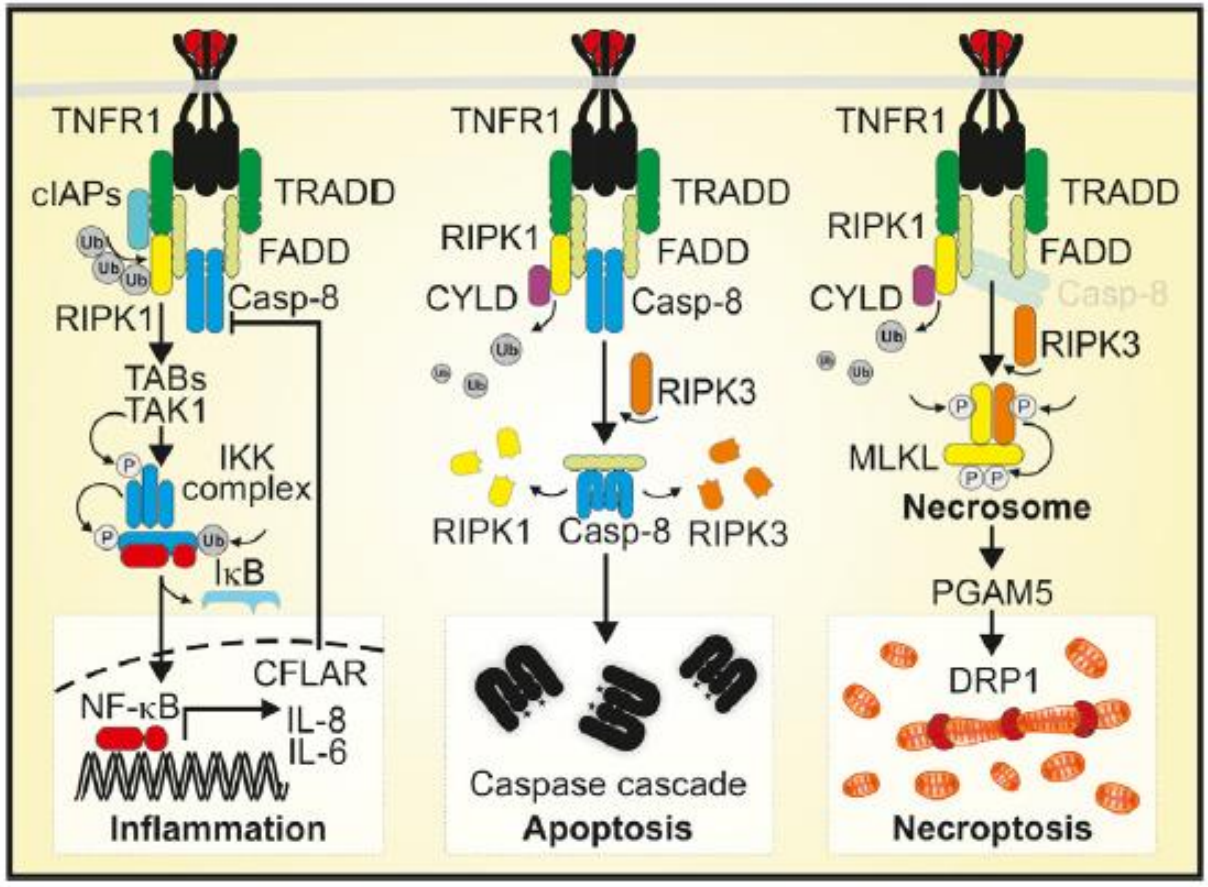
[1]INSERM, UMRS 769, LabEx LERMIT, F-92290 Châtenay Malabry, France; [2]Université de Paris Sud/Paris VI, Faculté de Pharmacie, F-92290 Châtenay Malabry, France; [3]Institut Gustave Roussy, F-94805 Villejuif, France; [4]Université Paris Descartes/Paris V, Sorbonne Paris Cité, F-75006 Paris, France; [5]Equipe 11 labellisée par la Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers, F-75006 Paris, France; [6]INSERM, U848, F-94805 Villejuif, France; [7]Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, F-94805 Villejuif, France; [8]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, F-75015 Paris, France

1. Nekróza buněk- zdroj nestabilních forem kyslíku - zánětová reakce

2. TNF-alfa zprostředkovaná apoptóza

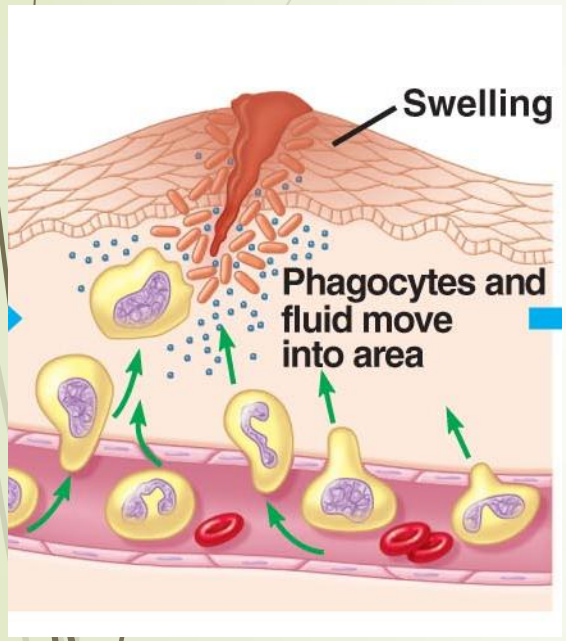
3. Mitochondriálně podmíněná apoptóza

4. Záchrana poškozené buňky intracelulárním procesem autofagie



Journal of Hepatology **2013** vol. 59 | 583–594

Patofyziologie hojení rány - zánět

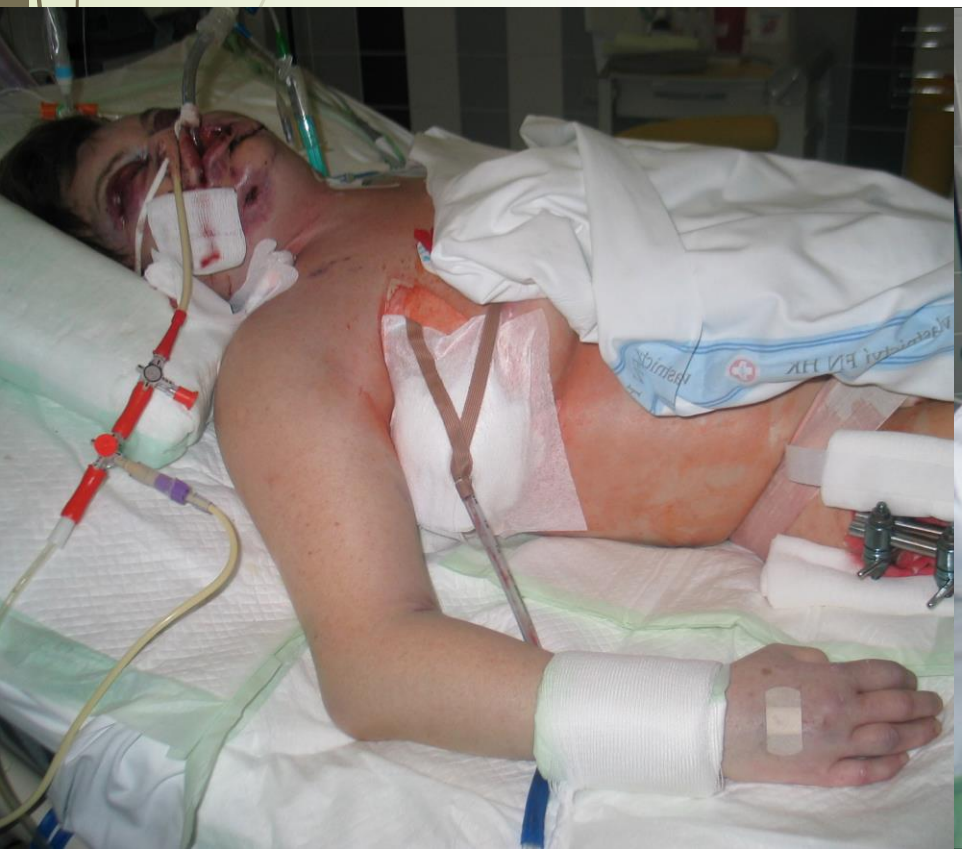


- Exsudace – rozložení a zkapalnění poškozené tkáně, influx vody imunokompetentních buněk, různých krevních látek do poškozené tkáně
- Proliferace – tvorba granulační tkáně, aktivace fibroblastů, kolagen a proteoglykany, novotvorba cév,
- Reparace – přestavba primitivní matrix, pevná kolagenová síť, regenerace funkčních buněk
- Remodelace, diferenciace – definitivní tkáňové uspořádání s retrakcí membrán fibroblastů a jejich uložení v kolagenové síti, strukturální definitiva kolagenových vláken podle zatížení

Intersticiální otok a průtok

Fascinující fenomén tekutinového přesunu

- výplach intersticia?



Higher vs. lower fluid volume for septic shock: clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort

Søren H Smith and Anders Perner*

Table 2 Characteristics dependent on fluid volume in the ICU in the first day and the first 3 days of shock in consecutive ICU patients with septic shock

	Day 1, *n* = 164			Day 1-3, *n* = 95		
	High fluid volume (> 4.0 L), *n* = 82	Low fluid volume (< 4.0 L), *n* = 82	*P* value	High fluid volume (> 7.5 L), *n* = 47	Low fluid volume (< 7.5 L), *n* = 48	*P* value
Total fluid volume, liters	6.3 (5.1-8.2)	2.3 (1.1-3.0)	< 0.0001	10.9 (8.7-13.3)	4.3 (3.0-5.7)	< 0.0001
Crystalloids, liters	3.9 (3.0-6.0)	2.0 (1.0-2.3), *n* = 59	< 0.0001	7.0 (4.5-9.8)	2.8 (0.5-4.3), *n* = 40	< 0.0001
Colloids, liters	1.1 (0.6-1.6), *n* = 72	0.5 (0.4-1.0), *n* = 64	< 0.0001	2.1 (1.0-2.5), *n* = 46	1.0 (0.5-1.5), *n* = 40	< 0.0001
Blood products, liters	1.2 (0.6-2.8), *n* = 53	0.5 (0.2-0.9), *n* = 34	< 0.0001	2.6 (1.1-4.3), *n* = 41	1.1 (0.5-1.9), *n* = 32	< 0.001
SAPS II on admission	54 (45-64)	54 (45-67)	0.73	53 (46-67)	55 (49-62)	0.47
SOFA score[a]	11 (9-13)	11 (9-13)	0.99	10 (8-13)	11 (10-14)	0.33
Maximum p-lactate in mmol/L[a]	3.4 (2.2-5.5)	2.0 (1.6-3.2), *n* = 81	< 0.0001	2.6 (1.7-3.4)	1.9 (1.6-2.4)	< 0.01
Minimum $ScvO_2$, percentage[a]	70 (63-77), *n* = 68	73 (66-78), *n* = 57	0.26	74 (66-80), *n* = 34	74 (68-79), *n* = 31	0.35
Maximum vasopressor in µg/kg per minute[a]	0.25 (0.12-0.43)	0.18 (0.10-0.32)	0.07	0.16 (0.10-0.24)	0.15 (0.08-0.22)	0.57
Renal replacement therapy, number (percentage)	32 (39)	32 (39)	1.00	18 (38)	16 (33)	0.61
90-day mortality, number (percentage)	38 (46)	45 (55)	0.27	19 (40)	29 (62)	0.03

Values are presented as median (interquartile range) or as number of patients (percentage). Group comparisons were done by Mann-Whitney *U* test including all patients in the groups (82 versus 82 and 47 versus 48 patients) or chi-squared test by relevance. The number (n) is given in the specific cell that applies; for all other variables, n was as given in the top of the column. [a]On days 1 and 3, respectively. ICU, intensive care unit; SAPS II, simplified acute physiology score II, $ScvO_2$, central venous oxygen saturation, SOFA, sequential organ failure assessment.

…wn. Therefore we
…atients with septic shock

…nts with septic shock
…in regional hospitals.
…ll median fluid volumes.
…e statistics.

…irst day of septic shock.
…2.0 (1.6-3.0) mmol l^{-1}, $P <$
…gy score (SAPS) II (54 (45-
… 11 (9-13), $P = 0.78$) and
…o still had shock on day 3
…ies (> 7.5 l) had higher p-
…y (40 vs. 62%, $P = 0.03$)
…/s. 55 (49-62), $P = 0.47$)

Conclusions: In this cohort of unselected ICU patients with septic shock, initial fluid volume was not associated with mortality. In patients with shock for three days or more, higher fluid volumes including crystalloids, colloids and blood products were associated with reduced mortality.

Smith and Perner *Critical Care* 2012, **16**:R76
http://ccforum.com/content/16/3/R76

Global end-diastolic volume increases to maintain fluid responsiveness in sepsis-induced systolic dysfunction

Ronald J Trof[1,2], Ibrahim Danad[1] and AB Johan Groeneveld[1,3*]

Srdce pacienta v sepsi se chová jinak než pacienta po kardiochirurgickém výkonu a jeho optimální parametry charakterizuje vyšší GEDVI (než 600-800 ml/m$^{2)}$

rdiac dysfunction may limit fluid responsiveness and the mechanism thereof
nction may affect the relative value of cardiac filling pressures, such as the
ressure (CVP), versus filling volumes in guiding fluid loading, we studied these
uid responsiveness, according to cardiac function.

0 min colloid fluid loading protocol was performed in 16 mechanically ventilated
otension and three 30 min consecutive fluid loading steps of about 450 mL per
nd-diastolic volume index (GEDVI), cardiac index (CI) and global ejection fraction
ulmonary dilution. Baseline and changes in CVP and GEDVI were compared among
nd ≥15%) and non-responding fluid loading steps, in patient with low (<20%, n = 9)
= 7) at baseline.

ith other indices of impaired cardiac (left ventricular) function, prior to and after
steps, 9 (of 27) were responding when GEF <20% and 6 (of 21) when GEF ≥20.
t differ between responding and non-responding steps and levels attained were
23 higher in the latter, regardless of GEF (P = 0.004). Prior to fluid loading, GEDVI (and CI) was higher in responding
on-responding steps (870 ± 236 mL/m^2) when GEF was low (P = 0.002), but did not differ
l. Increases in GEDVI were associated with increases in CI and fluid responsiveness,
1).

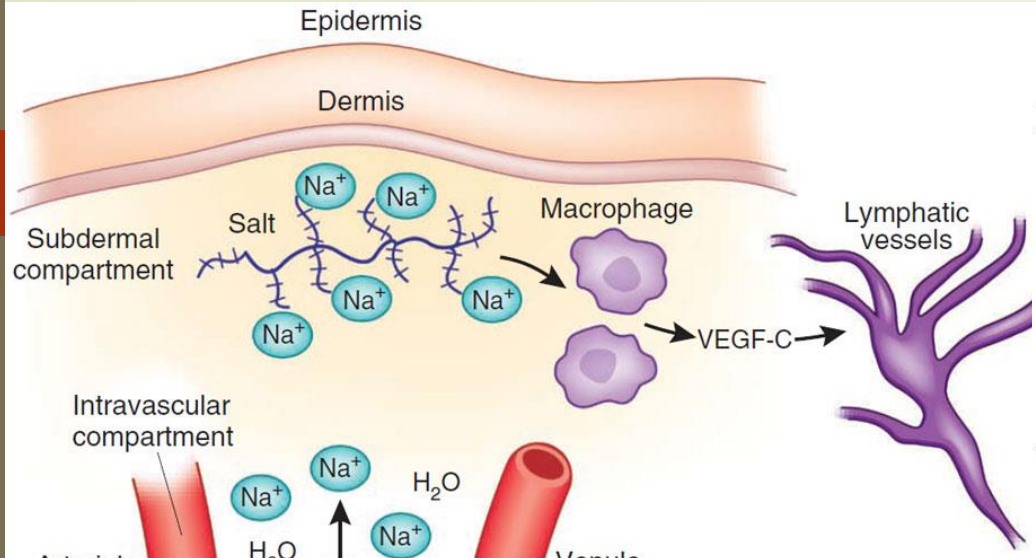
from transpulmonary dilution, about half of patients with sepsis-induced hypotension
nction. During dysfunction, cardiac dilation with a relatively high baseline GEDVI
ess by further dilatation (increase in GEDVI rather than of CVP) as in patients without
uid responsiveness during systolic cardiac dysfunction may be caused by diastolic
entricular dysfunction.

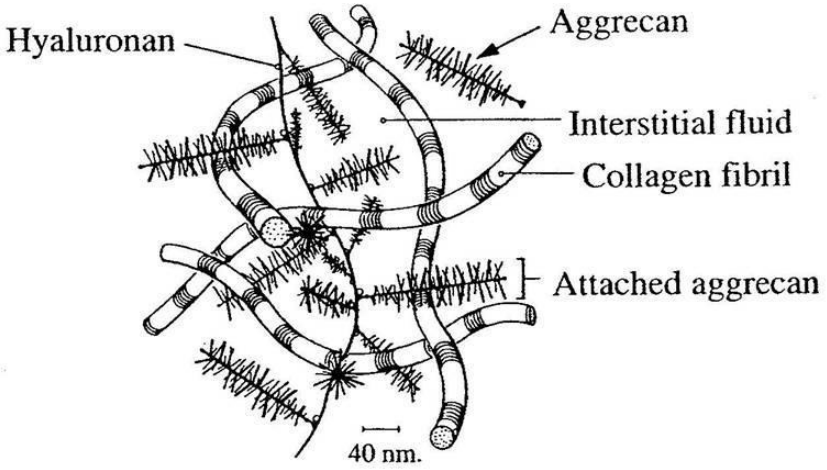
luid Loading, Myocardial Depression, Right Ventricular Afterload, Diastolic Compliance,
raction

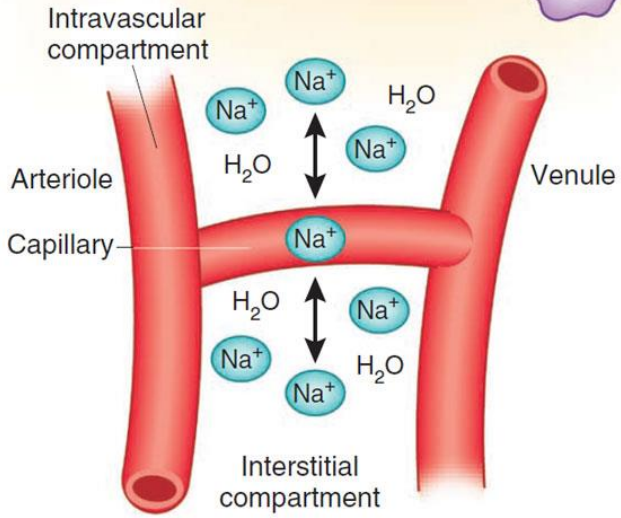
Conclusions

In conclusion, our study suggests that in patients with sepsis-induced hypotension and systolic cardiac dysfunction, occurring in about half of patients, fluid responsiveness is maintained by global cardiac dilatation, as measured by transpulmonary dilution-derived GEDVI, rather than by an increase in CVP. Absence of fluid responsiveness in systolic cardiac dysfunction may be explained by diastolic dysfunction and/or concomitant right ventricular dysfunction. Transpulmonary (thermo)dilution-derived GEDVI is more helpful than CVP in monitoring fluid responsiveness and non-responsiveness and their mechanisms in sepsis-induced hypotension, but normal or targeted levels of preload (GEDVI 680–800 mL/m^2) may not apply in this condition.

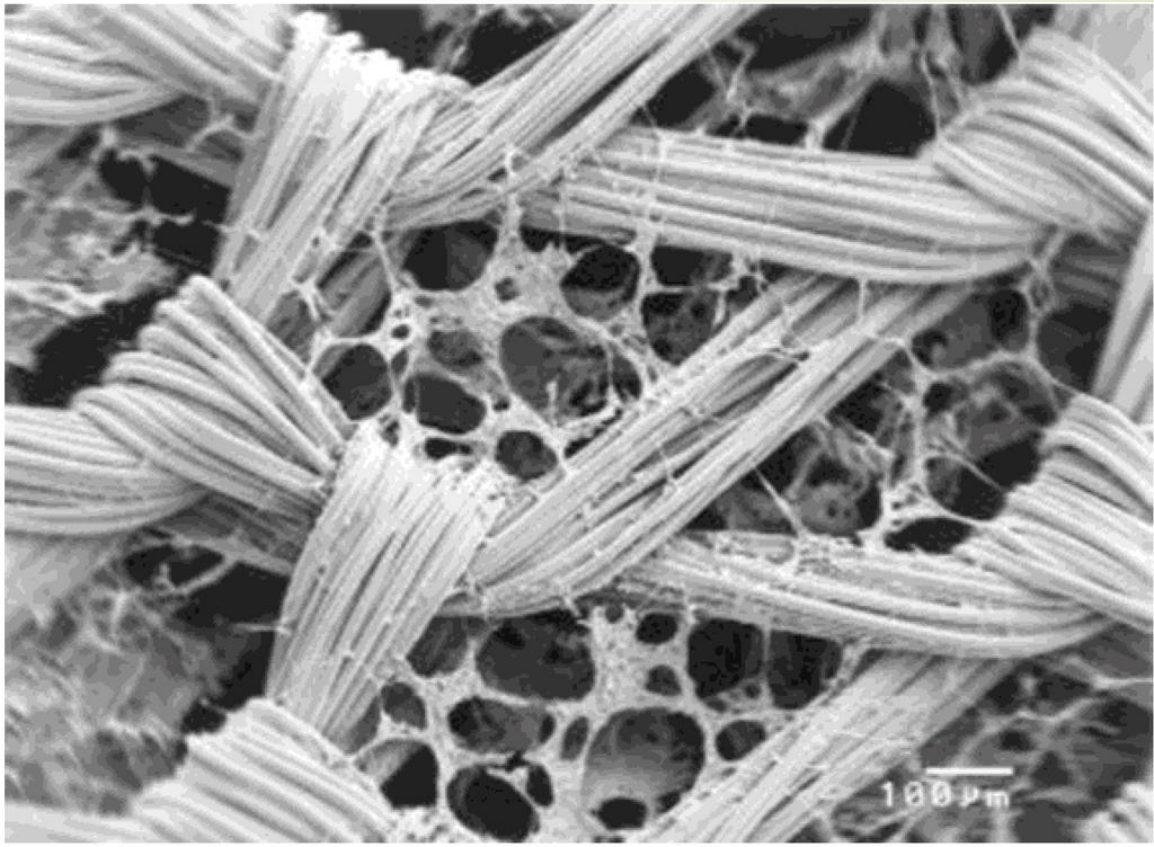
Trof *et al. BMC Anesthesiology* 2013, **13**:12
http://www.biomedcentral.com/1471-2253/13/12


Epidermis
Dermis
Subdermal compartment
Salt
Na+
Macrophage
VEGF-C
Lymphatic vessels


Hyaluronan
Aggrecan
Interstitial fluid
Collagen fibril
Attached aggrecan
40 nm.


Intravascular compartment
Arteriole
Capillary
Venule
Interstitial compartment
Na+
H2O


10 µm
IC


100 µm

Odsun vody z intersticia

- Lymfatická a kapilární drenáž
- Hydrostatický a onkotický tlak
- Hyaluronová a kolagenová síť s různě velkými oky podle expanze intersticia - bobtnání, hydraulická vodivost
- Vlastnosti cév – fenestrované krevní kapiláry, síťovaná bazální membrána lymfatických kapilár a otevírání mezibuněčných spojení
- Mastné kyseliny výrazněji zvyšují intersticiální tlak než glukóza a aminokyseliny a tím i lymfatický tok

Am J Physiol Heart Circ Physiol 284: H1771–H1777, 2003.
First published January 16, 2003; 10.1152/ajpheart.01008.2002.

Fibroblast alignment under interstitial fluid flow using a novel 3-D tissue culture model

Chee Ping Ng[1] and Melody A. Swartz[1,2]
[1]*Departments of Chemical Engineering and* [2]*Biomedical Engineering, Northwestern University, Evanston, Illinois 60208*

Submitted 21 November 2002; accepted in final form 10 January 2003

Ng, Chee Ping, and Melody A. Swartz. Fibroblast alignment under interstitial fluid flow using a novel 3-D tissue culture model. *Am J Physiol Heart Circ Physiol* 284: H1771–H1777, 2003. First published January 16, 2003; 10.1152/ajpheart.01008.2002.—Interstitial flow is an important component of the microcirculation and interstitial environment, yet its effects on cell organization and tissue architecture are poorly understood, in part due to the lack of in vitro models. To examine the effects of interstitial flow on cell morphology and matrix remodeling, we developed a tissue culture model that physically supports soft tissue cultures and allows microscopic visualization of cells within the three-dimensional matrix. In addition, pressure-flow relationships can be continuously monitored to evaluate the bulk hydraulic resistance as an indicator of changes in the overall matrix integrity. We observed that cells such as human dermal fibroblasts aligned perpendicular to the direction of interstitial flow. In contrast, fibroblasts in static three-dimensional controls remained randomly oriented, whereas cells subjected to fluid shear as a two-dimensional monolayer regressed. Also, the dynamic measurements of hydraulic conductivity suggest reorganization toward a steady state. These primary findings help establish the importance of interstitial flow on the biology of tissue organization and interstitial fluid balance.

interstitial fluid forces; this is in contrast to cells such as endothelial and epithelial cells that form a monolayer to create a lumen or surface and may be exposed to shear stresses across the surface.

Despite its importance, the biological regulation of interstitial fluid balance is poorly understood, largely because of the lack of experimental models. Although many in vivo and in vitro studies have been performed to characterize the mechanics of interstitial fluid balance and estimate the Darcy permeability of a variety of tissues, there have been very few studies to examine how interstitial flow affects cell response and how interstitial fluid is regulated in a soft tissue environment. In their seminal study, Wang and Tarbell (30) investigated the effects of transvascular flow on smooth muscle cells seeded in a collagen gel model and found that the production levels of prostaglandins were 10-fold lower in cells under interstitial fluid shear than in a two-dimensional (2-D) monolayer shear model using a rotating disk, demonstrating that cell response to fluid flow in 2-D configurations poorly mimics the response of fluid flow on interstitial cells in their natural 3-D environment. Furthermore, it has been dem-

Journal of
Cell Science

Interstitial fluid flow induces myofibroblast differentiation and collagen alignment in vitro

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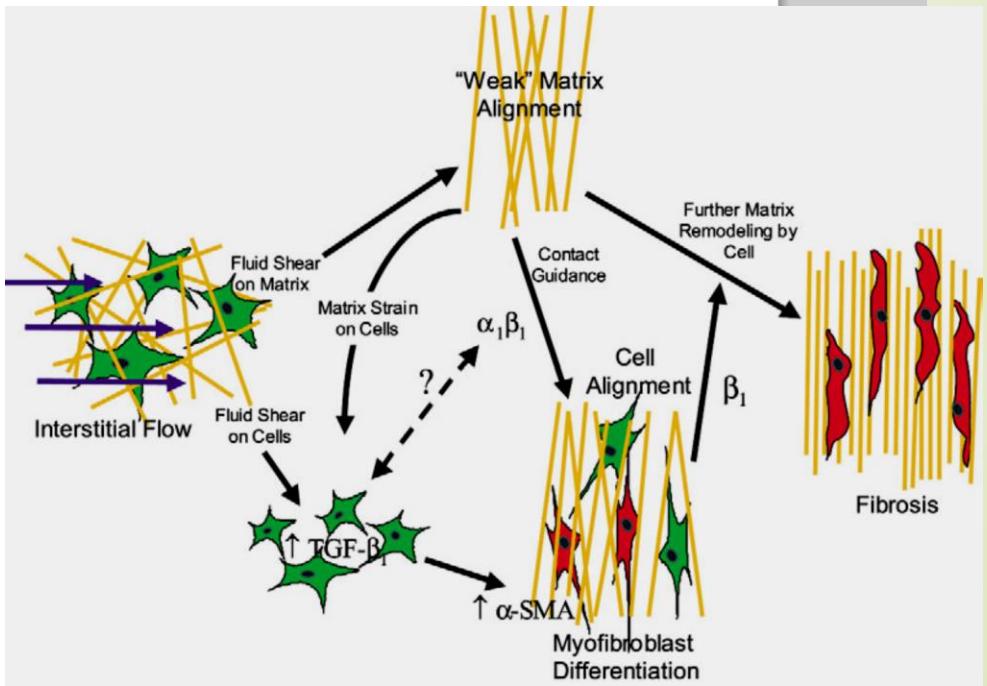
Accepted 1 August 2005
Journal of Cell Science 118, 4731-4739 Published by The Company of Biologists 2005
doi:10.1242/jcs.02605

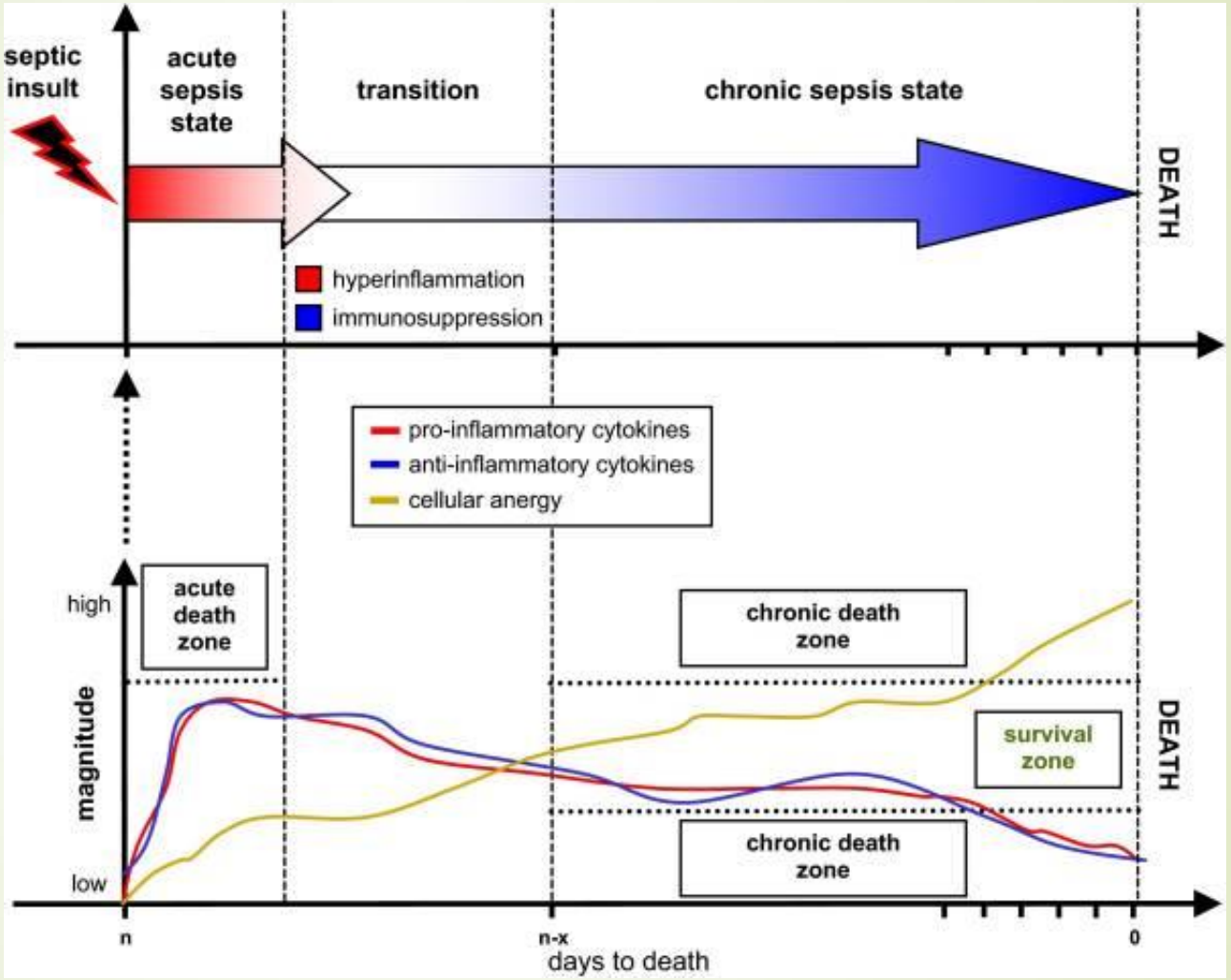
Summary

The differentiation of fibroblasts to contractile myofibroblasts, which is characterized by de novo expression of α-smooth muscle actin (α-SMA), is crucial for wound healing and a hallmark of tissue scarring and fibrosis. These processes often follow inflammatory events, particularly in soft tissues such as skin, lung and liver. Although inflammatory cells and damaged epithelium can release transforming growth factor β_1 (TGF-β_1), which largely mediates myofibroblast differentiation, the biophysical environment of inflammation and tissue regeneration, namely increased interstitial flow owing to vessel hyperpermeability and/or angiogenesis, may also play a role. We demonstrate that low levels of interstitial (3D) flow induce fibroblast-to-myofibroblast differentiation as well as collagen alignment and fibroblast proliferation, all in the absence of exogenous mediators. These effects



Pozdní letalita sepse

- imunitní anergie
- malnutrice



Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, et al. Sepsis: Multiple Abnormalities, Heterogeneous Responses, and Evolving Understanding.*Physiological Reviews* 2013;93(3):1247-1288. doi:10.1152/physrev.00037.2012.

Cellular and molecular mechanisms of muscle atrophy

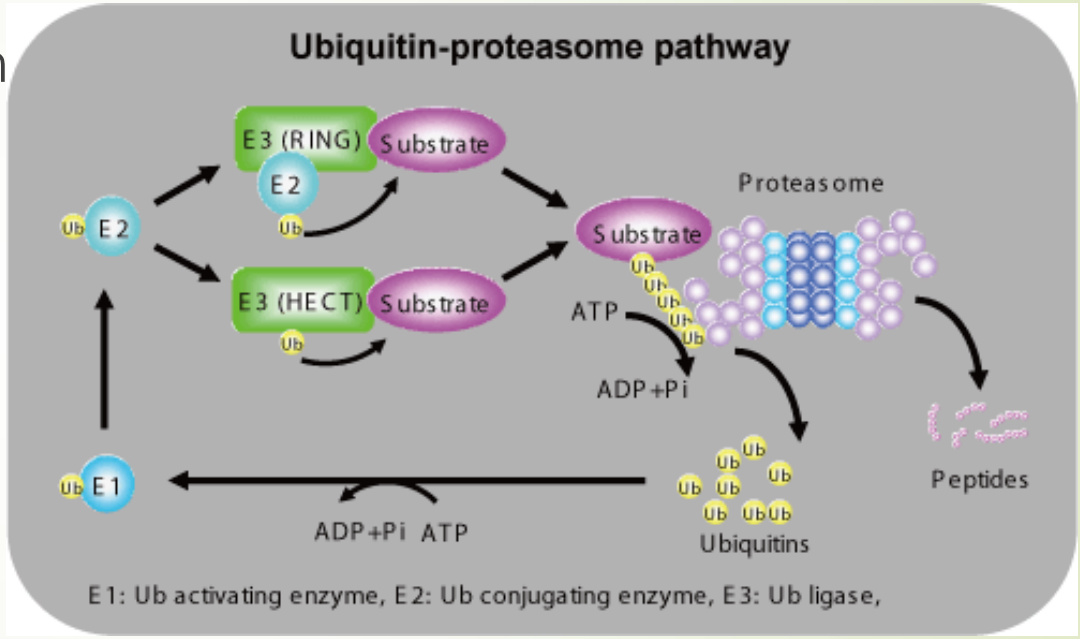
Paolo Bonaldo[1] and Marco Sandri[1,2]

1.Ubiquitinový systém

TNF-alfa

Hladovění

Inaktivita

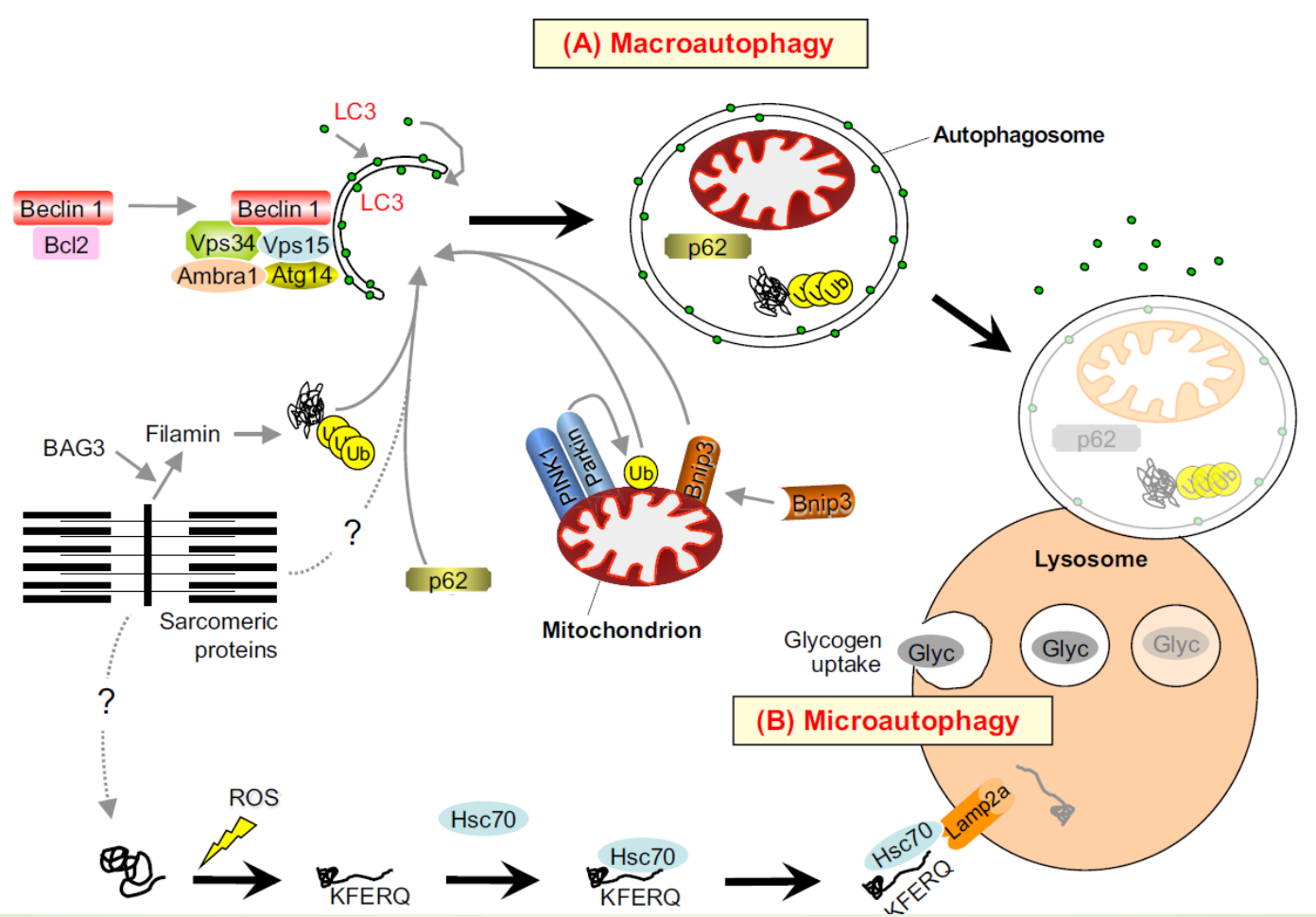


Disease Models & Mechanisms 6, 25-39 (2013) doi:10.1242/dmm.010389

2. Autofagie (makro, mikro, chaperon-zprostředkovaná)

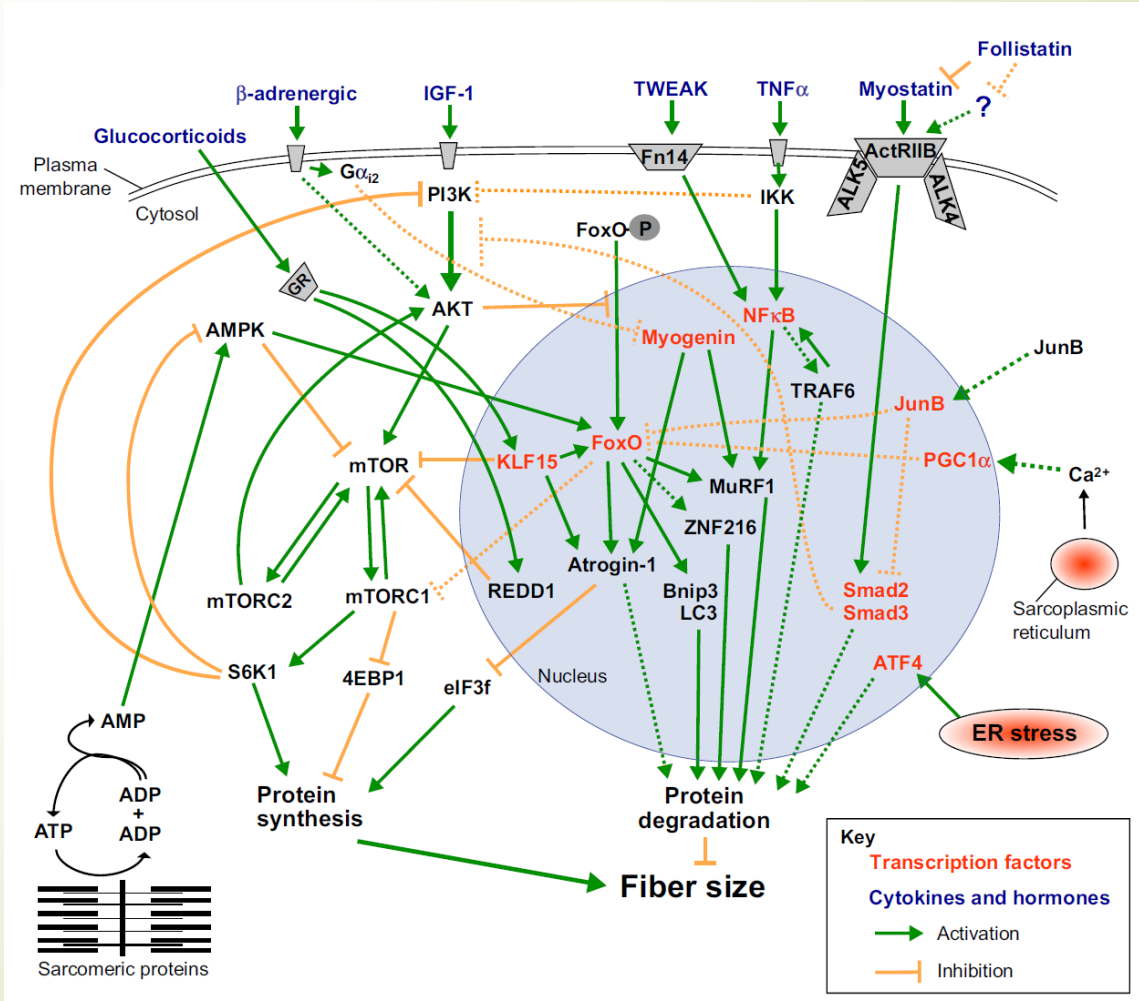
lysozomální degradace

Hladovění, stres, zánět, denervace



Regulační mechanizmy velikosti svalového vlákna

- IGF-1-Akt- Fox
- NFkB
- Myostatin
- Glukokortikoidy



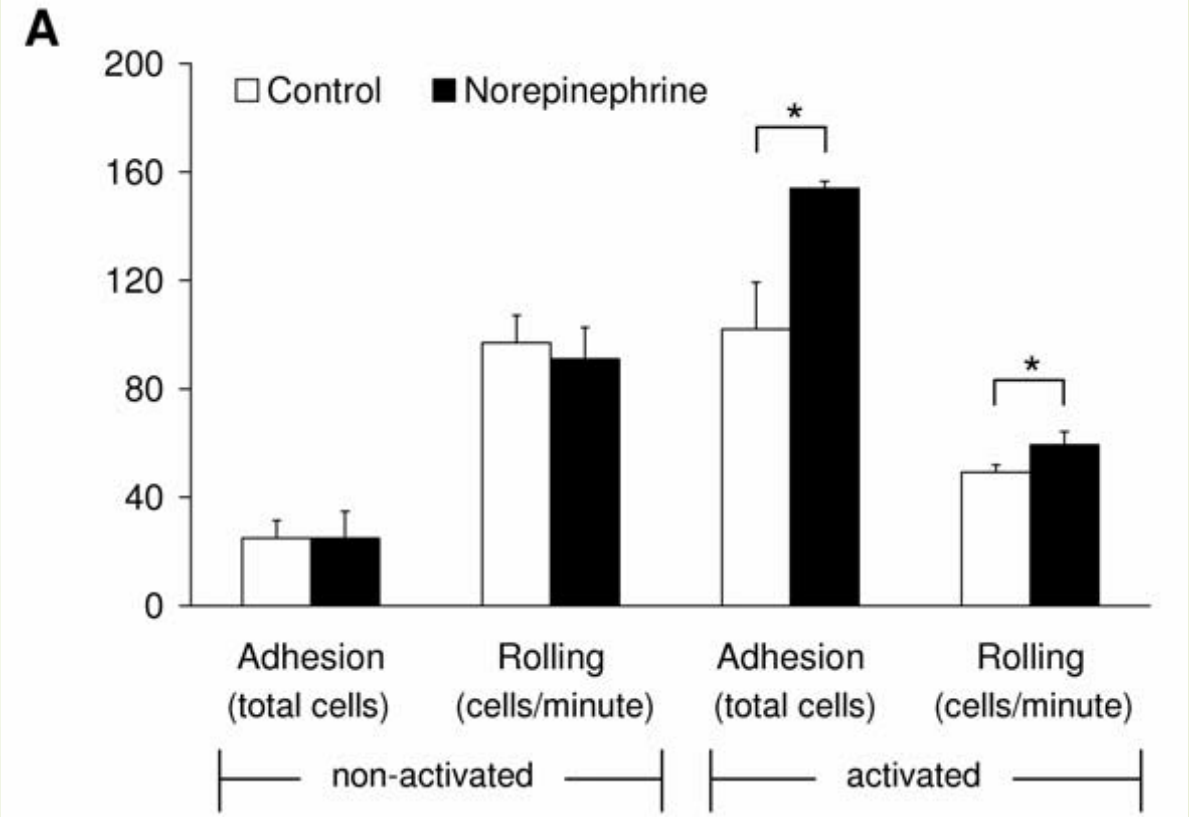
Regulace metabolických cest svalového růstu a degradace

- Řada teoretických možností pro nové léky
- Riziko vzniku a zachování defektních proteinů
- Riziko maligního bujení
- Kardiotoxicita

- Clenbuterol – beta adrenergní agonista
- Solubilní ActRIIB – inhibice myostatinu
- Bortezomib – inhibitor proteozómu

- 4-fenylbutyrát -↓ stresové reaktivity uvnitř buňky -↓apoptózy
- Tauroursodeoxycholová kyselina - ↓mitochondrií indukované aktivace kaspázy

Imunologický efekt katecholaminů – spíše supresivní



Divergent effects of norepinephrine, dopamine and substance P on the activation, differentiation and effector functions of human cytotoxic T lymphocytes

Carina Strell, Anne Sievers, Philipp Bastian, Kerstin Lang, Bernd Niggemann, Kurt S Zänker and Frank Entschladen*

Lucin KM, Sanders VM, Jones TB, Malarkey WB, Popovich PG: **Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation.** *Exp Neurol* 2007, **207**:75-84.

http://www.biomedcentral.com/1471-2172/10/62

Závěr
- trvající vysoká smrtnost sepse nás staví do role monitorů umírání

- Monitorování není léčba – jsou zažité parametry optimální?
- Hemodynamické versus terapeutické cíle
- Poznání buněčného zániku dává předpoklad výzkumu nových cytoprotektivních postupů, dosud selhaly pokusy se selektivními protilátkami cytokinů
- Modifikace zánětu akutní fáze (kortikoidy)
- Antiapoptotická aktivita IL-7
- Talaktoferrin (rekombinantní laktoferrin) zlepšuje integritu střeva
- Hemoperfuze s polymixinem B – adsorpce endotoxinu
- V úvodu rychlost v závěru vytrvalost, rezervy v potenciálu tekutin a výživy

Děkuji za pozornost