Jak pracovat s vědeckou literaturou

Typy vědecké literatury a zdrojů

- Učebnice, knihy
- Monografie – tematická kniha, číslo
- **Souhrnný článek** – review
- **Původní článek** – Original research
- Clinical case study
- Clinical trial
- Perspective, opinion, commentary
- Diplomové, dizertační práce
- Internetové zdroje – *wiki, neoficiální (pozor!)* x oficiální weby (CDC, WHO)

Sekundární literatura

Primární literatura

Vědecký článek - struktura

grafický abstrakt
Highlights

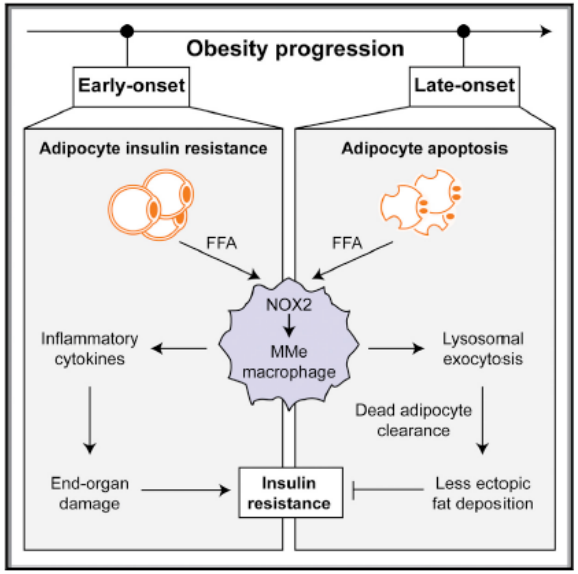
Rychlost, přehlednost

Article

Cell Reports

Metabolically Activated Adipose Tissue Macrophages Perform Detrimental and Beneficial Functions during Diet-Induced Obesity

Graphical Abstract



Authors

Brittney R. Coats, Kelly Q. Schoenfelt, Valéria C. Barbosa-Lorenzi, ..., Christopher J. Rhodes, Frederick R. Maxfield, Lev Becker

Correspondence

levb@uchicago.edu

In Brief

During obesity, adipose tissue macrophages are metabolically activated (MMe). Coats et al. show that MMe macrophages perform detrimental (potentiate inflammation) and beneficial (exocytose lysosomes to clear dead adipocytes) functions, controlled by NOX2. *Nox2*$^{-/-}$ mice exhibit improved or worsened metabolic phenotypes depending on high-fat-diet duration, highlighting the dynamic contributions of MMe macrophages in obesity.

Highlights

- Inflammation and dead adipocyte clearance by MMe macrophages require NOX2
- *Nox2*$^{-/-}$ improves the metabolic phenotype in early DIO but worsens it in late DIO
- Early improvements associate with suppressed ATM inflammation
- Late worsening associates with lower ATM lysosomal exocytosis to dead adipocytes

Summary Abstract

Nejdůležitější, shrnutí celého článku, omezený prostor

Metabolically Activated Adipose Tissue Macrophages Perform Detrimental and Beneficial Functions during Diet-Induced Obesity

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http://dx.doi.org/10.1016/j.celrep.2017.08.096

SUMMARY

During obesity, adipose tissue macrophages (ATMs) adopt a metabolically activated (MMe) phenotype. However, the functions of MMe macrophages are poorly understood. Here, we combine proteomic and functional methods to demonstrate that, in addition to potentiating inflammation, MMe macrophages promote dead adipocyte clearance through lysosomal exocytosis. We identify NADPH oxidase 2 (NOX2) as a driver of the inflammatory and adipocyte-clearing properties of MMe macrophages and show that, compared to wild-type, *Nox2*$^{-/-}$ mice exhibit a time-dependent metabolic phenotype during diet-induced obesity. After 8 weeks of high-fat feeding, *Nox2*$^{-/-}$ mice exhibit attenuated ATM inflammation and mildly improved glucose tolerance. After 16 weeks of high-fat feeding, *Nox2*$^{-/-}$ mice develop severe insulin resistance, hepatosteatosis, and visceral lipoatrophy characterized by dead adipocyte accumulation and defective ATM lysosomal exocytosis, a phenotype reproduced in myeloid cell-specific *Nox2*$^{-/-}$ mice. Collectively, our findings suggest that MMe macrophages perform detrimental and beneficial functions whose contribution to metabolic phenotypes during obesity is determined by disease progression.

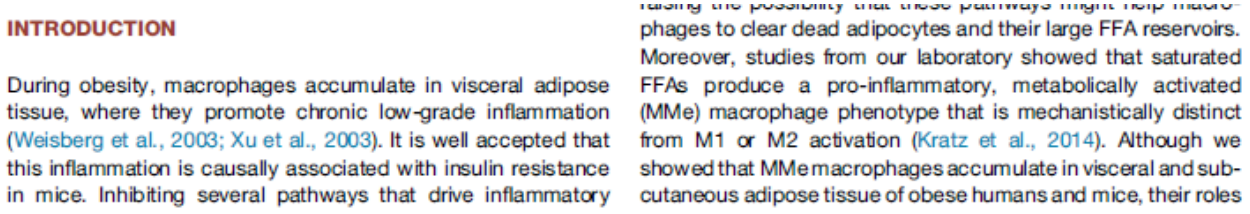
signaling and/or production in macrophages improves insulin sensitivity during obesity (Han et al., 2013; Patsouris et al., 2008; Saberi et al., 2009; Wei et al., 2016).

In addition to producing inflammatory cytokines, adipose tissue macrophages (ATMs) have also been postulated to perform beneficial functions during diet-induced obesity (DIO) (Fitzgibbons and Czech, 2016). They internalize excess free fatty acids (FFAs) released by insulin-resistant adipocytes, thereby buffering metabolic tissues from the damage caused by ectopic accumulation of saturated FFAs. They also clear dead adipocytes that accumulate during prolonged obesity when adipose tissue expands enough to produce hypoxia (Strissel et al., 2007; Sun et al., 2011). The clearance of these dead adipocytes promotes adipocyte turnover and maintains adipose tissue health during nutrient excess.

The diverse functions of macrophages, such as those described earlier, have often been conceptualized through an M1 and M2 paradigm (Gordon and Taylor, 2005). The M1 phenotype is caused by Th1 mediators such as lipopolysaccharide (LPS) and interferon gamma (IFNγ) and is characterized by increased production of pro-inflammatory cytokines, while the M2 phenotype is driven by Th2 mediators (e.g., interleukin-4 [IL-4]), which activates expression of immunosuppressive factors that promote macrophage clearance of dead cells and tissue remodeling (Odegaard et al., 2007). Although this M1/M2 paradigm has been a useful construct for understanding macrophage heterogeneity, studies suggest that it cannot adequately describe the functions of ATMs during obesity.

Studies from Xu et al., (2013) showed that macrophages from obese mice induce lysosomal and lipid metabolism pathways,

úvod - introduction



INTRODUCTION

During obesity, macrophages accumulate in visceral adipose tissue, where they promote chronic low-grade inflammation (Weisberg et al., 2003; Xu et al., 2003). It is well accepted that this inflammation is causally associated with insulin resistance in mice. Inhibiting several pathways that drive inflammatory

phages to clear dead adipocytes and their large FFA reservoirs. Moreover, studies from our laboratory showed that saturated FFAs produce a pro-inflammatory, metabolically activated (MMe) macrophage phenotype that is mechanistically distinct from M1 or M2 activation (Kratz et al., 2014). Although we showed that MMe macrophages accumulate in visceral and subcutaneous adipose tissue of obese humans and mice, their roles

- popis řešené problematiky
  - úvod do problematiky
  - aktuálnost – shrnutí nejnovějších poznatků
  - důležitost – proč je třeba toto studovat
  - popis, co čtenáře čeká v článku, jak článek přispívá k řešení problematiky (výsledky, metody)

Metody

- použitá zvířata, buňky, materiál
- postup experimentů
- použitá statistika
- bývá za úvodem nebo na konci článku

EXPERIMENTAL PROCEDURES

Mice

All animal studies were approved by the University of Chicago Institutional Animal Care and Use Committee (ACUP 72209). Wild-type, *Gp91*$^{-/-}$, *Tlr2*$^{-/-}$, *Tlr4*$^{-/-}$, and *Myd88*$^{-/-}$ male mice on the C57BL/6 background are from Jackson Laboratory. For DIO studies, wild-type, *Gp91*$^{-/-}$, *Tlr2*$^{-/-}$, and *Tlr4*$^{-/-}$ mice were placed on an LFD or HFD (45% fat, Research Diets, D12451) at 8 weeks of age for up to 16 weeks.

Nox2$^{fl/fl}$ Mice

Nox2$^{fl/fl}$ mice were described (Sag et al., 2017) and were crossed with *LysM-cre* knockin mice (Jackson Laboratory, 004781) to generate LysM-cre$^{+/-}$ *Nox2*$^{fl/fl}$ mice and littermate control *Nox2*$^{fl/fl}$ mice. See Supplemental Experimental Procedures for genotyping details.

Differentiation and Activation of BMDMs

Murine BMDMs were differentiated from bone marrow stem cells as previously described (Kratz et al., 2014). For M1 activation, BMDMs were treated with LPS (5 ng/mL) and IFNγ (12 ng/mL) for 24 hr. For MMe activation, macrophages were treated with a combination of glucose (30 mM), insulin (10 nM), and palmitate (0.4 mM) for 24 hr. Macrophages were also treated with media conditioned by live 3T3-L1 adipocytes, apoptotic 3T3-L1 adipocytes, or apoptotic neutrophils for 24 hr.

Výsledky - Results

- Popis výsledků
- může být dohromady s diskuzí
- Obrázky s popisem v textu i v legendě
- Statistika
- Většinou neobsahují reference

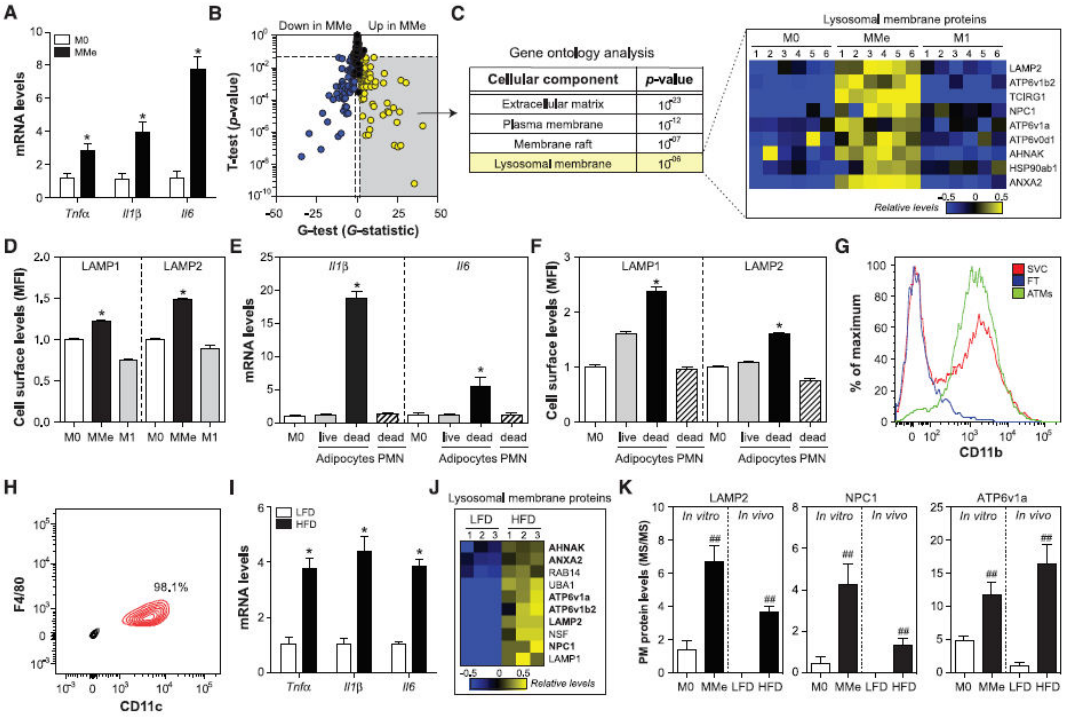


Figure 1. MMe Macrophages Overexpress Cytokines and Accumulate Cell Surface Lysosomal Membrane Proteins In Vitro and In Vivo

(A–D) BMDMs (M0) were metabolically activated (MMe) or classically activated (M1). (A) Inflammatory cytokine expression levels. (B) Plasma membrane proteomics analysis with the t test and G test identifies proteins induced (yellow) and suppressed (blue) on the cell surface of MMe macrophages (relative to M0). (C) Gene ontology analysis of plasma membrane proteins elevated on the cell surface of MMe macrophages (relative to M0). Relative abundances of proteins are presented as a heatmap. (D) Flow cytometric quantification of cell surface LAMP1 and LAMP2.

(E and F) BMDMs (M0) were treated with conditioned media collected from 3T3-L1 adipocytes (live or apoptotic) or apoptotic neutrophils (polymorphonuclear neutrophils [PMN]). (E) Inflammatory cytokine expression levels. (F) Flow cytometric quantification of cell surface LAMP1 and LAMP2.

(G–J) Analysis of ATMs from C57BL/6 mice fed a low-fat (LFD) or high-fat diet (HFD) for 16 weeks. (G) ATMs were isolated from the stromal vascular fraction (SVC) using anti-CD11b-coupled magnetic beads. ATM purity and recover were confirmed by staining for CD11b in the purified ATMs, SVC, and flowthrough (FT). (H) ATM purity was assessed by staining for CD11c and F4/80. (I) Inflammatory cytokine expression levels. (J) Heatmap of the relative abundance of cell surface lysosomal membrane proteins.

(K) A comparison of cell surface levels of LAMP2, NPC1, and ATP6v1a in vitro and in vivo; proteins were quantified by mass spectrometry.

Results are mean ± SEM; n = 3–6, *p < 0.05 Student's t test, ##p < 0.05 Student's t test and G > 1.5 G test. See also Figure S1 and Table S1.

Results are mean ± SEM; n = 5–15, *p < 0.05 Student's t test. !

Diskuze

- Vyvození závěrů z výsledků
- porovnání s literaturou – shoduje se/odporuje

DISCUSSION

Accumulating evidence suggests that ATMs perform both detrimental and beneficial functions during obesity. They produce inflammatory cytokines that promote insulin resistance (Chawla et al., 2011; Olefsky and Glass, 2010). They also might protect metabolic tissues from the deleterious effects of excess FFAs and contribute to adipose tissue homeostasis by clearing dead adipocytes. Traditionally, these diverse functions have been attributed to distinct ATM populations; the detrimental functions have been associated with M1-like macrophages, which may predominate during early DIO (Lumeng et al., 2007), while the beneficial functions have been ascribed to M2-like macrophages, which may accumulate during prolonged DIO (Shaul et al., 2010).

Here we provide evidence that inflammatory cytokine production and dead adipocyte clearance are functional properties of a single MMe macrophage phenotype that is present during early and late DIO. We further show that inflammatory signaling through NOX2, TLR2, and MYD88 coordinately regulates both the detrimental and the beneficial functions of MMe macrophages. Accordingly, ablating *Nox2* produces a complex metabolic phenotype determined by the duration of high-fat feeding, which in turn highlights the relative importance of macrophage

Závěr - conclusion

- shrnutí toho, co článek přinesl
- výhled do budoucna

Poděkování - Acknowledgements

- granty, financování
- poděkování neautorům

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, seven figures, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.celrep.2017.08.096.

AUTHOR CONTRIBUTIONS

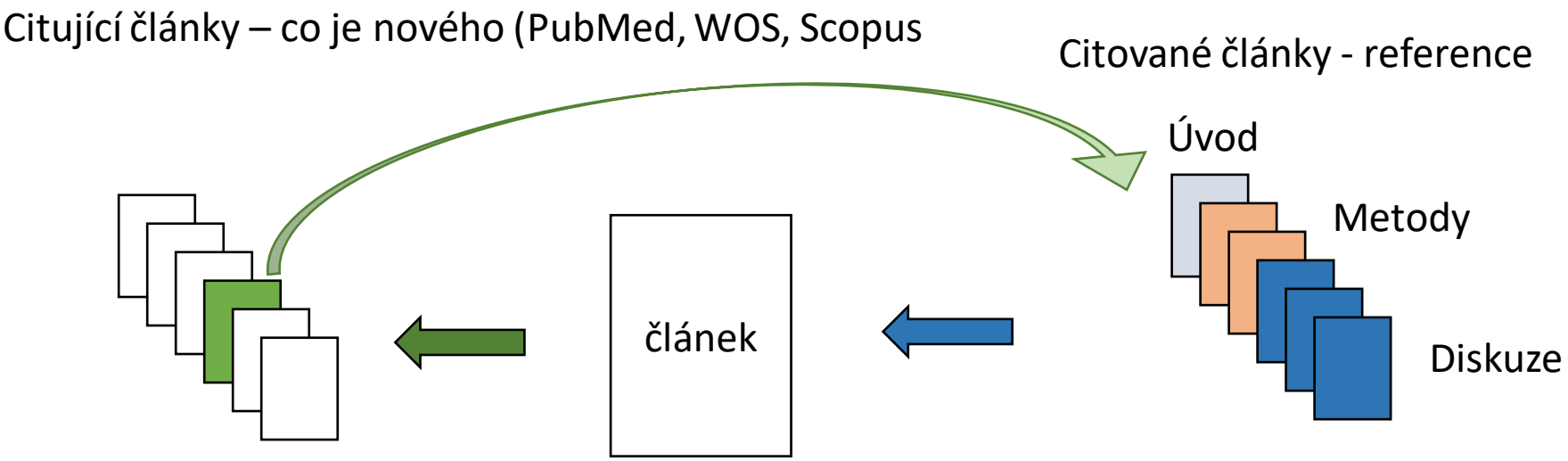
Conceptualization, all authors; Investigation, B.R.C., K.Q.S., V.C.B.-L., G.Z., E.P., A.H., S.F., L.Z., B.A.H., A.S.H., and C.C.; Writing – Original Draft, L.B.; Writing – Reviewing & Editing, all authors; Supervision, L.B. and F.R.M.; Funding Acquisition, L.B. and F.R.M.

ACKNOWLEDGMENTS

This research was supported by grants from the NIH (R01DK102960 to L.B.; R37DK27083 to F.R.M.; R01HL093324 to F.R.M.; R01DK055267 to C.J.R.; P30 DK020595 to the DRTC Cell Biology Core, University of Chicago; T32DK087703 as support for B.R.C. and S.F.; and T32DK007074 as support for A.H.), the Bernice Goldblatt Endowment Fellowship, the University of Chicago (as support for C.C.), and the American Heart Association (10SDG3600027 to L.B.).

Seznam referencí

- různé styly – dle časopisu
- (Smith et al., 2018), [1], (1), [1]
- možno používat programy – EndNote, Mendeley
- https://www.mendeley.com/
- reference důležité pro „křížové“ vyhledávání



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- Výsledky výzkumu, metody, spekulace, atd.
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  - Fabrication, Falsification, Plagiarism

Jak postupovat při zpracovávání tématu

1. Obecná znalost problematiky – učebnice (nové!), wiki, google – O co jde?
2. Review – obvykle shrnuje úžeji vymezenou část, detailnější porozumění kontextu, termíny, zkratky. Vyhledávám v databázích pomocí specifických a úžeji vymezujících termínů.
3. Původní výzkum – obsahuje původní experimenty, metody, statistiky – nejnáročnější na porozumění (zkratky, hutná formulace, předpokládá se znalost problematiky)

Jak pracovat s textem

1. Přečíst abstrakt – zjistím, jestli mě to zajímá
2. Zajímá mě výsledek → projdu v rychlosti obrázky a závěr
3. Zajímají mě metody → Projdu celé metody
4. Zajímá mě, co z toho plyne → Abstrakt, Diskuze, Závěr
5. Zajímá mě vše →pečlivě prostuduju celý článek
6. Pozor na supplementary data

Databáze publikací a vyhledávače

- **PubMed** - nejdůležitější
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- Wiley online library
- GoPubMed – umožňuje hledat v souvislostech
- Web of Science – navíc citace, profily autorů, IF,…
- Scopus – podobně jako WoS, širší záběr

NCBI – National Centre for Biotechnology information

- https://www.ncbi.nlm.nih.gov
- přes 40 databází – nukleotidy, proteiny, struktury, genomy, transkriptomy,…
- PubMed – biomedicínská literatura (nejen)
- https://www.ncbi.nlm.nih.gov/pubmed/

Jak používat PubMed

- klíčová slova – oddělená mezerou, každé další slovo upřesňuje výraz
- Hledání autorů – Smith JC
- Stopwords –výrazy typu and, about, with, mainly, and, using,… **jsou ignorovány**
- Advanced – možnost hledat konkrétněji, vyloučit některé termíny atd.
- Postranní lišty u seznamu nalezených článků
  - levá – omezení výběru dle typu článku, dostupnosti, stáří
  - pravá – rok, podobné hledání, obrázky, jiné databáze, úprava hledaného výrazu, nedávná aktivita

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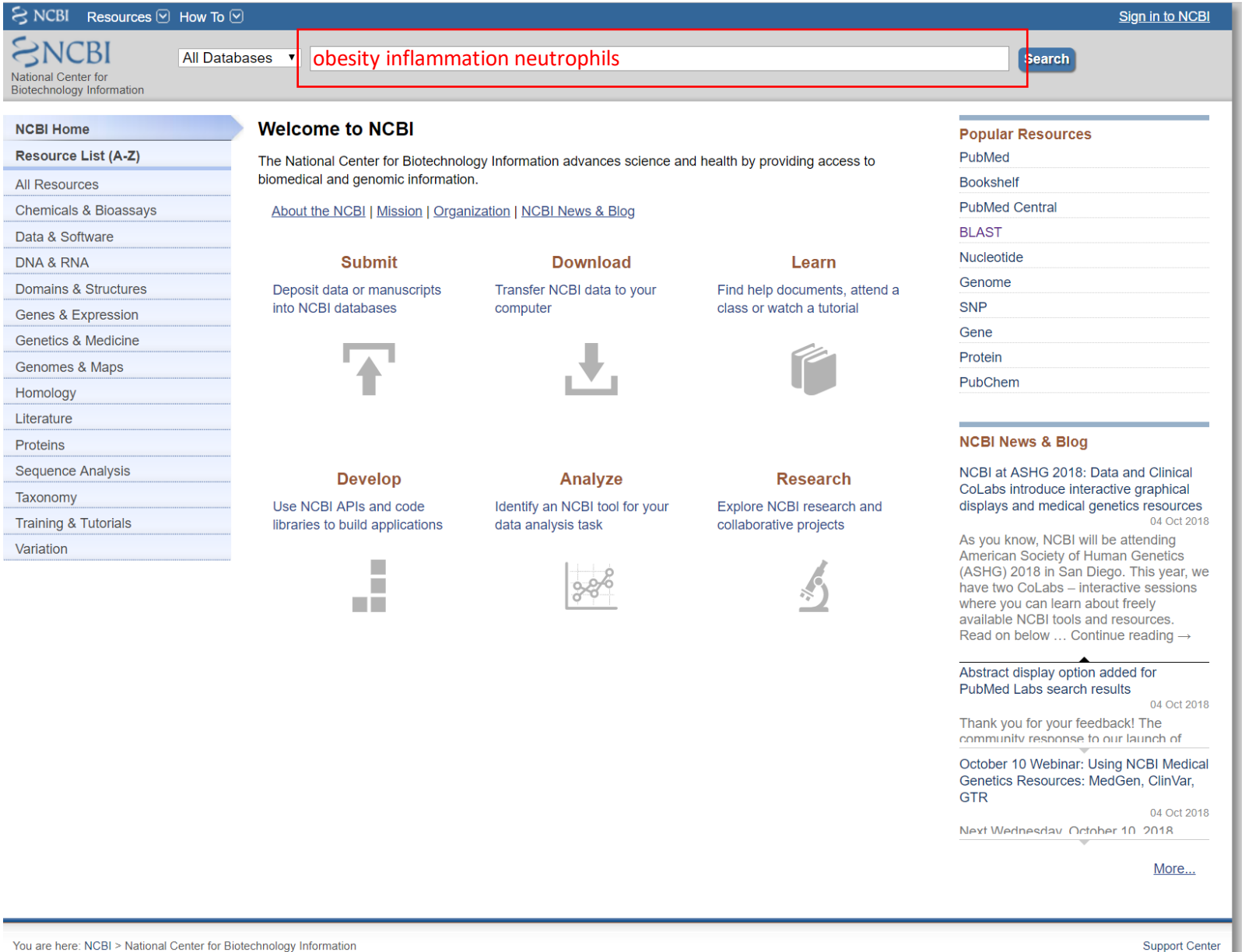

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Genes

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GEO DataSets	4	Functional genomics studies
GEO Profiles	3	Gene expression and molecular abundance profiles
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PopSet	0	Sequence sets from phylogenetic and population studies
UniGene	0	Clusters of expressed transcripts

Genetics

ClinVar	0	Human variations of clinical significance
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GTR	6	Genetic testing registry
MedGen	0	Medical genetics literature and links
OMIM	11	Online mendelian inheritance in man
SNP	0	Short genetic variations

Proteins

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Structure	1	Experimentally-determined biomolecular structures

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FASEB J. 2017 Sep 13. pii: fj.201700372RR. doi: 10.1096/fj.201700372RR. [Epub ahead of print]
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2. Adipose Tissue **Inflammation** Induces B Cell **Inflammation** and Decreases B Cell Function in Aging.
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Front Immunol. 2017 Aug 28;8:1003. doi: 10.3389/fimmu.2017.01003. eCollection 2017. Review.
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3. Immunomodulatory effects of anesthetics in obese patients.
Heil LBB, Silva PL, Pelosi P, Rocco PRM.
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4. Effect of Low vs. High Intensity Exercise Training on Biomarkers of **Inflammation** and Endothelial Dysfunction in Adolescents With **Obesity**: A 6-Month Randomized Exercise Intervention Study.
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Turn Off Clear

J Clin Invest. 2003 Dec;112(12):1796-808.

Obesity is associated with macrophage accumulation in adipose tissue.

Weisberg SP[1], McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr.

Author information

Abstract

Obesity alters adipose tissue metabolic and endocrine function and leads to an increased release of fatty acids, hormones, and proinflammatory molecules that contribute to obesity associated complications. To further characterize the changes that occur in adipose tissue with increasing adiposity, we profiled transcript expression in perigonadal adipose tissue from groups of mice in which adiposity varied due to sex, diet, and the obesity-related mutations agouti (Ay) and obese (Lepob). We found that the expression of 1,304 transcripts correlated significantly with body mass. Of the 100 most significantly correlated genes, 30% encoded proteins that are characteristic of macrophages and are positively correlated with body mass. Immunohistochemical analysis of perigonadal, perirenal, mesenteric, and subcutaneous adipose tissue revealed that the percentage of cells expressing the macrophage marker F4/80 (F4/80+) was significantly and positively correlated with both adipocyte size and body mass. Similar relationships were found in human subcutaneous adipose tissue stained for the macrophage antigen CD68. Bone marrow transplant studies and quantitation of macrophage number in adipose tissue from macrophage-deficient (Csf1op/op) mice suggest that these F4/80+ cells are CSF-1 dependent, bone marrow-derived adipose tissue macrophages. Expression analysis of macrophage and nonmacrophage cell populations isolated from adipose tissue demonstrates that adipose tissue macrophages are responsible for almost all adipose tissue TNF-alpha expression and significant amounts of iNOS and IL-6 expression. Adipose tissue macrophage numbers increase in obesity and participate in inflammatory pathways that are activated in adipose tissues of obese individuals.

Comment in

Leptin Deficiency Shifts Mast Cells toward Anti-Inflammatory Actions and Protects Mice from Obesity and Diabetes by Polarizing M2 Macrophages. [Cell Metab. 2015]

Obesity-induced inflammatory changes in adipose tissue. [J Clin Invest. 2003]

PMID: 14679176 PMCID: PMC296995 DOI: 10.1172/JCI19246

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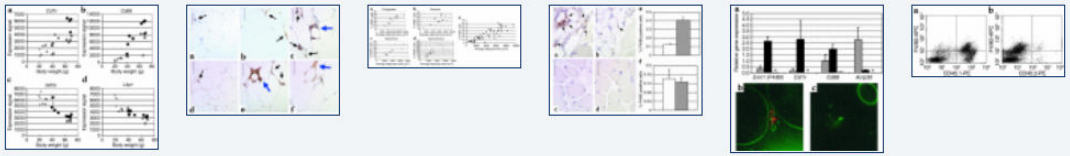

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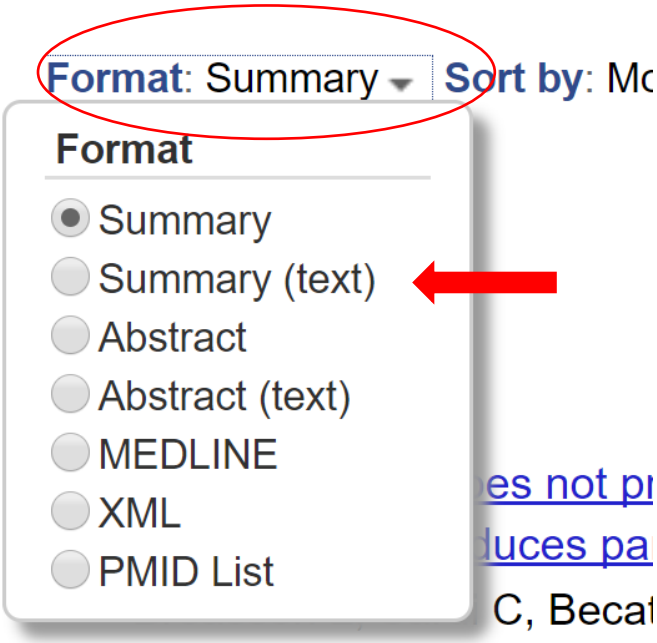

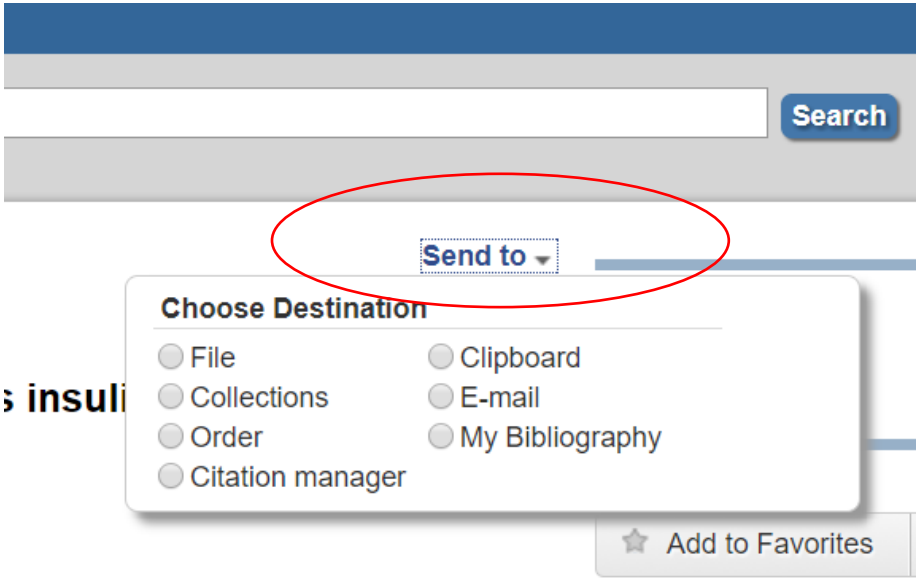

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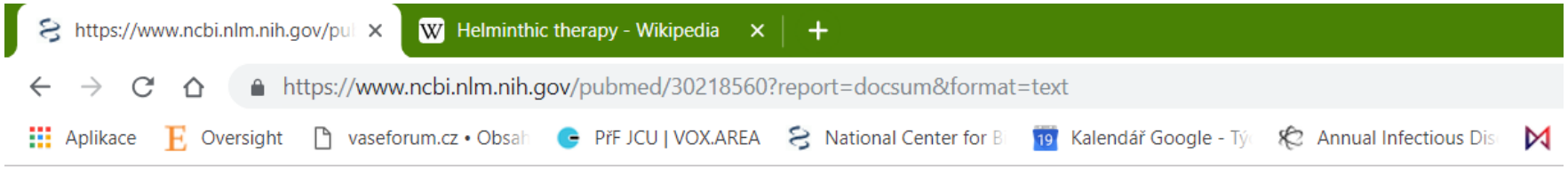

1: Gałecki P, Talarowska M. Inflammatory theory of depression. Psychiatr Pol. 2018 Jun 30;52(3):437-447. doi: 10.12740/PP/76863. Epub 2018 Jun 30. Review. English, Polish. PubMed PMID: 30218560.

ZKOPÍROVAT JEN OZNAČENÉ

v textu rešerše citace: (Galecki et al., 2018)

Za textem v referencích dle abecedy:

Gałecki P, Talarowska M. Inflammatory theory of depression. Psychiatr Pol. 2018 Jun 30;52(3):437-447. doi: 10.12740/PP/76863.

Jak na přípravu prezentace

1. Porozumět tématu – o čem článek je (nemoc, metoda, mechanismus,…)
2. Porozumět jednotlivým termínům – buněčné populace, proteiny, molekuly, léčiva,… - co je co
3. Porozumět zkratkám
    1. Specifická pravidla - jména myších kmenů, jména genů, proteinů, buněčných linií, mutací, transgenů
    2. Dohodnutá nomenklatura – CD markery (cluster of differentiation)

mutace - (c.236C>G; p.S79W)

mutace v proteinu - G2019S

$Kit^{W\text{-}sh/W\text{-}sh}$

$mcpt4^{-/-}$

$mcpt4^{+/-}$

protein - TNF

gen - tnf

Prezentace

- úvod k tématu – 1-2 slidy o oblasti výzkumu – důležitost výzkumu, základní pojmy, mechanismy důležité k pochopení článku
- Co chtěli autoři zjistit
- Co zjistili a jak to dělali – ukázat obrázek s výsledkem, popsat jak k němu došli
- Co je závěrem práce

Jak na rešerši

- Od obecného ke konkrétnímu
  1. učebnice, wiki, google – základ
  2. Pubmed – vhodná klíčová slova, review
  3. Review – shrnují původní články – práce s referencemi
  4. Původní články
- Struktura
  1. Shrnutí
  2. Úvod
  3. Systematické rozdělení do kapitol – inspirace v review
  4. Závěr
  5. Seznam referencí
- Požadavky
  - reference – učebnice (max 2), review (2 – 4), původní výzkum (min 5)
  - rozsah 5 – 10 stran A4 včetně referencí, 12pt, max 1,5 řádkování
  - může být obrázek (vlastní) – grafický abstrakt