

Serveur Académique Lausannois SERVAL serval.unil.ch

Author Manuscript

Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

Title: Acetate is the master of its fate, genetics, and molecular biology bimonthly update.

Authors: Amati F, Widmann C

Journal: Current opinion in lipidology

Year: 2016 Dec

Volume: 27

Issue: 6

Pages: 636-637

DOI: 10.1097/MOL.0000000000000360

In the absence of a copyright statement, users should assume that standard copyright protection applies, unless the article contains an explicit statement to the contrary. In case of doubt, contact the journal publisher to verify the copyright status of an article.

Acetate is the master of its fate

Francesca Amati and Christian Widmann

Department of Physiology, Lausanne University, Switzerland.

Word counts: 382 (+189 for the “further recommending reading” part)

Address correspondence: Christian Widmann, Department of Physiology, Rue du
Bugnon 7, 1005 Lausanne, Switzerland, Phone: +41 21 692 5123, Fax: +41 21 692
5505, E-mail: Christian.Widmann@unil.ch.

Control of nutrient intake and usage is of paramount importance for cells. This is especially true in conditions of high metabolic and anabolic activity seen in rapidly dividing cells for example. Cancer cells rewire their metabolic pathways to insure that key building blocks required for the synthesis of proteins, amino acids, and lipids are generated. A well-known example comes from the Warburg effect where glycolysis is stimulated in aerobic conditions to produce, besides ATP, metabolic intermediates that will be used for cataplerosis (i.e. synthesis of biomolecules): ribose sugars for nucleotides, glycerol and citrate for lipids, and non-essential amino acids for proteins [1]. Acetate is another bioenergetics substrate that can be used by cells [2]. It can be acquired through diet but can also be derived from ethanol metabolism. Cancer cells can use acetate, alongside glucose, as an important carbon source for lipid synthesis, in particular under stress conditions such as hypoxia [2]. How the acetate conversion to acetyl-CoA, the building block for lipid synthesis, is regulated was unknown. Now a study published by Chinese researchers reveals that acetate controls its own metabolism by regulating the expression of lipogenic enzymes [3]. Exogenous acetate molecules were found on acetylated histones associated with the promoters of fatty acid synthase and acetyl-CoA carboxylase α , key enzymes in the lipogenesis pathway. Hence, exogenous acetate turns on the expression of genes that will promote its conversion to fatty acids. This regulation was mainly occurring in hypoxic conditions. It had little impact on the expression of fatty acid synthase and acetyl-CoA carboxylase α in normoxic conditions. It is known that in the presence of normal levels of oxygen, glucose and glutamine are the main carbon providers for acetyl-CoA (>90%) [4]. In these conditions, it may not be necessary to boost the cell's capacity to convert acetate into acetyl-CoA. However, in hypoxic conditions, the contribution of glucose and glutamine to acetyl-CoA generation drops dramatically and alternative source of carbon are used, acetate in particular [4]. It makes sense consequently that it is in conditions of low oxygen that acetate promotes its

conversion to acetyl-CoA. Acetate therefore controls its own fate in hypoxic cancer cells by epigenetic regulation to ensure that following its conversion to acetyl-CoA, it efficiently flows through the lipogenic pathway to generate the lipid constituents of dividing cells.

Acknowledgements

None

Financial support

C.W. is supported by grants from the Swiss National Science Foundation (no. 31003A_160181/1, CRSII3_154420, and IZLSZ3_148907/1). F.A. is supported by grants from the Swiss National Science Foundation (PZ00P3_149398), the Leenaards foundation and the Fondation pour la Recherche sur le Diabète.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Reference List

1. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB: **The biology of cancer: metabolic reprogramming fuels cell growth and proliferation.** *Cell Metab* 2008, **7**:11-20.
2. Mashimo T, Pichumani K, Vemireddy V, Hatanpaa KJ, Singh DK, Sirasanagandla S, Nannepaga S, Piccirillo SG, Kovacs Z, Foong C, Huang Z, Barnett S, Mickey BE, DeBerardinis RJ, Tu BP, Maher EA, Bachoo RM: **Acetate is a bioenergetic substrate for human glioblastoma and brain metastases.** *Cell* 2014, **159**:1603-1614.
- 3. Gao X, Lin SH, Ren F, Li JT, Chen JJ, Yao CB, Yang HB, Jiang SX, Yan GQ, Wang D, Wang Y, Liu Y, Cai Z, Xu YY, Chen J, Yu W, Yang PY, Lei QY: **Acetate functions as an epigenetic metabolite to promote lipid synthesis under hypoxia.** *Nat. Commun.* 2016, **7**:11960.

This article indicates that acetate, which can be the main carbon source for cells in certain conditions, is physically involved in histone acetylation events that will affect the expression of genes controlling its own utilization. These data further document that carbon sources (here acetate) are not passive when it comes to the manner by which they are metabolized.

4. Kamphorst JJ, Chung MK, Fan J, Rabinowitz JD: **Quantitative analysis of acetyl-CoA production in hypoxic cancer cells reveals substantial contribution from acetate.** *Cancer Metab* 2014, **2**:23.

FURTHER RECOMMENDED READING

Diabetic retinopathy is a frequent microvascular complication and one of today's major causes of blindness [1]. Epidemiological studies have shown that plasma LDL cholesterol levels were not associated with the incidence of retinopathy but with its severity [2;3]. Yu and collaborators present novel evidence for the role of LDL in diabetic retinopathy progression [4]. Injecting human preparations of LDL in the vitreous humour, they observed that oxidized glycated LDL, but not normal LDL, induced inflammation with progressive disruption of retinal layers in diabetic mice but not in non-diabetic mice. Thus, the cytotoxic effect of lipoproteins seems to be linked with the extravasation into the retinal tissue and their modification by glycation and oxidation. This was accompanied with an increased retinal vascular permeability resembling clinical diabetic retinopathy. In addition of retinal inflammation and injuries to retinal vessels, oxidized glycated LDL induced alterations to retinal architecture, impaired function, ER stress and propensity to apoptosis. This data supports the concept that lipoproteins have important consequences in diabetic retinopathy when extravasated and modified. This is of importance in the quest of therapeutic strategies to ameliorate prognosis of diabetic retinopathy and thus preserve vision.

Reference List

1. Leasher JL, Bourne RR, Flaxman SR, Jonas JB, Keeffe J, Naidoo K, Pesudovs K, Price H, White RA, Wong TY, Resnikoff S, Taylor HR: **Global estimates on the number of people blind or visually impaired by diabetic retinopathy: a meta-analysis from 1990 to 2010**. *Diabetes Care* 2016, **39**:1643-1649.
2. Lloyd CE, Klein R, Maser RE, Kuller LH, Becker DJ, Orchard TJ: **The progression of retinopathy over 2 years: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study**. *J.Diabetes Complications* 1995, **9**:140-148.
3. Chew EY, Klein ML, Ferris FL, III, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D: **Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22**. *Arch.Ophthalmol.* 1996, **114**:1079-1084.

4. Yu JY, Du M, Elliott MH, Wu M, Fu D, Yang S, Basu A, Gu X, Ma JX, Aston CE, Lyons TJ: **Extravascular modified lipoproteins: a role in the propagation of diabetic retinopathy in a mouse model of type 1 diabetes.** *Diabetologia* 2016, **59**:2026-2035.