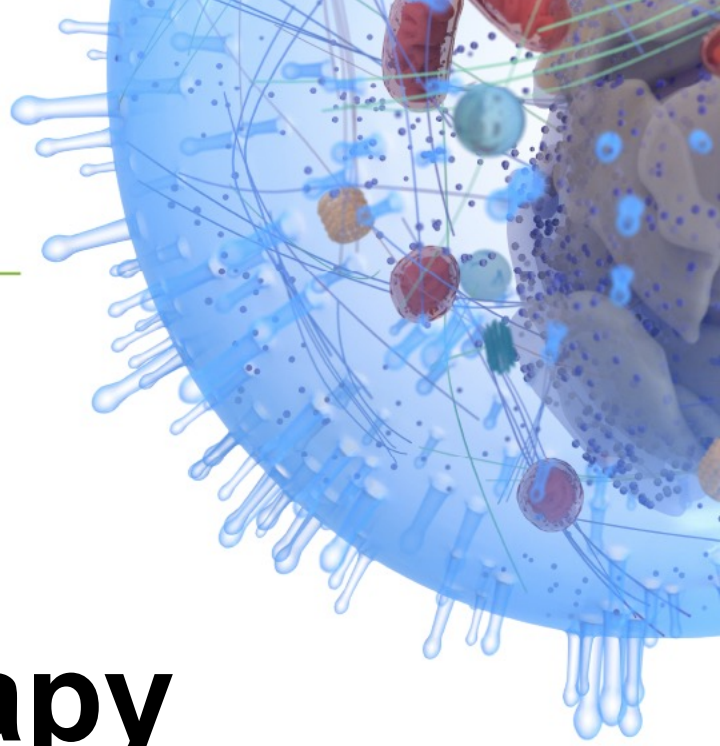


Metformin in cancer therapy

Dr. Matthias Kraft

BioMed-Klinik
Fachklinik für Onkologie,
Immunologie und Hyperthermie
Bad Bergzabern

History of metformin

- Belongs to the so-called class of **biguanides**
- Origin is linked to a plant called ***Galega officinalis*** (goat's rue)
- In 1918 this herbal medicine was shown to reduce blood glucose levels
- Some of its derivatives were used to treat diabetes, but they were withdrawn based on associated toxicities – lactate acidosis

  Bailey C. J., Day C. Metformin: its botanical background. *Practical Diabetes International.* doi: 10.1002/pdi.606
- Jean Stearne followed this discovery up
- In 1957, the use of metformin to treat diabetes was established

  Stearne J. Du nouveau dans les antidiabetiques. La NN dimethylamineguanylguanide *Maroc Médical.* 1957;36:1295–1296

- Metformin was only licensed in the USA in 1994
- Since 2012 it has become the most widely prescribed oral antidiabetic drug in the USA

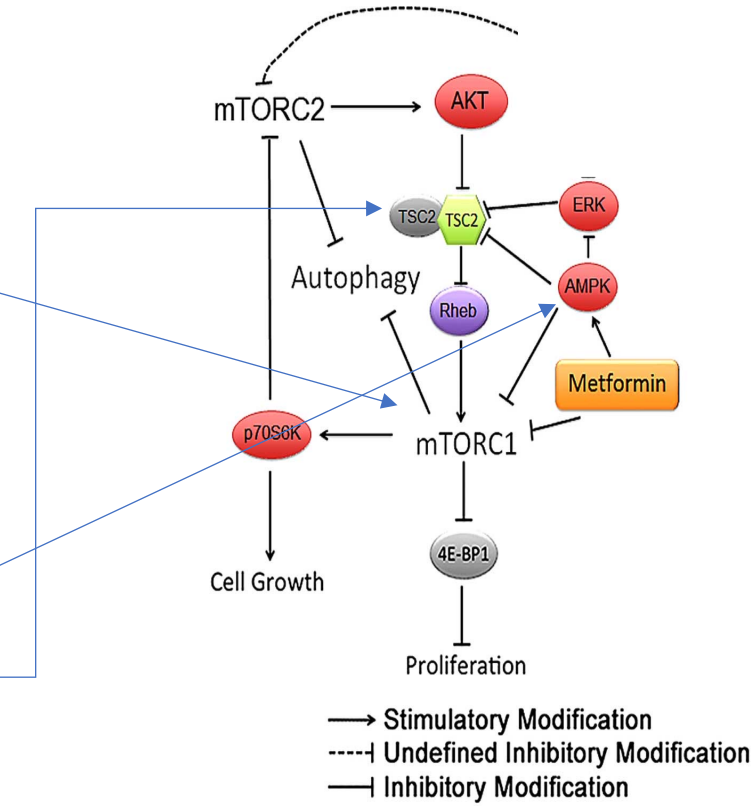
Mechanism of action - Metformin

Metformin and mammalian target of Rapamycin Complex I (mTORC1)

- Inhibition of cancer cell growth by suppressing mTORC1

- mTORC1 is a multiprotein complex composed essentially of
  - protein kinase mTOR and
  - scaffolding protein raptor

- Metformin:
  - upregulates Adenosine monophosphate protein kinase (AMPK)
  - phosphorylates tuberous sclerosis complex (TSC2)
  - thereby promoting its inhibition of mTORC1



Laplante M., Sabatini D. M. mTOR signaling in growth control and disease. *Cell.* 2012;doi: 10.1016/j.cell.2012.03.017

Pezze P. D., Ruf S., Sonntag A. G., et al. A systems study reveals concurrent activation of AMPK and mTOR by amino acids. *Nature Communications.* doi: 10.1038/ncomms13254.

Viollet B., Guigas B., Garcia N. S., Leclerc J., Foretz M., Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clinical Science.* doi: 10.1042/CS20110386.

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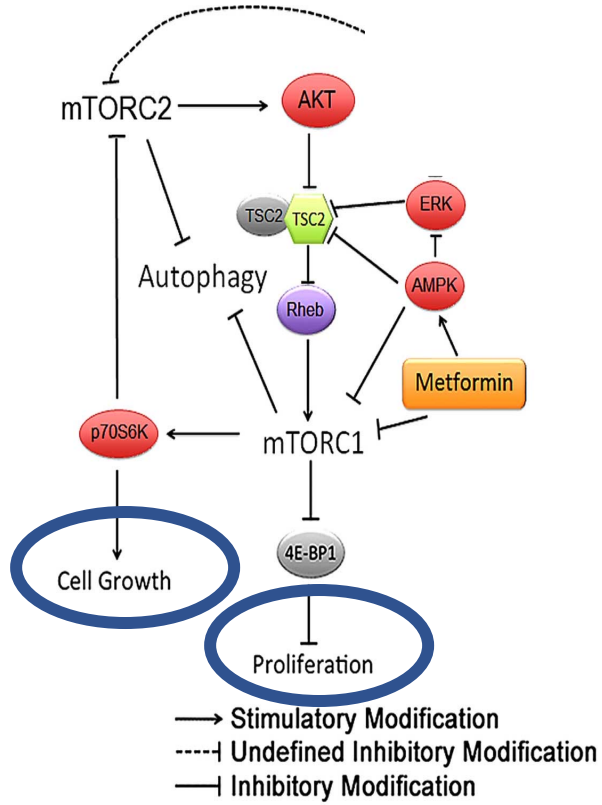
The stimulatory effect of protein synthesis by mTOR emphasizes its role in the metabolism and proliferation of malignant cells



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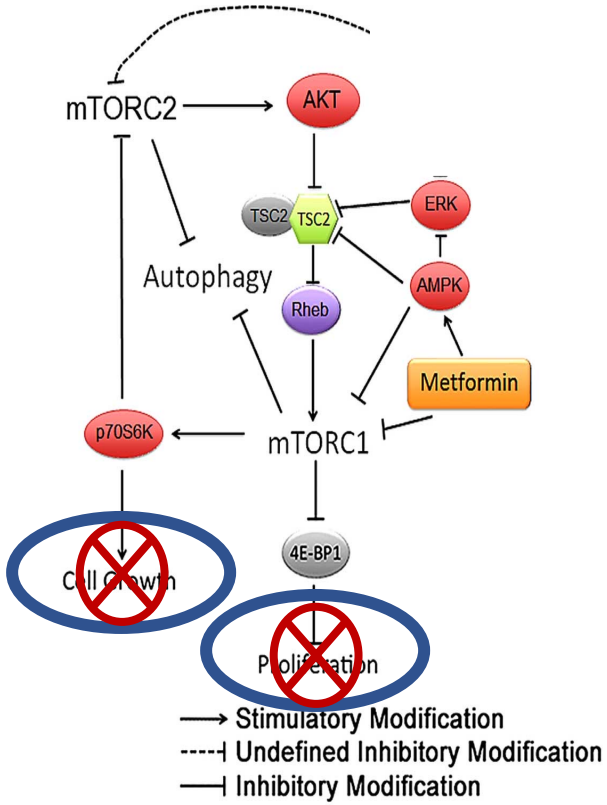
The stimulatory effect of protein synthesis by mTOR emphasizes its role in the metabolism and proliferation of malignant cells which is hampered by metformin



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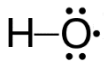
Metformin: Inhibition of ROS

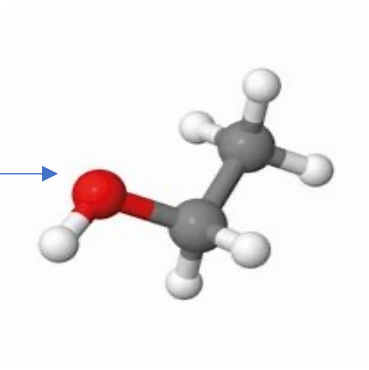
Reactive **O**xygen **S**pecies (**ROS**) signaling pathways are markedly increased in many types of cancer

- they give rise to abnormal proliferation and differentiation

Reactive oxygen species include

- peroxides
- superoxides
- hydroxyl radicals
- singlet oxygen
- alpha oxygen





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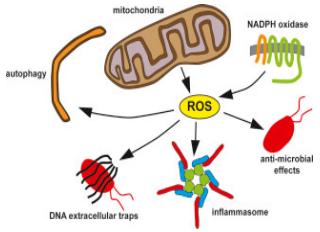


- The inhibition of ROS generation is mediated by the action of metformin complex 1 of the respiratory chain which reduces entry of electrons to the chain in ***mitochondria***
  - Algire, O. Moiseeva, X. Deschenes-Simard et al., "Metformin Reduces Endogenous Reactive Oxygen Species and Associated DNA Damage," *Cancer Prevention Research*, vol. 5, no. 4, pp. 536–543, 2012
- In isolated ***mitochondria*** *in vitro* the concentrations required to directly inhibit complex 1 molecule is high (20-100 mM)
  - G. Vial, D. Detaille, and B. Guigas, "Role of mitochondria in the mechanism(s) of action of metformin," *Frontiers in Endocrinology*, vol. 10, 2019
- *In vivo* inhibition of complex 1 molecule can be achieved with micromolar concentrations
  - B. Wessels, J. Ciapaite, N. M. A. van den Broek, K. Nicolay, and J. J. Prompers, "Metformin impairs mitochondrial function in skeletal muscle of both lean and diabetic rats in a Dose-Dependent manner," *PLoS One*, vol. 9, no. 6, article e100525, 2014
- The explanation is based on the positive charge of metformin which allows **slow accumulation within the mitochondrial matrix**
  - H. R. Bridges, A. J. Jones, M. N. Pollak, and J. Hirst, "Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria," *The Biochemical Journal*, vol. 462, no. 3, pp. 475–487, 2014
- The inhibition of endogenous generation of ROS is **independent of the AMPK*α*** system
  - C. Algire, O. Moiseeva, X. Deschenes-Simard et al., "Metformin Reduces Endogenous Reactive Oxygen Species and Associated DNA Damage," *Cancer Prevention Research*, vol. 5, no. 4, pp. 536–543, 2012
- One of the vital targets of ROS-induced cellular damage is the DNA, with a consequent structural distortion of its integrity (mutation)
  - M. Aljofan and D. Riethmacher, "Anticancer activity of metformin: a systematic review of the literature," *Future Science OA*, vol. 5, no. 8, p. FSO410, 2019.

Metformin and **ADORA1**

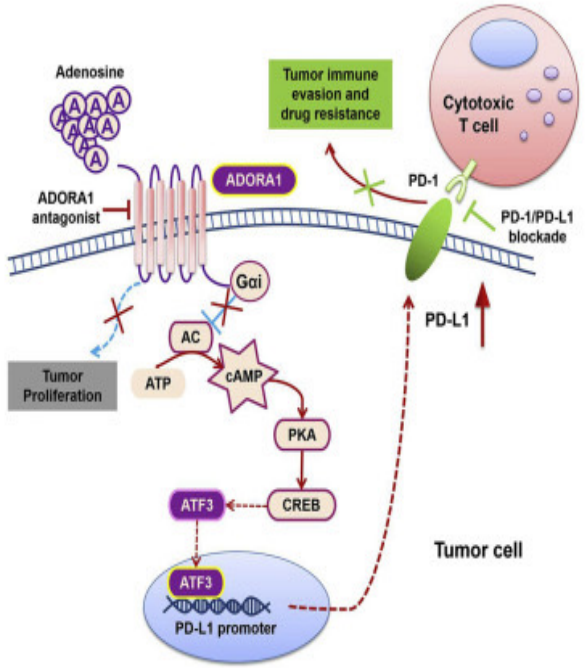
Lan et al. described a new pathway involved in the antineoplastic effect of metformin

B. Lan, J. Zhang, P. Zhang et al., “Metformin suppresses CRC growth by inducing apoptosis via ADORA1,” *Frontiers in Bioscience*, vol. 22, no. 2, pp. 248–257, 2017

Metformin and **ADORA1**

Lan et al. described a new pathway involved in the antineoplastic effect of metformin

- It involves the modulation of adenosine A1 receptor (ADORA1) expression in human colorectal cancer and breast cancer cells
- ADORA1 receptors play an essential role in the supply of cellular energy
- Malignant cells are, therefore, deprived of energy in the course of downregulation of ADORA1 receptors
- Metformin treatment appreciably upregulates ADORA1 expression in colorectal cancer cells
- The ADORA1-mediated growth inhibition and apoptosis induced by metformin are AMPK-mTOR pathway dependent in human colorectal cancer cells



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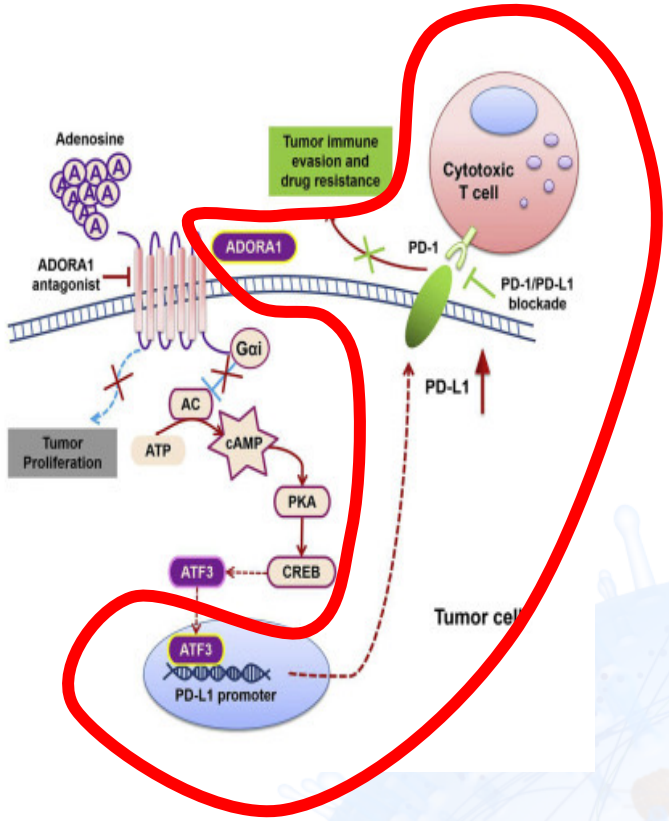
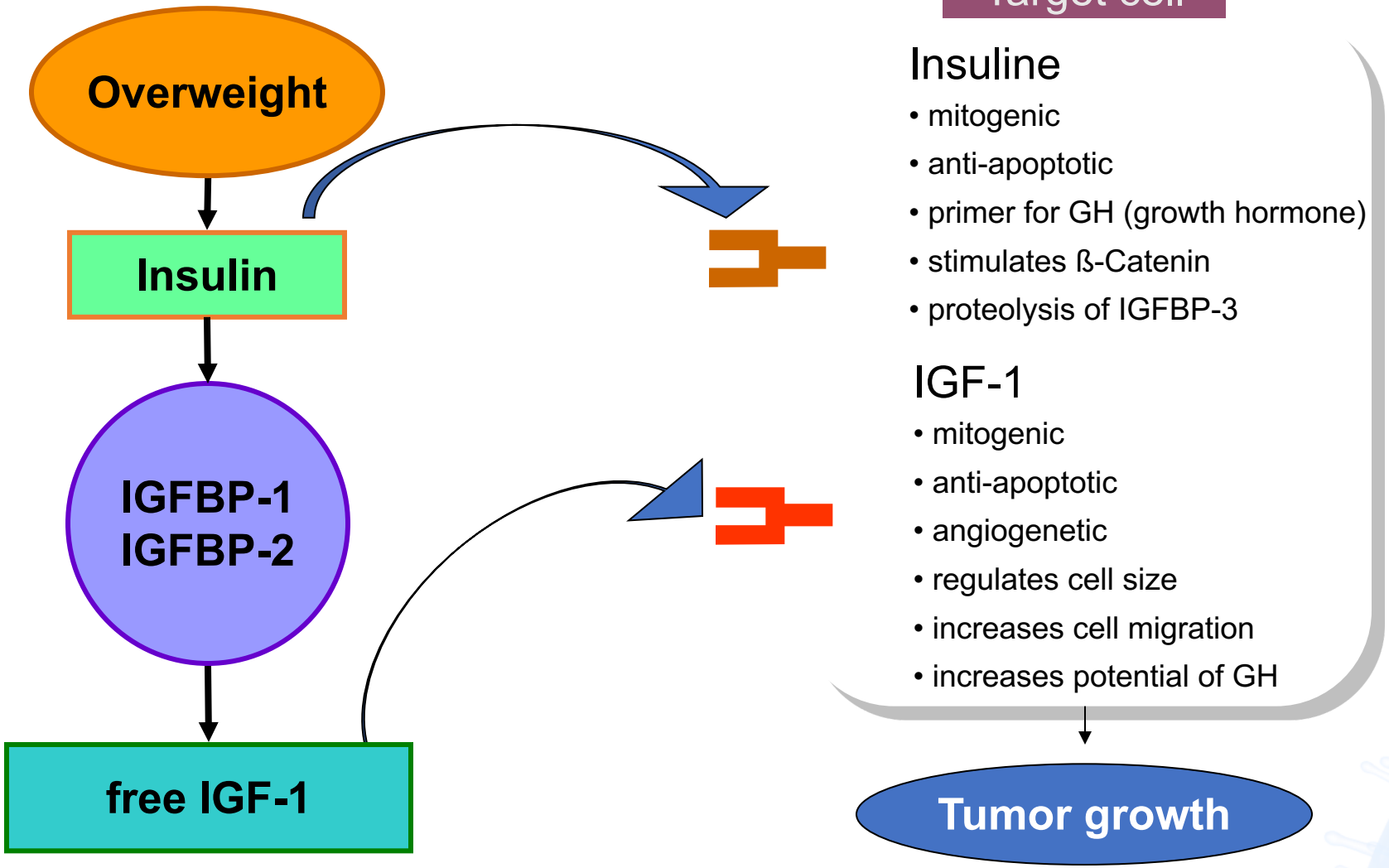


Only recently it was shown that ADORA1 inhibition promotes tumor immune evasion by regulating the ATF3-PD-L1 axis, which might be inhibited by metformin

B. Lan, J. Zhang, P. Zhang et al., "Metformin suppresses CRC growth by inducing apoptosis via ADORA1," *Frontiers in Bioscience*, vol. 22, no. 2, pp. 248–257, 2017

Metformin and insulin



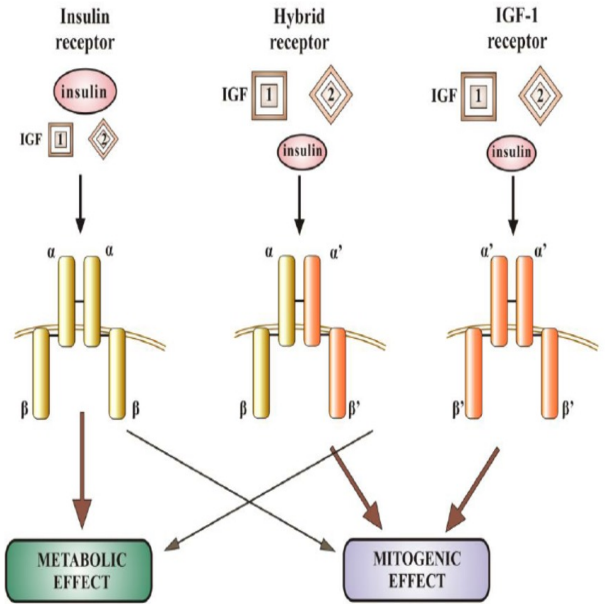
Reduction of serum levels of insulin, IGF-1 and IGF-2

Metformin reduces the levels of stimuli that promote cancer cell proliferation

High levels of IGF-1 and IGF-2 are linked to the growth of cancer or with cancer recurrence in cancer survivors

M. Pollak, “The insulin and insulin-like growth factor receptor family in neoplasia: an update,” *Nature Reviews Cancer*, vol. 12, no. 3, pp. 159–169, 2012

The actions of IGF proteins are mediated by IGF-IR, a transmembrane tyrosine kinase which is structurally related to insulin receptor



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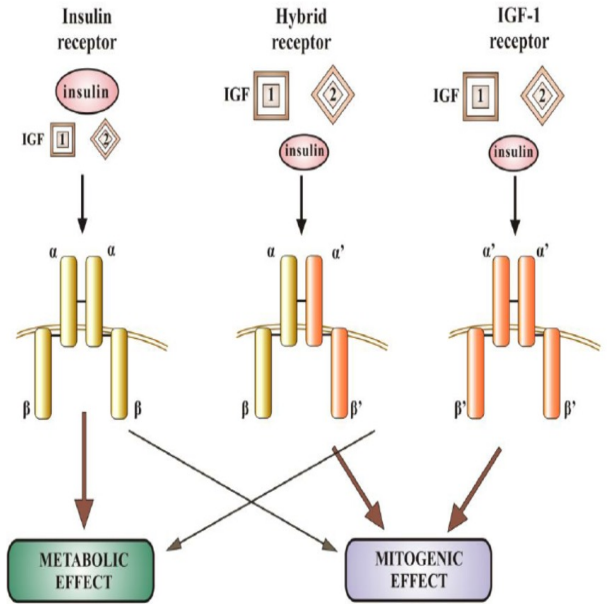
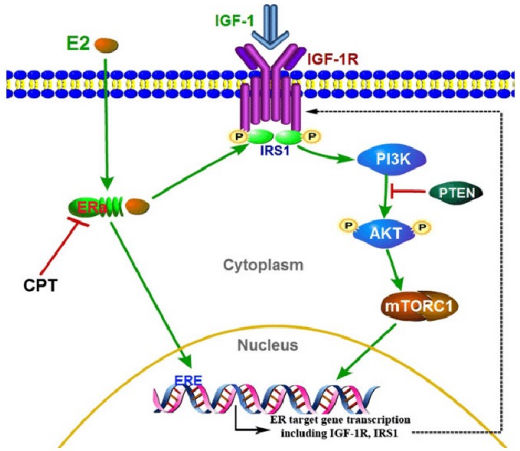
The binding of IGF-1 and IGF-2 on IGF-receptors eventually results in the activation of mTOR, which enhances cellular proliferation and inhibition of apoptosis

M. Navarro and R. Baserga, “Limited redundancy of survival signals from the type 1 insulin-like growth factor receptor,” *Endocrinology*, vol. 142, no. 3, pp. 1073–1081, 2001





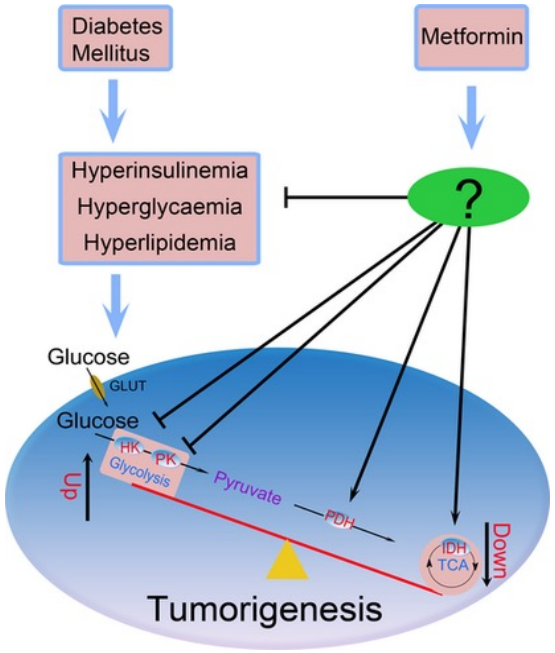
Metformin and Warburg effect

The antitumor activity of metformin is related to the downregulation of gluconeogenesis in the mitochondria.

Shaw R. J., Lamia K. A., Vasquez D., et al. *Science.* 2005;310(5754):1642–1646. doi: 10.1126/science.1120781.

Hyperglycaemia modulates various pathways that control cell proliferation, migration and invasion

Li W., Zhang X., Sang H., et al. Effects of hyperglycemia on the progression of tumor diseases. *Journal of Experimental & Clinical Cancer Research.* 2019;38(1):p. 327. doi: 10.1186/s13046-019-1309-6



Warburg phenomenon refers to rapid glucose uptake and metabolism by cancer cells via a process of aerobic glycolysis for the purpose of generating energy

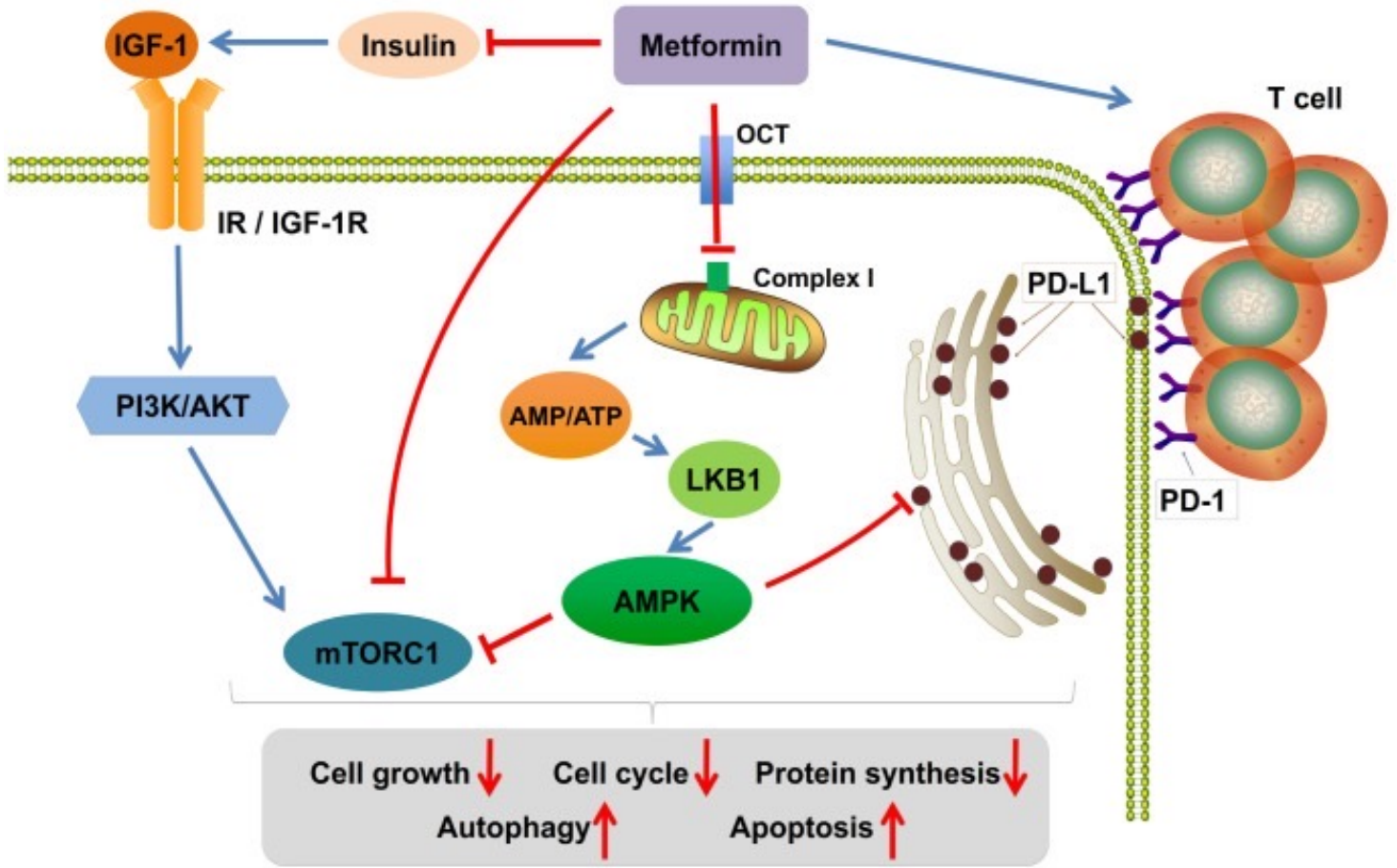
Liberti M. V., Locasale J. W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends in Biochemical Sciences.* 2006;41(3):211–218. doi: 10.1016/j.tibs.2015.12.001

Hyperglycaemia provides the necessary adenosine triphosphate (ATP) which is required by cancer cells to proliferate rapidly

Metformin prevents DMH-induced colorectal cancer in diabetic rats by reversing the Warburg effect

Yanglei Jia, et al. doi: 10.1002/cam4.521

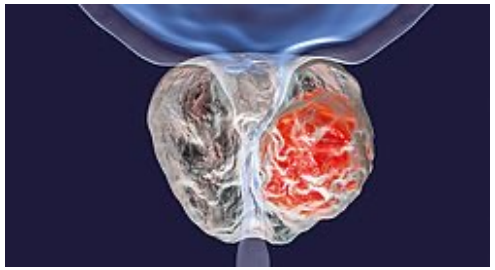
Mechanisms of action of metformin in cancer therapy



Transferring to clinical data

Metformin and prostate cancer

Real world data on prostate cancer



- 87,344 men, 17% of whom were diabetic and on metformin
  vs. 22% without metformin
  18% significant reduction in death risk as well as skeletal related events

K. A. Richards, J. I. Liou, V. L. Cryns, T. M. Downs, E. J. Abel, and D. F. Jarrard, "Metformin use is associated with improved survival for patients with advanced prostate Cancer on androgen deprivation therapy," *The Journal of Urology*, vol. 200, no. 6, pp. 1256–1263, 2018

- Among 3837 patients, the longer duration of metformin treatment after diagnosis of prostate cancer was associated with a **decline in all-cause mortality.**

- D. Margel, D. R. Urbach, L. L. Lipscombe et al., "Metformin use and All-Cause and prostate Cancer–Specific mortality among men with diabetes," *Journal of Clinical Oncology*, vol. 31, no. 25, pp. 3069–3075, 2012

- Metformin decreases androgen receptor (AR) and androgen receptor-V7 expression and enhances apoptotic cell death.
- Metformin improved the antiprostate activity of abiraterone and enzalutamide combination.

Y. Xie, L. Wawng, and A. Hussain, *Metformin enhances the anti-prostate cancer activity of abiraterone and enzalutamide*, 2016.

- A significant reduction in prostate cancer risk was observed among 2906 metformin cohort and 2906 non metformin cohort who were followed up for 5-10 years (95%, CI= 0,49; p = 0,0039)

Y. J. Kuo, F. C. Sung, P. F. Hsieh, H. P. Chang, K. L. Wu, and H. C. Wu, "Metformin reduces prostate cancer risk among men with benign prostatic hyperplasia: a nationwide population-based cohort study," *Cancer Medicine*, vol. 8, no. 5, pp. 2514–2523, 2019.

Metformin and colorectal cancer (CRC)

The prognosis of colorectal cancer in diabetic patients tends to be worse…

K.T. Millis, et al. “Diabetes mellitus and colorectal cancer prognosis: a meta-analysis,” Diseases of the Colon and Rectum, vol. 11, pp. 1304–1319, 2013

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Metformin use in colorectal cancer

- improves **overall survival** and
- reduces **cancer-specific mortality** (pooled HR = 0:75, 95% CI = 0:65-0.87)

  F. Meng, L. Song, and W. Wang, “Metformin Improves Overall Survival of Colorectal Cancer Patients with Diabetes: A Meta-Analysis,” Journal of Diabetes Research, vol. 2017, Article ID 5063239,
- **better overall survival** (HR = 0:56, 95% CI = 0:41-0.77) compared to nonusers

  Z. B. Mei, Liu et al., “Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and Meta-Analysis,” PLoS One, vol. 9, no. 3, article e91818, 2014
- chemopreventive effect on sporadic CRC in patients with high risk of recurrent Adenoma

  T. Higurashi, et al. “Metformin for chemoprevention of metachronous colorectal adenoma or polyps in post-polypectomy patients without diabetes: a multicenter double-blind, placebo-controlled, randomised phase 3 trial,” The Lancet Oncology, vol. 17, no. 4, pp. 475–483, 2016
- lower mortality in diabetic patients with colon cancer compared to non-users (p = 0:012)
- female patients with colon cancer on metformin had lower specific mortality rates than their male counterparts (p = 0:025)

  J. W. Park, J. H. Lee, Y. H. Park et al., “Sex-dependent difference in the effect of metformin on colorectal cancer-specific mortality of diabetic colorectal cancer patients,” World Journal of Gastroenterology, vol. 23, no. 28, pp. 5196–5205, 2017

Metformin and CRC

A Cohort Study of Metformin and Colorectal Cancer Risk among Patients with Diabetes Mellitus

Antidiabetic drug use	Person years	No. of events	Adjusted[a] HR (95% CI)
Sulfonlyurea only	80,847.12	167	1.00 (reference)
Sulfonylurea+metformin	58,725.95	122	0.85 (0.65-1.12)
Duration metformin			
Never	80,847.12	167	1.00 (reference)
<2.0 years	25,050.73	50	0.93 (0.67-1.29)
2.0-4.9 years	20,701.60	44	0.88 (0.60-1.27)
≥5.0 years	12,973.62	28	0.62 (0.38-1.01)
			$P_{trend} = 0.08$

- Prospective study
  - 47,351 participants in Northern California
  - diabetes on OAD followed up for 15 years
  - **long-term use (≥ 5 year)** was associated with reduced risk of colon cancer in the study population (HR, 0.78; 95% CI, 0.60-1.02)

M. C. Bradley, A. Ferrara, N. Achacoso, S. F. Ehrlich, C. P. Quesenberry Jr., and L. A. Habel, "A cohort study of metformin and colorectal cancer risk among patients with diabetes mellitus," Cancer Epidemiology Biomarkers & Prevention, vol. 27, no. 5, pp. 525–530, 2018

- Further deductions from the study showed:
  - Inverse relationship between cumulative doses of metformin and colorectal cancer risk
  - switching patients from sulphonylureas to metformin or adding metformin is associated with decreased colon CA risk.

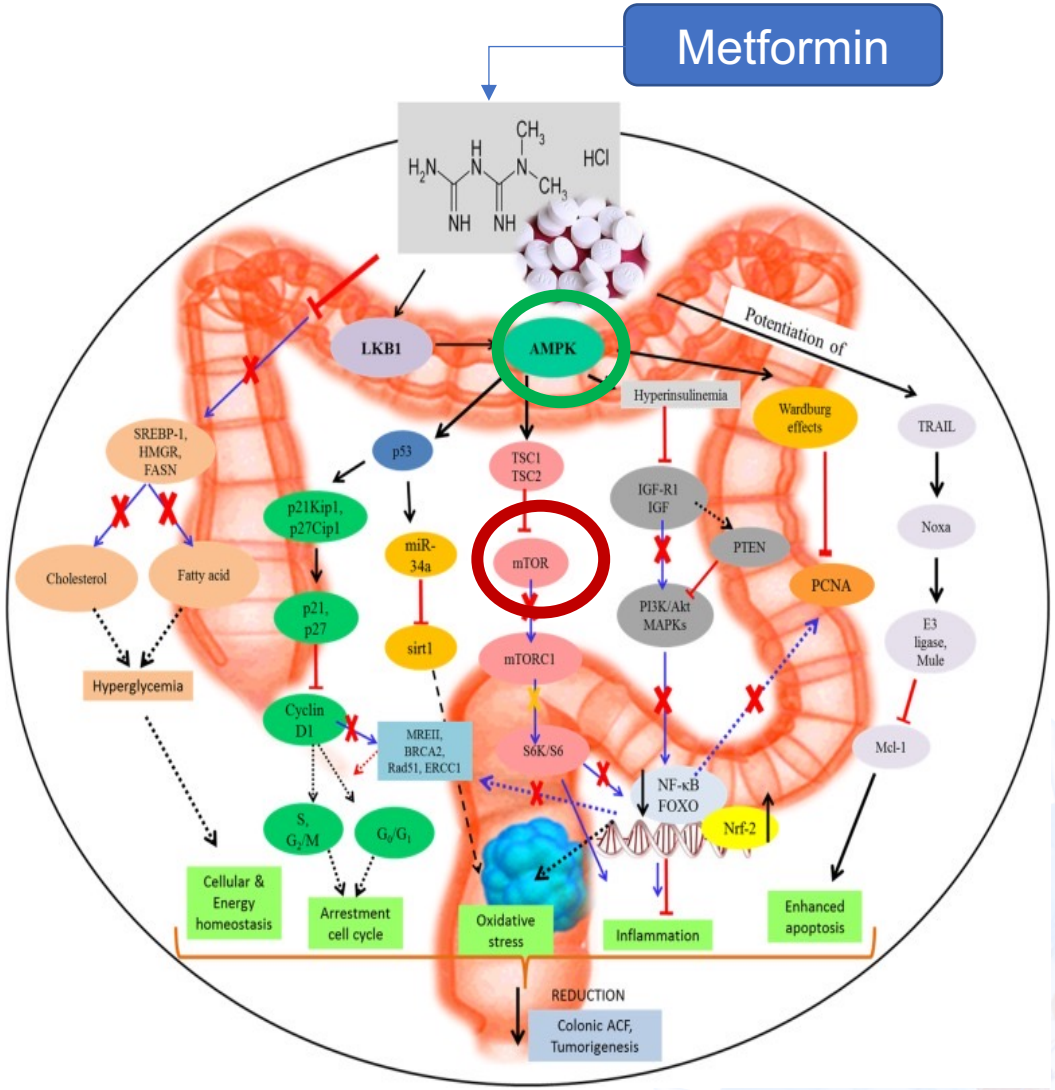
M. C. Bradley, A. Ferrara, N. Achacoso, S. F. Ehrlich, C. P. Quesenberry Jr., and L. A. Habel, "A cohort study of metformin and colorectal cancer risk among patients with diabetes mellitus," Cancer Epidemiology Biomarkers & Prevention, vol. 27, no. 5, pp. 525–530, 2018

- Similar findings have been shown by Smiechowski et al.

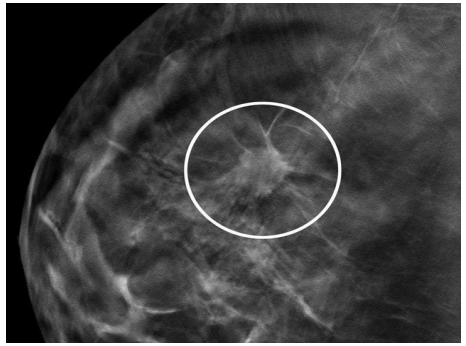
Smiechowski B., Azoulay L., Yin H., Pollak M. N., Suissa S. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. *Cancer Epidemiology, Biomarkers & Prevention.* 2010;22(10):1877–1883. doi: 10.1158/1055-9965.epi-13-0196

Metformin and CRC

AMPK activation and inhibition of mTOR are one of the main potential mechanisms for the anti-colon cancer effect of metformin



Metformin and breast cancer



Metformin

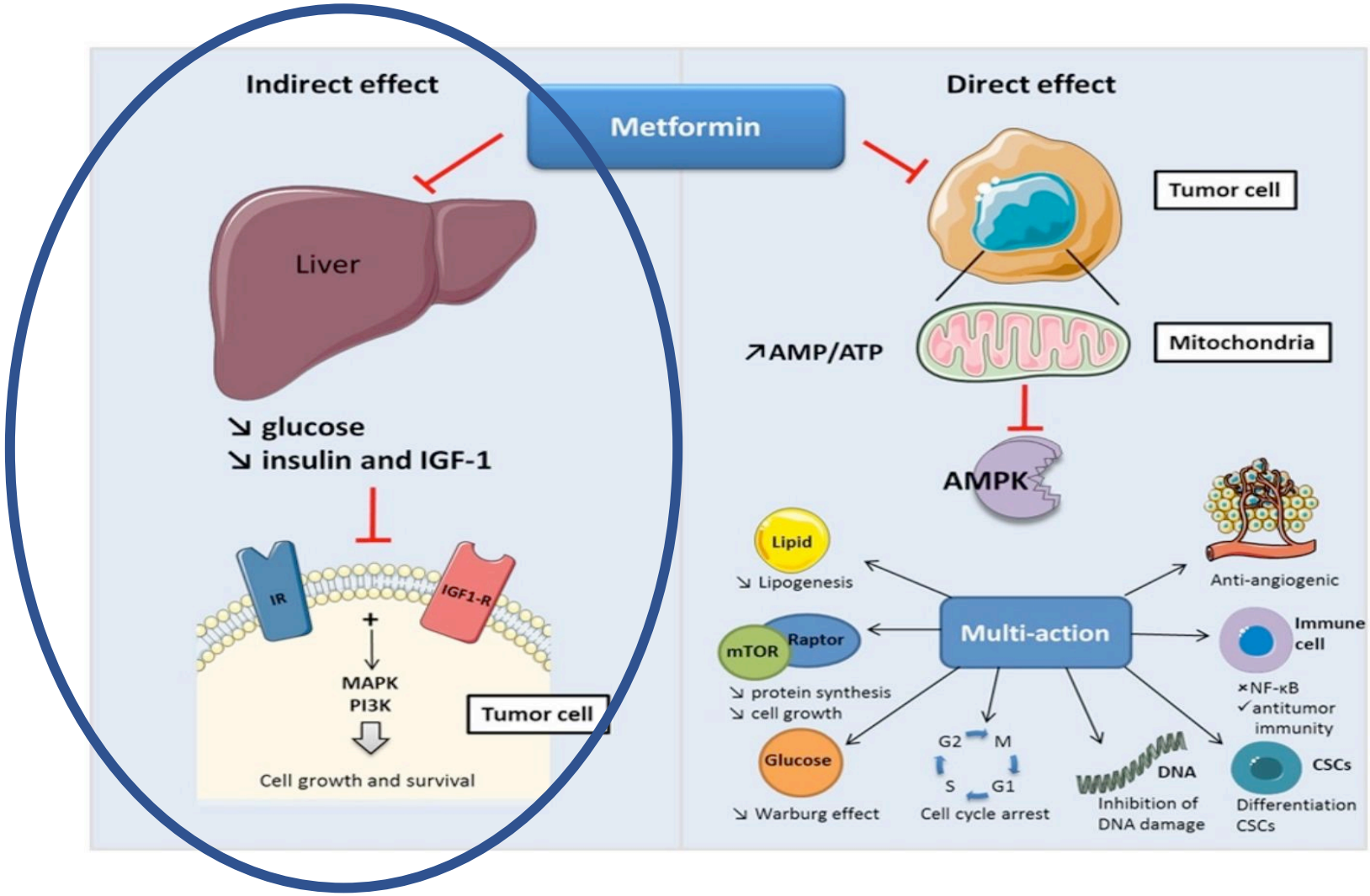
- decreased breast cancer incidence and mortality vs. other antidiabetic drugs
- high levels of phosphatidylinositol-3-kinase (PI3K)/Akt and mTOR signaling molecules are expressed by breast cancer cells leading to impaired ability to undergo apoptosis
- works synergistically with chemotherapeutic agents and reduces the development of resistance of breast cancer to them C. Porta, C. Paglino, and A. Mosca, "Targeting PI3K/Akt/-mTOR signaling in cancer," Frontiers in Oncology, vol. 4,p. 64, 2014
- mechanism in breast cancer is not limited to AMPK pathways it induces cell cycle arrest and apoptosis by activating apoptotic pathways with downregulation of differentiated embryo chondrocyte 1 (DEC1) and p53S M. H. K. Roshan, Y. K. Shing, and N. P. Pace, "Metformin as an adjuvant in breast cancer treatment," Sage open Medicine, vol. 7, p.

  M. H. Li, S.-T. Liu, Y.-L. Chang, C.-L. Ho, and S.-M. Huang, "Metformin causes cancer cell death through downregulation of p53-dependent differentiated embryo chondrocyte 1," Journal of Biomedical Science, vol. 25, no. 1,p. 81, 2018
- inhibits STAT3 phosphorylation in triple-negative and HER2-positive breast cancer → inhibition of cellular proliferation and induction of apoptosis mediated by reduction in the phosphorylation of Tyr 705 and Ser727

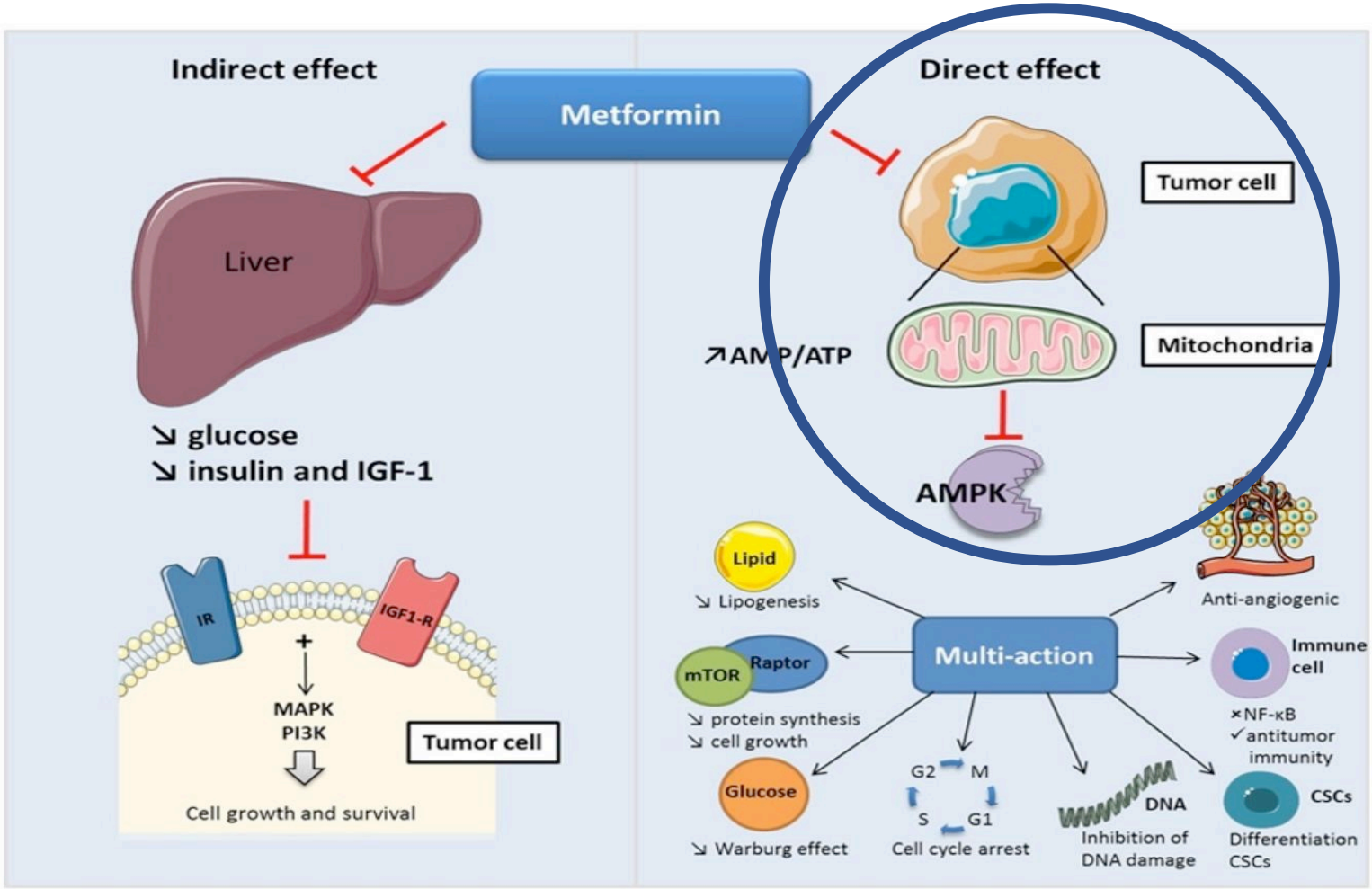
  P. Zhu, M. Davis, A. J. Blackwelder et al., "Metformin selectively targets tumor-initiating cells in ErbB2-overexpressing breast cancer models," Cancer Prevention Research, Vol. 7, no. 2, pp. 199–210, 2014

  X.-S. Deng, S. Wang, A. Deng et al., "Metformin targets STAT3 to inhibit cell growth and induce apoptosis in triple negative breast cancers," Cell Cycle, vol. 11, no. 2, pp. 367– 376, 2012

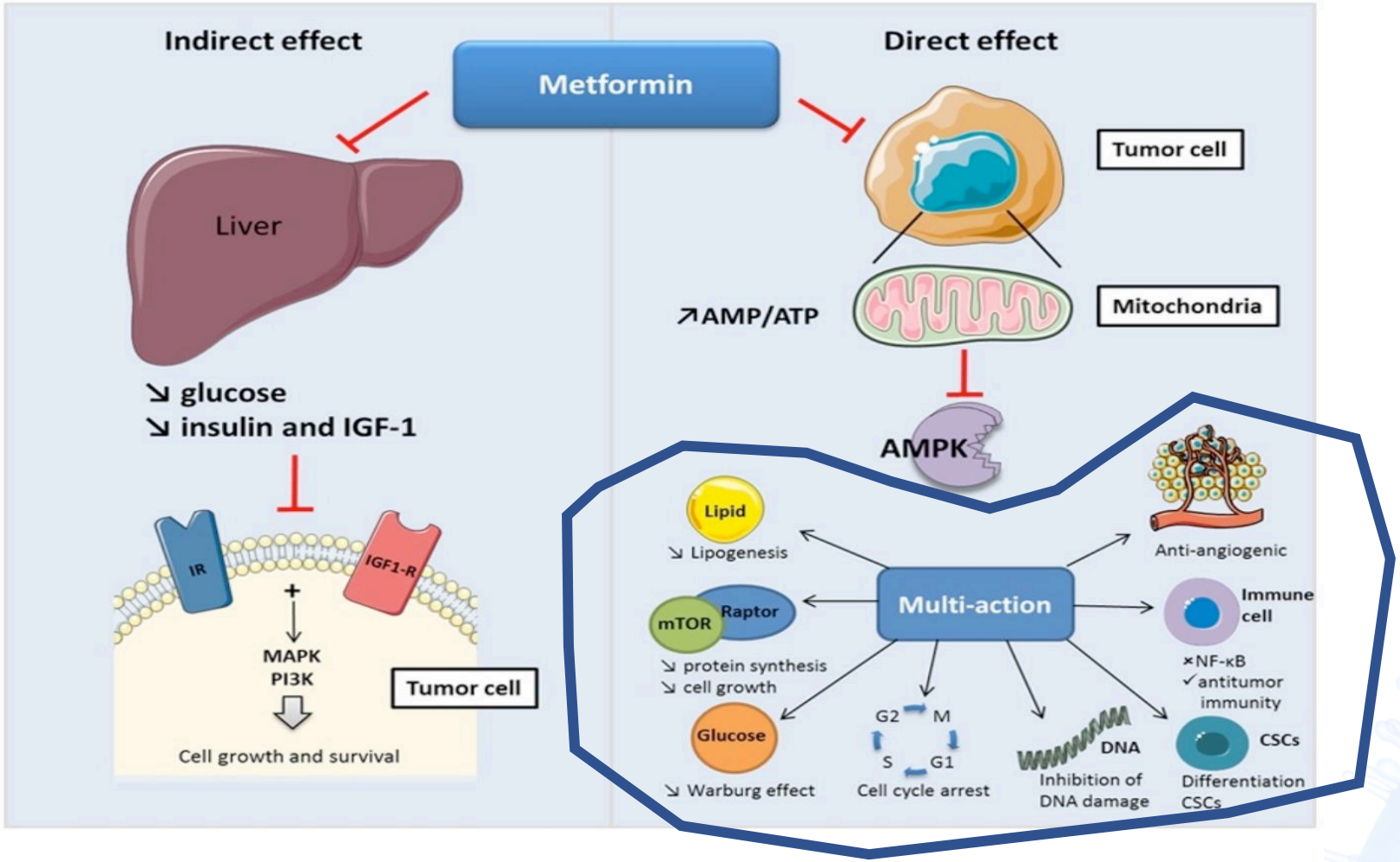
Metformin: main topics



Metformin: main topics

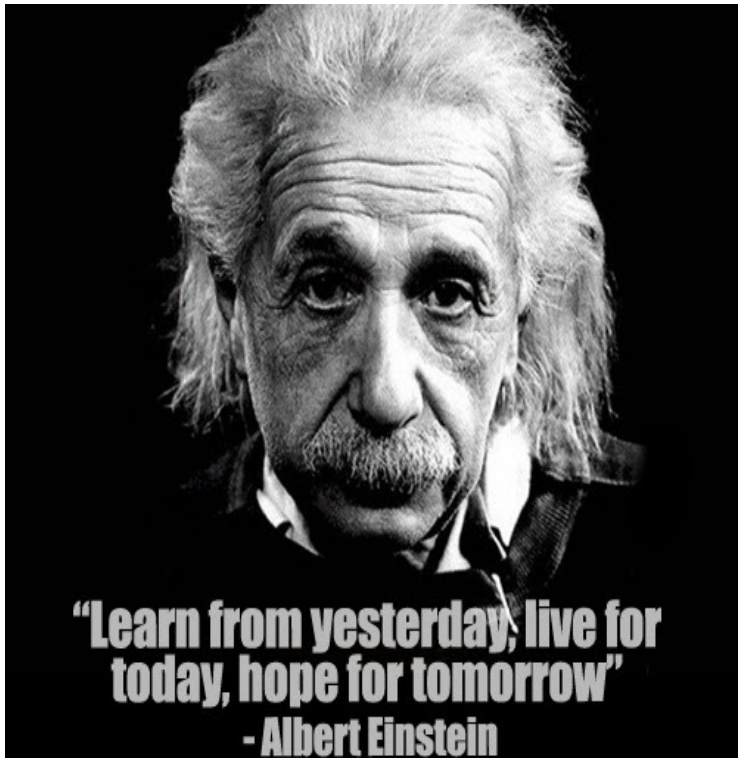


Metformin: main topics



Metformin: Take home message

- Metformin is well-known for its use in the treatment of patients with diabetes mellitus.
- Several molecular properties such as the inhibition of reactive oxygen species, mTORC1, ADORA1 and activation of AMPK have suggested its utility as an antitumor agent.
- Several population studies have suggested a protective effect of metformin in different types of cancer, including breast, colon, pancreas, prostate and liver cancer.
- As the results of ongoing clinical trials are awaited, further investigational research may focus on validating these findings with the aim of metformin use in cancer chemotherapy even in non-diabetic patients.



Thank you for your attention!

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For further information

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