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Eosinophil function in adipose tissue is regulated by Krüppel-like factor 3 (KLF3)

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Abstract
The conversion of white adipocytes to thermogenic beige adipocytes represents a potential mechanism to treat obesity and related metabolic disorders. However, the mechanisms involved in converting white to beige adipose tissue remain incompletely understood. Here we show profound beiging in a genetic mouse model lacking the transcriptional repressor Krüppel-like factor 3 (KLF3). Bone marrow transplants from these animals confer the beige phenotype on wild type recipients. Analysis of the cellular and molecular changes reveal an accumulation of eosinophils in adipose tissue. We examine the transcriptomic profile of adipose-resident eosinophils and posit that KLF3 regulates adipose tissue function via transcriptional control of secreted molecules linked to beiging. Furthermore, we provide evidence that eosinophils may directly act on adipocytes to drive beiging and highlight the critical role of these little-understood immune cells in thermogenesis. © 2020, The Author(s).

Index Keywords
cell component, disability, molecular analysis, physiology; adipocyte, adipose tissue, adult, animal cell, animal experiment, animal model, article, bone marrow transplantation, controlled study, eosinophil, human, immunocompetent cell, male, mouse, mouse model, nonhuman, phenotype, repressor gene, resident, thermogenesis, wild type, adipose tissue, animal, Chlorocebus aethiops, chromatin immunoprecipitation, CV-1 cell line, eosinophil, flow cytometry, genetics, metabolism, obesity, physiology, signal transduction, software; Animalia; Klf3 protein, mouse, kruppel like factor; Adipose Tissue, Adiposity, Animals, Chlorocebus aethiops, Chromatin Immunoprecipitation, COS Cells, Eosinophils, Flow Cytometry, Kruppel-Like Transcription Factors, Male, Mice, Obesity, Signal Transduction, Software

Chemicals/CAS
Klf3 protein, mouse; Kruppel-Like Transcription Factors

References

- Wu, J.
  Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human
  (2012) *Cell*, 150, pp. 366-376.
  COI: 1:CAS:528:DC%2BC38XhtVekur3I, PID: 22796012

- Wu, J., Cohen, P., Spiegelman, B.M.
  Adaptive thermogenesis in adipocytes: is beige the new brown?
  (2013) *Genes Dev.*, 27, pp. 234-250.
  COI: 1:CAS:528:DC%2BC3sXjt1Cgtr0%3D, PID: 23388824

- Qiu, Y.
  Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat
  (2014) *Cell*, 157, pp. 1292-1308.
  COI: 1:CAS:528:DC%2BC2cXpslagtrs%3D, PID: 24906148

- Wu, D.
  Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis
  (2011) *Science*, 332, pp. 243-247.
  COI: 1:CAS:528:DC%2BC3MXksV2qtbw%3D, PID: 21436399

- Rao, R.R.
  Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis
  (2014) *Cell*, 157, pp. 1279-1291.
  COI: 1:CAS:528:DC%2BC2cXpslagtrg%3D, PID: 24906147

- Lee, E.-H.
  Eosinophils support adipocyte maturation and promote glucose tolerance in obesity
  (2018) *Sci. Rep.*, 8.
  PID: 29967467

- Bolus, W.R.
  Elevating adipose eosinophils in obese mice to physiologically normal levels does not rescue metabolic impairments
  (2018) *Mol. Metab.*, 8, pp. 86-95.
  COI: 1:CAS:528:DC%2BC2sXitVWls7bN, PID: 29306658

- Nguyen, K.D.
  Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis
  (2011) *Nature*, 480, pp. 104-108.
  COI: 1:CAS:528:DC%2BC3MXhsV2gtr3J, PID: 22101429

- Pirzgalska, R.M.
  Sympathetic neuron[−]associated macrophages contribute to obesity by importing and metabolizing norepinephrine
  (2017) *Nat. Med*, 23, pp. 1309-1318.
  COI: 1:CAS:528:DC%2BC2sXhs1aisrzN, PID: 29035364

- Camell, C.D.
  Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing
  (2017) *Nature*, 550, pp. 119-123.
  COI: 1:CAS:528:DC%2BC2sXhsFKmsL%2FI, PID: 28953873

- Fischer, K.
  Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis
  (2017) *Nat. Med*, 23, pp. 623-630.
  COI: 1:CAS:528:DC%2BC2sXmtFGhtLg%3D, PID: 28414329

- Bell-Anderson, K.S.
  Loss of Kruppel-like factor 3 (KLF3/BKLF) leads to upregulation of the insulin-sensitizing factor adipolin (FAM132A/CTRP12/C1qdc2)
  (2013) *Diabetes*, 62, pp. 2728-2737.
  COI: 1:CAS:528:DC%2BC3sXht1Snu7vI, PID: 23633521

- Sue, N.
  Targeted disruption of the basic Kruppel-like factor gene (Klf3) reveals a role in adipogenesis
  (2008) *Mol. Cell Biol.*, 28, pp. 3967-3978.
  COI: 1:CAS:528:DC%2BD1cXntFanurY%3D, PID: 18391014

- Brestoff, J.R.
  Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity
  (2015) *Nature*, 519, pp. 242-246.
  COI: 1:CAS:528:DC%2BC2cXitFKltb%2FP, PID: 25533952

- Lee, M.W.
  Activated type 2 innate lymphoid cells regulate beige fat biogenesis
  (2015) *Cell*, 160, pp. 74-87.
  COI: 1:CAS:528:DC%2BC2MXnslGlsw%3D%3D, PID: 25543153

- Min, S.Y.
  Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice
  (2016) *Nat. Med.*, 22, pp. 312-318.
  COI: 1:CAS:528:DC%2BC28XhsFyisrg%3D, PID: 26808348

- Jia, R.
  Characterization of cold-induced remodelling reveals depot-specific differences across and within brown and white adipose tissues in mice
  (2016) *Acta Physiol.*, 217, pp. 311-324.
  COI: 1:CAS:528:DC%2BC28XmsF2qsbs%3D

- Ghorbani, M., Himms-Hagen, J.
  Appearance of brown adipocytes in white adipose tissue during CL 316,243-induced reversal of obesity and diabetes in Zucker fa/fa rats
  (1997) *Int. J. Obes. (Lond.)*, 21, pp. 465-475.
  COI: 1:CAS:528:DyaK2sXksVWqsrY%3D

- Harms, M., Seale, P.
  Brown and beige fat: development, function and therapeutic potential
  (2013) *Nat. Med.*, 19, pp. 1252-1263.
  COI: 1:CAS:528:DC%2BC3sXhsFOit7vM, PID: 24100998

- Seale, P.
  Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice
  (2011) *J. Clin. Investig.*, 121, pp. 96-105.
  COI: 1:CAS:528:DC%2BC3MXis1ynsA%3D%3D, PID: 21123942

- Roh, H.C.
  Warming Induces Significant Reprogramming of Beige, but Not Brown, Adipocyte Cellular Identity
  (2018) *Cell Metab.*, 27, pp. 1121-1137. e5.
  COI: 1:CAS:528:DC%2BC1cXnsFCks7k%3D, PID: 29657031

- Pollard, A.E.
  AMPK activation protects against diet-induced obesity through Ucp1-independent thermogenesis in subcutaneous white adipose tissue
  (2019) *Nat. Metab.*, 1, pp. 340-349.
  COI: 1:CAS:528:DC%2BB3cXks1Krs7k%3D, PID: 30887000

- Ikeda, K.
  UCP1-independent signaling involving SERCA2b-mediated calcium cycling regulates beige fat thermogenesis and systemic glucose homeostasis
  (2017) *Nat. Med*, 23, pp. 1454-1465.
  COI: 1:CAS:528:DC%2BC2sXhsl2ntLbP, PID: 29131158

- Kazak, L.
  Ablation of adipocyte creatine transport impairs thermogenesis and causes diet-induced obesity
  (2019) *Nat. Metab.*, 1, pp. 360-370.
  COI: 1:CAS:528:DC%2BB3cXks1Krs7g%3D, PID: 31161155

- Kazak, L.
  A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat

(2015) *Cell*, 163, pp. 643-655.
COI: 1:CAS:528:DC%2BC2MXhslWrsLnL, PID: 26496606

- Ye, L.
  Fat cells directly sense temperature to activate thermogenesis
  (2013) *Proc. Natl Acad. Sci. USA*, 110, pp. 12480-12485.
  COI: 1:CAS:528:DC%2BC3sXht1emu7bE, PID: 23818608

- Davis, T.R.
  Chamber cold acclimatization in man
  (1961) *J. Appl. Physiol.*, 16, pp. 1011-1015.
  COI: 1:STN:280:DyaF38%2FisFakug%3D%3D, PID: 13883973

- Passmore, R., Durnin, J.V.
  Human energy expenditure
  (1955) *Physiol. Rev.*, 35, pp. 801-840.
  COI: 1:STN:280:DyaG28%2FhvVClsA%3D%3D, PID: 13266530

- Knights, A.J.
  Kruppel-like factor 3 (KLF3/BKLF) is required for widespread repression of the inflammatory modulator galectin-3 (Lgals3)
  (2016) *J. Biol. Chem.*, 291, pp. 16048-16058.
  COI: 1:CAS:528:DC%2BC28Xht1GisbjJ, PID: 27226561

- Knights, A.J.
  Krüppel-like factor 3 (KLF3) suppresses NF-kB–driven inflammation in mice
  (2020) *J. Biol. Chem.*,
  https://doi.org/10.1074/jbc.RA120.013114

- Funnell, A.P.
  Generation of mice deficient in both KLF3/BKLF and KLF8 reveals a genetic interaction and a role for these factors in embryonic globin gene silencing
  (2013) *Mol. Cell Biol.*, 33, pp. 2976-2987.
  COI: 1:CAS:528:DC%2BC3sXht1arur7N, PID: 23716600

- Funnell, A.P.
  The CACCC-binding protein KLF3/BKLF represses a subset of KLF1/EKLF target genes and is required for proper erythroid maturation in vivo
  (2012) *Mol. Cell Biol.*, 32, pp. 3281-3292.
  COI: 1:CAS:528:DC%2BC38XhtF2itrnP, PID: 22711990

- Vu, T.T.
  Impaired B cell development in the absence of Kruppel-like factor 3
  (2011) *J. Immunol.*, 187, pp. 5032-5042.
  COI: 1:CAS:528:DC%2BC3MXhsVSitLfJ, PID: 22003205

- Heng, T.S., Painter, M.W.
  The Immunological Genome Project: networks of gene expression in immune cells
  (2008) *Nat. Immunol.*, 9, pp. 1091-1094.
  COI: 1:CAS:528:DC%2BD1cXhtFeit7zE, PID: 18800157

- Lucas, E.C.
  Haemopedia RNA-seq: a database of gene expression during haematopoiesis in mice and humans
  (2018) *Nucleic Acids Res*, 47, pp. D780-D785.

- de Graaf, C.A.
  Haemopedia: An Expression Atlas of Murine Hematopoietic Cells
  (2016) *Stem Cell Rep.*, 7, pp. 571-582.

- Abugessaisa, I.
  FANTOM5 transcriptome catalog of cellular states based on Semantic MediaWiki
  (2016) *Database*, 2016.

- Bouffi, C.
  Transcription factor repertoire of homeostatic eosinophilopoiesis
  (2015) *J. Immunol.*, 195, pp. 2683-2695.
  COI: 1:CAS:528:DC%2BC2MXhsVygs7bP, PID: 26268651

- Lee, S.D., Tontonoz, P.
  Eosinophils in fat: pink is the new brown
  (2014) *Cell*, 157, pp. 1249-1250.
  COI: 1:CAS:528:DC%2BC2cXpslagt7w%3D, PID: 24906141

- Knights, A.J., Vohralik, E.J., Hoehn, K.L., Crossley, M., Quinlan, K.G.R.
  Defining eosinophil function in adiposity and weight loss
  (2018) *Bioessays*, 40.
  PID: 30132936

- Vohralik, E.J., Psaila, A.M., Knights, A.J., Quinlan, K.G.R.
  EoTHINophils: Eosinophils as key players in adipose tissue homeostasis
  (2020) *Clin. Exp. Pharmacol. Physiol.*,
  (,)

- Eaton, S.A.
  A network of Kruppel-like factors (Klfs). Klf8 is repressed by Klf3 and activated by Klf1 in vivo
  (2008) *J. Biol. Chem.*, 283, pp. 26937-26947.
  COI: 1:CAS:528:DC%2BD1cXhtFKhu7bI, PID: 18687676

- Suo, J., Zhao, X., Guo, X., Zhao, X.
  Met-enkephalin improves metabolic syndrome in high fat diet challenged mice through promotion of adipose tissue browning
  (2018) *Toxicol. Appl. Pharm.*, 359, pp. 12-23.
  COI: 1:CAS:528:DC%2BC1cXhslOjt7vE

- Zuberi, R.I.
  Critical role for galectin-3 in airway inflammation and bronchial hyperresponsiveness in a murine model of asthma
  (2004) *Am. J. Pathol.*, 165, pp. 2045-2053.
  COI: 1:CAS:528:DC%2BD2MXhs1Kntg%3D%3D, PID: 15579447

- Ge, X.N., Ha, S.G., Liu, F.T., Rao, S.P., Sriramarao, P.
  Eosinophil-expressed galectin-3 regulates cell trafficking and migration
  (2013) *Front Pharm.*, 4, p. 37.
  COI: 1:CAS:528:DC%2BC3sXms12qtLg%3D

- Vasanthakumar, A.
  The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells
  (2015) *Nat. Immunol.*, 16, pp. 276-285.
  COI: 1:CAS:528:DC%2BC2MXpvFWhtg%3D%3D, PID: 25599561

- Han, J.M.
  IL-33 Reverses an obesity-induced deficit in visceral adipose tissue ST2+ T regulatory cells and ameliorates adipose tissue inflammation and insulin resistance
  (2015) *J. Immunol.*, 194, pp. 4777-4783.
  COI: 1:CAS:528:DC%2BC2MXnsFOlu7o%3D, PID: 25870243

- Spallanzani, R.G.
  Distinct immunocyte-promoting and adipocyte-generating stromal components

coordinate adipose tissue immune and metabolic tenors
(2019) *Sci Immunol*, 4, p. eaaw3658.

- Mahlakoiv, T.
Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33
(2019) *Sci. Immunol.*, 4, p. eaax0416.
COI: 1:CAS:528:DC%2BC1MXitV2rt7%2FF, PID: 31053655

- Moysidou, M.
CD8+ T cells in beige adipogenesis and energy homeostasis
(2018) *JCI Insight*, 3.

- Rajbhandari, P.
IL-10 signaling remodels adipose chromatin architecture to limit thermogenesis and energy expenditure
(2018) *Cell*, 172, pp. 218-233. e217.
COI: 1:CAS:528:DC%2BC2sXhvF2js77I, PID: 29249357

- Burdach, J.
Regions outside the DNA-binding domain are critical for proper in vivo specificity of an archetypal zinc finger transcription factor
(2014) *Nucleic Acids Res.*, 42, pp. 276-289.
COI: 1:CAS:528:DC%2BC2cXkvFGj, PID: 24106088

- Coats, B.R.
Metabolically activated adipose tissue macrophages perform detrimental and beneficial functions during diet-induced obesity
(2017) *Cell Rep.*, 20, pp. 3149-3161.
COI: 1:CAS:528:DC%2BC2sXhsFOhs7jP, PID: 28954231

- Lumeng, C.N., Bodzin, J.L., Saltiel, A.R.
Obesity induces a phenotypic switch in adipose tissue macrophage polarization
(2007) *J. Clin. Investig.*, 117, pp. 175-184.
COI: 1:CAS:528:DC%2BD2sXmvV2quw%3D%3D, PID: 17200717

- Jun, H.
An immune-beige adipocyte communication via nicotinic acetylcholine receptor signaling
(2018) *Nat. Med*, 24, pp. 814-822.
COI: 1:CAS:528:DC%2BC1cXhtVShu7vM, PID: 29785025

- Fabbiano, S.
Caloric restriction leads to browning of white adipose tissue through type 2 immune signaling
(2016) *Cell Metab.*, 24, pp. 434-446.
COI: 1:CAS:528:DC%2BC28XhsVWmtLjJ, PID: 27568549

- Abdullahi, A.
IL-6 signal from the bone marrow is required for the browning of white adipose tissue post burn injury
(2017) *Shock*, 47, pp. 33-39.
COI: 1:CAS:528:DC%2BC2sXhsVGru70%3D, PID: 27648696

- Haldar, S.M.
Kruppel-like factor 15 regulates skeletal muscle lipid flux and exercise adaptation
(2012) *Proc. Natl Acad. Sci. USA*, 109, pp. 6739-6744.
COI: 1:CAS:528:DC%2BC38XmslGhtb4%3D, PID: 22493257

- Liao, X.
Kruppel-like factor 4 is critical for transcriptional control of cardiac mitochondrial

homeostasis
(2015) *J. Clin. Investig.*, 125, pp. 3461-3476.
PID: 26241060

- Oishi, Y.
SUMOylation of Kruppel-like transcription factor 5 acts as a molecular switch in transcriptional programs of lipid metabolism involving PPAR-delta
(2008) *Nat. Med*, 14, pp. 656-666.
COI: 1:CAS:528:DC%2BD1cXmvVCnu7s%3D, PID: 18500350

- Loft, A.
Browning of human adipocytes requires KLF11 and reprogramming of PPARgamma superenhancers
(2015) *Genes Dev.*, 29, pp. 7-22.
PID: 25504365

- Guillaumond, F.
Kruppel-like factor KLF10 is a link between the circadian clock and metabolism in liver
(2010) *Mol. Cell Biol.*, 30, pp. 3059-3070.
COI: 1:CAS:528:DC%2BC3cXotFGqsL0%3D, PID: 20385766

- Folch, J., Lees, M., Sloane Stanley, G.H.
A simple method for the isolation and purification of total lipides from animal tissues
(1957) *J. Biol. Chem.*, 226, pp. 497-509.
COI: 1:STN:280:DyaG2s%2FnsFCjtw%3D%3D

- Saito, H.
Establishment and characterization of a new human eosinophilic leukemia cell line
(1985) *Blood*, 66, pp. 1233-1240.
COI: 1:STN:280:DyaL28%2FltFyrug%3D%3D, PID: 2415185

- Ran, F.A.
Genome engineering using the CRISPR-Cas9 system
(2013) *Nat. Protoc.*, 8, pp. 2281-2308.
COI: 1:CAS:528:DC%2BC2cXjvFajsA%3D%3D, PID: 24157548

- Chung, K.-J.
A self-sustained loop of inflammation-driven inhibition of beige adipogenesis in obesity
(2017) *Nat. Immunol.*, 18, pp. 654-664.
COI: 1:CAS:528:DC%2BC2sXmtVGktLw%3D, PID: 28414311

- Schmidt, D.
ChIP-seq: using high-throughput sequencing to discover protein-DNA interactions
(2009) *Methods*, 48, pp. 240-248.
COI: 1:CAS:528:DC%2BD1MXotl2lsrs%3D, PID: 19275939

- Robinson, J.T.
Integrative genomics viewer
(2011) *Nat. Biotechnol.*, 29, pp. 24-26.
COI: 1:CAS:528:DC%2BC3MXjsFWrtg%3D%3D, PID: 21221095

- Thorvaldsdottir, H., Robinson, J.T., Mesirov, J.P.
Integrative Genomics Viewer (IGV): high-performance genomics data visualization and exploration
(2013) *Brief. Bioinform.*, 14, pp. 178-192.
COI: 1:CAS:528:DC%2BC3sXkvFKrur4%3D, PID: 22517427

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