

COMMENTARY

Tumour immunogenicity goes with the (mitochondrial electron) flow

 Asma Ahmed^{1,2} and Stephen W. G. Tait^{1,2} 

1 School of Cancer Sciences, University of Glasgow, UK

2 Cancer Research UK Scotland Institute, Glasgow, UK

Keywords

complex II; electron transport chain; major histocompatibility complex class I; succinate

Correspondence

 A. Ahmed and S. W. G. Tait, School of Cancer Sciences, University of Glasgow, Switchback Road, Glasgow G61 1BD, UK
 E-mail: asma.ahmedhassanelshiekh@glasgow.ac.uk; stephen.tait@glasgow.ac.uk

(Received 13 December 2023, revised 8 February 2024, accepted 27 February 2024, available online 22 March 2024)

doi:10.1002/1878-0261.13627

Mitochondrial metabolism and electron transport chain (ETC) function are essential for tumour proliferation and metastasis. However, the impact of ETC function on cancer immunogenicity is not well understood. In a recent study, Mangalharra et al. found that inhibition of complex II leads to enhanced tumour immunogenicity, T-cell-mediated cytotoxicity and inhibition of tumour growth. Surprisingly, this antitumour effect is mediated by succinate accumulation affecting histone methylation. Histone methylation promotes the transcriptional upregulation of major histocompatibility complex–antigen processing and presentation (MHC-APP) genes in a manner independent of interferon signalling. Modulating mitochondrial electron flow to enhance tumour immunogenicity provides an exciting new therapeutic avenue and may be particularly attractive for tumours with reduced expression of MHC-APP genes or dampened interferon signalling.

Mitochondria are essential for tumour metabolism, growth and invasion. They generate cellular energy in the form of ATP through the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC). The ETC is composed of four enzyme complexes; complex I (CI) that transfers electrons from NADH produced in the TCA cycle, complex II (CII), which is succinate dehydrogenase (SDH), that transfers electrons from flavin adenine dinucleotide (FADH₂), complex III and complex IV [1,2]. Hanahan and Weinberg [3] have highlighted the reprogramming of cellular metabolism to sustain tumour proliferation and the evasion of immune destruction, as emerging cancer hallmarks. However, the interplay between metabolism and tumour immunogenicity remains unclear. Moreover, while mitochondrial ETC is key for tumour growth [2], the relative contribution of CI and CII in tumour development is poorly understood.

Upon metabolic deregulation, some metabolites can have oncogenic properties and are commonly referred to

as oncometabolites. For instance, SDH mutations associated with cancers of neuroendocrine origin, lead to accumulation of succinate that can have various oncogenic functions. Succinate accumulation as a consequence of SDH mutations has been shown as an epigenetic regulator whereby succinate inhibits DNA and histone demethylases. Thus, SDH-deficient tumours displayed a hypermethylated phenotype that is oncogenic, underscoring a potential for epigenetic approaches to cancer therapy [2,4]. Nevertheless, despite the apparent crosstalk between metabolism and epigenetics, whether epigenetic reprogramming affects tumour immunogenicity is unclear.

Tumours often evade the immune system by downregulating the expression of major histocompatibility class I (MHC I) molecules that are key for antigen presentation and the subsequent activation of cytotoxic T cells [5]. Mangalharra et al. investigated the interaction between tumour growth, CI and CII of the ETC and

Abbreviations

CI, complex I; CII, complex II; ETC, electron transport chain; FADH₂, flavin adenine dinucleotide; KDMs, lysine-specific demethylases; MCJ, methylation-controlled J protein; MHC I, major histocompatibility complex class I; MHC-APP, major histocompatibility complex–antigen processing and presentation; SDH, succinate dehydrogenase; TCA, tricarboxylic acid.

tumour immunogenicity by implanting CI or CII knockout mouse melanoma cells into immunocompetent mice. The authors found that the inhibition of CII but not CI reduced tumour growth as a result of increased expression of MHC I and several major histocompatibility complex–antigen processing and presentation (MHC-APP) genes that enhance antigen presentation and T-cell activation potentiating T-cell-mediated killing of tumour cells [6] (Fig. 1). Importantly, the authors showed that the increased tumour cell antigen presentation is caused by mitochondrial succinate accumulation (resulting from reduced complex II activity) and is independent of interferon-gamma signalling (a common means of upregulating MHC-APP genes). The clinical relevance of these findings is underscored by an inverse correlation between the expression of SDHC (a subunit of CII) and MHC-APP genes in

both skin and breast cancer. These findings highlight the role of CII inhibition on antigen presentation and T-cell activation and raise the question of whether CII has a role in other immune cell types.

Paradoxically, loss of complex II function—causing succinate accumulation—also has reporting oncogenic functions in some human cancers, underpinning succinate as an oncometabolite [7,8]. How can these opposing, pro and antitumourigenic, effects of succinate be reconciled? As the authors discuss, oncogenic germline mutations of CII that are present early in life, lead to succinate accumulation that promotes tumour initiation. In contrast, in the current study, succinate impacts tumour growth control by potentiating tumour immunogenicity. Intriguingly, succinate accumulation does not always lead to tumorigenesis [9] and sometimes requires additional mutations for

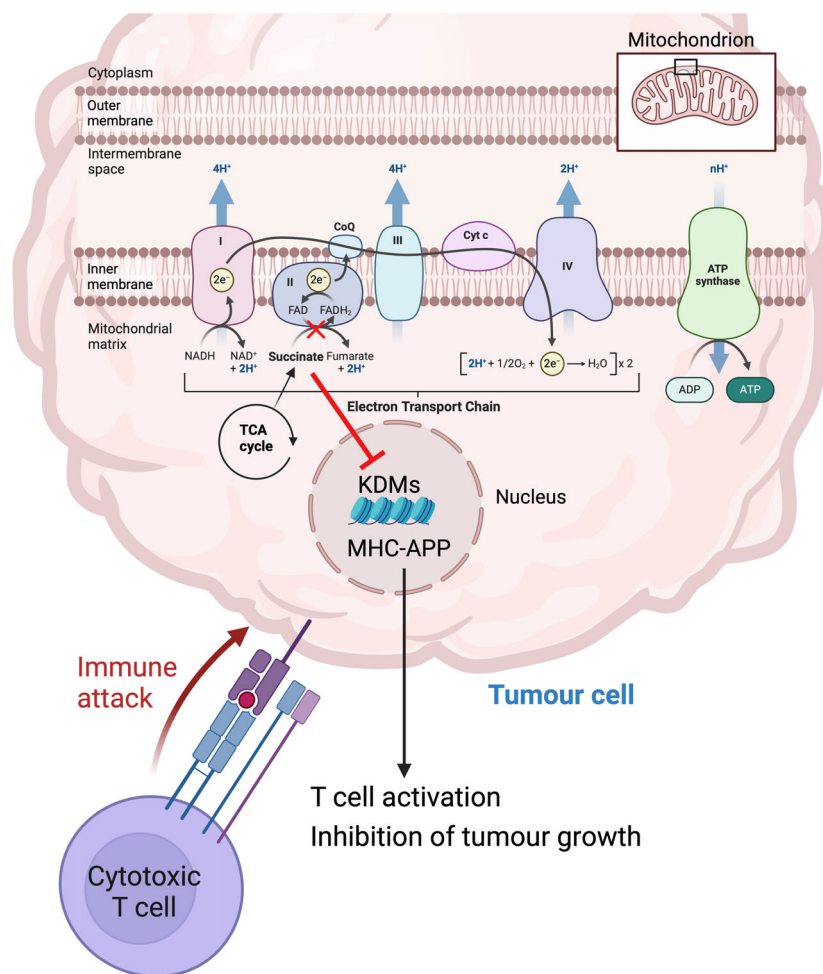


Fig. 1. Inhibition of mitochondrial complex II (CII) induces succinate accumulation that inhibits lysine-specific demethylases (KDMs). This causes upregulation of major histocompatibility complex–antigen processing and presentation (MHC-APP) genes leading to increased tumour immunogenicity and cytotoxic T cell activation.

tumorigenesis to occur [10], which indicates that the oncogenic potential of SDH loss and succinate accumulation is dependent on the microenvironment. Furthermore, CII deficiency might cause immunoediting and the selective growth of tumours that escaped immune destruction. Nonetheless, further research is needed to decipher the tumour-promoting versus the tumour-suppressive effects of succinate and to explore which mutations are coupled to which phenotype. Moreover, it will be important to investigate whether these antitumour effects of CII inhibition are also evident in other cancer types.

How does succinate accumulation induce MHC I expression? Metabolism and epigenetic control of gene expression are intimately linked [11]. In this vein, the authors found that the reduced α -ketoglutarate/succinate ratio caused by the reduction in CII activity resulted in inhibition of lysine-specific demethylases (KDMs). This led to increased trimethylation of histone H3 at lysine 4 (H3K4me3), and upregulation of the NLRC5 transcription factor and a transcriptional increase in MHC I and other APP genes expression (Fig. 1). This effect was reversed by the inhibition of histone methylation. Furthermore, H3K4me3 was significantly enriched at the promoter of Nlr5 and Tap1. Additionally, succinate accumulation induced a marked increase of H3K4me3 in the Tap1 gene body that was rescued by α -ketoglutarate. Thus, succinate primarily impacts MHC I expression through epigenetic effects.

The authors next sought to exploit these findings for therapeutic benefit, aiming to increase succinate levels to promote antitumour immunity. Inhibition of CII is neurotoxic and can induce inflammatory responses [12,13] and systemic CII inhibition can induce tumorigenesis and significant disruption of the ETC in healthy cells, hence precluding direct targeting of CII as a therapeutic option. Therefore, the authors took an alternative approach to trigger succinate accumulation by targeting the ETC to enhance CI-driven electron flow. To this end, the authors took an elegant approach, knocking out an endogenous CI-interacting protein in the inner mitochondrial membrane, called Methylation-controlled J protein (MCJ), that acts as a negative regulator of CI [14], on the premise that the loss of MCJ will lead to the selective activation of CI and hence the rewiring of electron flow leading to succinate accumulation and enhanced tumour immunogenicity. Indeed, MCJ knockout resulted in increased CI activity and intracellular succinate accumulation leading to immune-mediated suppression of tumour growth.

In summary, Mangalharra et al. provide further compelling evidence that modulation of mitochondrial metabolism represents a promising therapeutic target

for cancer. This can be achieved by rewiring the ETC in tumour cells without affecting normal cell respiration and thus minimising treatment side effects. Remarkably, the observed antitumorigenic effect and the enhanced immunogenicity of melanoma cells are independent of interferon-gamma signalling. This is particularly exciting and can be utilised as a treatment strategy for tumours with defective interferon-gamma pathways that are resistant to immunotherapy [15]. This approach could be particularly promising in immune cold tumours, by making them visible to the immune system and potentially more responsive to combinatorial immunotherapy, for example with immune checkpoint blockade. Nonetheless, the feasibility of rewiring the electron flow in a therapeutic setting requires careful consideration. Moreover, as succinate can act as an oncometabolite, it is of utmost importance to dissect the tumour-promoting versus the tumour-inhibitory effects of succinate before delving into enhancing succinate accumulation as a treatment strategy.

Acknowledgements

Our laboratory is supported by funding from Cancer Research UK (DRCNPG-Jun22\100011) and Prostate Cancer UK (RIA17-ST2-002). AA is funded by a Career Acceleration Fellowship from Prostate Cancer UK (TLD-CAF22-012). Graphical abstract figure was created in BioRender.

Conflict of interest

SWGT consults for Exo Therapeutics. AA declares no conflict of interest.

References

- Greene J, Segaran A, Lord S. Targeting OXPHOS and the electron transport chain in cancer; molecular and therapeutic implications. *Semin Cancer Biol.* 2022;**86**:851–9.
- Nakhle J, Rodriguez A-M, Vignais M-L. Multifaceted roles of mitochondrial components and metabolites in metabolic diseases and cancer. *Int J Mol Sci.* 2020;**21** (12):4405.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;**144**(5):646–74.
- Selak MA, Armour SM, MacKenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF- α prolyl hydroxylase. *Cancer Cell.* 2005;**7** (1):77–85.

- 5 Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer immune evasion through loss of MHC class I antigen presentation. *Front Immunol.* 2021;**12**:636568.
- 6 Mangalhara KC, Varanasi SK, Johnson MA, Burns MJ, Rojas GR, Esparza Moltó PB, et al. Manipulating mitochondrial electron flow enhances tumor immunogenicity. *Science.* 2023;**381**(6664):1316–23.
- 7 Dalla Pozza E, Dando I, Pacchiana R, Liboi E, Scupoli MT, Donadelli M, et al. Regulation of succinate dehydrogenase and role of succinate in cancer. *Semin Cell Dev Biol.* 2020;**98**:4–14.
- 8 MacFarlane J, Seong KC, Bisambar C, Madhu B, Allinson K, Marker A, et al. A review of the tumour spectrum of germline succinate dehydrogenase gene mutations: beyond pheochromocytoma and paraganglioma. *Clin Endocrinol (Oxf).* 2020;**93**(5):528–38.
- 9 Al Khazal F, Kang S, Nelson Holte M, Choi D-S, Singh R, Ortega-Sáenz P, et al. Unexpected obesity, rather than tumorigenesis, in a conditional mouse model of mitochondrial complex II deficiency. *FASEB J.* 2021;**35**(2):e21227.
- 10 Armstrong N, Storey CM, Noll SE, Margulis K, Soe MH, Xu H, et al. SDHB knockout and succinate accumulation are insufficient for tumorigenesis but dual SDHB/NF1 loss yields SDHx-like pheochromocytomas. *Cell Rep.* 2022;**38**(9):110453.
- 11 Lu C, Thompson CB. Metabolic regulation of epigenetics. *Cell Metab.* 2012;**16**(1):9–17.
- 12 Ludolph AC, He F, Spencer PS, Hammerstad J, Sabri M. 3-Nitropropionic acid – exogenous animal neurotoxin and possible human striatal toxin. *Can J Neurol Sci.* 1991;**18**(4):492–8.
- 13 Chen X, Sunkel B, Wang M, Kang S, Wang T, Gnanaprakasam JNR, et al. Succinate dehydrogenase/complex II is critical for metabolic and epigenetic regulation of T cell proliferation and inflammation. *Sci Immunol.* 2022;**7**(70):eabm8161.
- 14 Hatle KM, Gummadidala P, Navasa N, Bernardo E, Dodge J, Silverstrim B, et al. MCJ/DnaJC15, an endogenous mitochondrial repressor of the respiratory chain that controls metabolic alterations. *Mol Cell Biol.* 2013;**33**(11):2302–14.
- 15 Gao J, Shi LZ, Zhao H, Chen J, Xiong L, He Q, et al. Loss of IFN- γ pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. *Cell.* 2016;**167**(2):397–404.e9.