Lipid metabolism of cancer stem cells (Review)

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Abstract. Cancer stem cells (CSCs), also termed cancer-initiating cells, are a special subset of cells with high self-replicating and self-renewing abilities that can differentiate into various cell types under certain conditions. A number of studies have demonstrated that CSCs have distinct metabolic properties. The reprogramming of energy metabolism enables CSCs to meet the needs of self-renewal and stemness maintenance. Increasing evidence supports the view that alterations in lipid metabolism, including an increase in fatty acid (FA) uptake, *de novo* lipogenesis, formation of lipid droplets and mitochondrial FA oxidation, are involved in CSC regulation. In the present review, the metabolic characteristics of CSCs, particularly in lipid metabolism, were summarized. In addition, the potential mechanisms of CSC lipid metabolism in treatment resistance were discussed. Given their significance in cancer biology, targeting CSC metabolism may serve an important role in future cancer treatment.

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1. Introduction

The occurrence and development of tumors is a complicated process involving numerous factors. Cancer stem cells (CSCs) are considered to be the seed of the tumor and are characterized by self-renewal and differentiation (1). CSCs serve an important role in maintaining the proliferation, invasion, drug resistance, metastasis and recurrence of malignant tumors (2). In recent years, the CSC model has received increasing attention.

Energy metabolism serves a significant role in the process of substance metabolism. Metabolic reprogramming is one of the most important hallmarks of cancer (3). Tumor-initiating cells (TICs) and CSCs exhibit different biology behaviors compared with non-stem cancer cells (4). The metabolic regulation of ATP synthesis and biological building block formation in CSCs is different compared with that in differential non-stem cancer cells, but similar to that in normal tissue-derived stem cells (5). In the past decade, the role of metabolism in CSC biology has developed into an active area of research, particularly in lipid metabolism. Previous studies have shown that lipid metabolism serves an important role in maintaining the stemness of CSCs (6) and meeting their energy needs, ultimately leading to cancer growth and invasion. In the present review, the origin and evolution of the CSC model are summarized. In addition, the characteristics and mechanisms of lipid metabolism of CSCs, as well as their role in radiotherapy and chemotherapy resistance are discussed.

2. CSCs

Concept and origin of CSCs. Rudolf Virchow observed similarities between tumor tissues and embryonic tissues ~150 years ago, establishing the Embryonic-Rest hypothesis of tumor formation (7). Subsequently, his student Julius Cohnheim extended this theory, suggesting that tumors originate from stem cells remaining from embryonic development and sustained in the tissues (7). Since the 19th century, significant progress has been achieved in understanding CSC biology and the existence of CSCs has also been confirmed in a variety of solid tumor types, including breast carcinoma (8), ovarian carcinoma (9), colon carcinoma (10), pancreatic carcinoma (11) and liver cancer (12).

CSCs, also termed tumor-initiating cells, display significant self-renewing abilities (13). As well as being responsible for the origin and development of tumors (14), CSCs are resistant

to chemotherapy and radiotherapy (15), which allows for recurrence and metastasis (16).

Epigenetics in CSCs. Epigenetic regulation of the genome is associated with tumor progression. A variety of epigenetic pathways can contribute to the development and progression of tumors, especially in CSC maintenance and survival. Abnormal epigenetic changes may transform normal stem cells into CSCs. DNA methylation and histone modifications are two key factors involved in the developmental programming of stem cells to specific cell and tissue differentiation lineages (17). The important role of DNA methylation in maintaining CSC properties has been reported in leukemia, lung and colon stem cells (18,19). DNA methylation serves a critical role in this transformation process in the presence of DNA methyltransferases (20). Increasing evidence indicates that the silencing of tumor suppressor genes and activation of various cancer genes, which contribute to the formation of CSCs, are closely related to DNA hypermethylation (21).

In addition, epigenetic mechanisms regulate a number of key CSC pathways, including the Wnt/β-catenin, Hedgehog (Hh) and Notch signaling pathways. Specifically, the Wnt/β-catenin signaling pathway serves an important role in normal tissue development and maintenance, as well as in the self-renewal and differentiation of CSCs (22,23). The Hh signaling pathway also regulates the proliferation and maintains the stemness of progenitor cells and CSCs in several tissues (24). Notch signaling is an evolutionarily conserved pathway that regulates proliferation and differentiation in a wide range of cell types and different stages of cell lineage progression, as well as in CSC differentiation and self-renewal (25).

Role of CSCs in tumor biology. CSCs are considered to be the seed in tumor initiation, angiogenesis and maintenance. As aforementioned, CSCs are also an important factor in tumor therapy resistance and metastasis (26). Compared with non-stem cancer cells, CSCs are more resistant to radiotherapy and chemotherapy (27). The following characteristics contribute to CSC chemotherapy or radiotherapy resistance (28): Quiescent phenotype, efficient DNA repair, high expression of drug efflux pumps and antiapoptotic protein expression.

The target of radiotherapy and/or chemotherapy is primarily focused on fast growing cells (29). CSCs and normal stem cells are quiescent, thus CSCs may be insensitive to traditional radiotherapy and/or chemotherapy (15). CSCs express a high level of ATP-binding cassette transporters (ABC transporters), which contributes to the efflux of chemotherapeutic agents, leading to multidrug resistance (15,30).

CSCs are inherently resistant to DNA damage. The innate defense system of CSCs protects them against DNA-targeted chemicals and radiotherapy (31). Moreover, even under a radiation dose that causes DNA damage, CSCs can repair the damaged DNA more quickly (26). Indeed, checkpoint kinase (Chk)1 and Chk2, DNA damage and replication Chks, become activated on genotoxic stress to initiate cell cycle arrest and attempt repair or induce apoptosis if the damage is too great (32,33). Chk1 and Chk2 are highly expressed in CSCs. Inhibition of the Chk1/2 kinases with a small molecule inhibitor disrupted the radioresistance of CSCs (34). Moreover, overamplifying apoptotic inhibitor proteins also contributes to CSC treatment resistance. Various CSCs express higher levels of apoptosis protein inhibitors, including X-linked inhibitor of apoptosis protein (XIAP) isoform, which are associated with poor therapeutic responses (35). XIAP can alleviate the radioresistance of CSCs by promoting apoptosis (36).

Numerous other mechanisms also account for CSC resistance to therapy, including the increased production of free-radical scavengers and molecular metabolism mediators (37). Furthermore, certain mutated genes, including tumor suppressors P53, can help to rescue CSCs under stress conditions, including radiation therapy, tissue damage and exposure to toxins (38).

Therefore, to target CSCs more effectively, the molecular mechanisms of CSCs in proliferation and survival require further investigation.

3. Metabolic properties of CSCs

Due to the heterogeneity of tumor cells, the energy metabolism of cancer cells is distinct from that of normal cells and they are heavily dependent on glucose and aerobic oxidation for their energy supply (39). Metabolic reprogramming is one of the hallmarks of cancer cells (3). Cancer cells display a disrupted metabolism; even under oxygen-rich conditions, these cells still depend on glycolysis for energy and survival, a phenomenon termed the Warburg effect (40). Compared to oxidative phosphorylation (OXPHOS), glycolysis results in rapid production of ATP and an increase in metabolic intermediates for anabolic reactions (41). Although the metabolic characteristics of CSCs have been researched in recent years, the exact metabolism of CSCs remains to be elucidated.

A number of studies have reported that CSCs preferentially utilize glycolysis for survival, while others have shown that CSCs may also rely on OXPHOS (42,43). Ciavardelli *et al* (42) demonstrate that inhibiting the glycolysis of $CD44^+$ $CD24^-$ breast CSCs reduces their proliferation, indicating that this population is glycolytic (42). Nasopharyngeal carcinoma, ovarian cancer, osteosarcoma, glioblastoma (GBM) and colon cancer are primarily dependent on mitochondrial OXPHOS for energy (44-48).

Increasing evidence has indicated that non-stem cancer cell population dedifferentiation to CSCs is accompanied by the transformation of metabolic pathways from mitochondrial OXPHOS to glycolysis (49). Therefore, CSCs display highly metabolic heterogeneity and plasticity abilities that allow them to adapt to the changing tumor microenvironment.

4. Lipid metabolism of cancer stem cells

Role of lipid metabolism in cancer cells. Despite the dependence of cancer on glycolysis, glycolytic inhibitors, such as 2-deoxyglucose, exhibit minimal effects on tumor growth inhibition. Therefore, other metabolic pathways are also critical to cancer cell survival, such as lipid metabolism (50). In addition to providing and storing energy as nutrients, lipids also function as the major component of the cell and signal molecules. Phospholipids, including glycerophospholipids and sphingolipids and cholesterol are the main components of the cell membrane (51). Changes in lipid metabolism could directly affect cell membrane synthesis and proliferation.

In addition, various lipid molecules and their metabolic intermediates participate in cell signal transduction, proliferation,

cell adhesion and movement, inflammation and vascular regulation (51). The unlimited proliferation of cancer cells requires more fatty acids (FAs) and increased lipid droplet metabolism (52).

Unlike normal cells that preferentially utilize free FAs, cancer cells are dependent on reconstituted FAs, thus display enhanced *de novo* synthesis of FAs. A series of lipid synthesis enzymes are upregulated in cancer cells, including sterol-regulatory element binding proteins (SREBPs), acetyl-CoA carboxylase (ACC), FA synthase (FASN) and stearoyl-CoA desaturase 1 (SCD1) (53-60). In addition, citrate derived from the citrate (TCA) cycle can be used to produce acetyl-groups for FA synthesis (61). Therefore, lipid metabolism is also critical for the maintenance of cancer cell malignant biological behaviors.

Lipid metabolism of CSCs. In contrast to the dedifferentiation of non-stem cancer cells, increasing studies have reported that lipid metabolism is highly related to the stemness of CSCs (62). In addition to energy generation, biosynthesis and redox homeostasis, FA metabolism has a vital role in determining the fate of CSCs (63-65). FA synthesis and oxidation are essential for the maintenance of CSCs. For example, NANOG, a critical regulator of CSCs, can promote mitochondrial FA oxidation (FAO) to satisfy energy requirements for TICs (66). NANOG promotes the self-renewal abilities, tumor-initiation properties and generation of stem-like TICs, as well as the hepatocellular carcinoma (HCC) oncogenesis of TICs through metabolic reprogramming from OXPHOS to FAO (66). Peroxisomal proliferation-activated receptors (PPARδ) have significant effects on lipid metabolism and are strongly associated with NANOG expression (67). Overexpression of PPARδ or NANOG in TICs increases the probability of FAO occurring (66).

FAs are strictly regulated by CSCs to maintain their self-renewal ability and therapy resistance (65). As a critical intracellular organelle for the storage of excess lipids (68), the content of lipid droplets (LDs) is significantly increased in several solid tumor CSCs, including colorectal, breast, prostate (69-71) and ovarian CSCs (64). Of note, *de novo* lipogenesis is more active in GBM CSCs compared with that in non-stem cancer cells (72).

Key modulators of lipid metabolism in CSCs

De novo lipogenesis. A number of studies (73,74) have demonstrated higher intracellular lipid accumulation in various CSCs (Table I), which mainly results from *de novo* lipogenesis activity. The majority of the key regulators of *de novo* lipogenesis are also critical for CSCs. SCD1, an enzyme that converts saturated FAs into monounsaturated FAs (MUFAs) (75), is expressed at a high level in various tumors and is closely related to the progression and undesirable clinical outcomes of various types of cancer. SCD1 is critical for CSC/TIC generation and stemness maintenance (76) in ovarian (64), breast (77) and liver cancer (78,79). SCD1 overexpression also promotes CSC proliferation and prevents apoptosis (77,80). The enhanced activation of SCD1 and the consequent production of MUFAs could be considered as hallmarks of CSCs.

Sterol regulatory element binding protein 1 (SREBP1) belongs to the SREBP transcription factor family and serves an important role in the biosynthesis of FAs and cholesterol (81). SREBP1 is the major transcriptional regulator of lipogenesis and directly regulates several lipogenic enzymes, including ATP citrate lyase (ACLY), ACC1 and FASN (57,81). Overexpression of SREBP1 can promote the growth of various tumors and maintain the stemness of CSCs (81). On the other hand, SREBP1 can also induce the expression of SCD1, which further induces CSC generation and stemness maintenance (82).

FAO. It has been reported that elevated FAO could help nutrient-deficient and hypoxic cancer cells survival, especially those with glycolytic deficiency (83,84). On the one hand, FAO plays a key role in meeting the heightened energy demands of CSCs. On the other hand, FAO could reduce intracellular reactive oxygen species production and maintain an internal steady state (84).

Mevalonate pathway. 3-hydroxy-3-methylglutharyl-coenzyme A reductase is the rate-limiting enzyme in the mevalonate pathway and the molecular target of statins (85). The mevalonate pathway represents a metabolic pathway leading to the production of steroid hormones, cholesterol and non-sterol isoprenoids. The mevalonate cascade culminates in the production of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are essential for correct membrane anchoring of Rho family of small guanosine triphosphatases (GTPases). A number of oncogenic receptor tyrosine kinases require Ras proteins for signaling and EGFR signaling is particularly important for CSC maintenance. Furthermore, Rho GTPases maintain stemness by activating the Hippo transducers yes1 associated transcriptional regulator/tafazzin and by promoting the degradation of $P27^{kip}$, leading to inhibition of retinoblastoma protein activation, which is ultimately conducive to the differentiation of CSCs (86).

5. Lipid metabolism of several solid cancer CSCs

HCC. Liver cancer is the second leading cause of cancer mortality in the world. Among primary liver cancer, HCC is the major histological subtype (87). HCC CSCs are currently considered as a specific subpopulation with significant tumorigenic potential and contribute to the development and recurrence of HCC (88). At present, several special markers have been identified for HCC CSCs, including CD133. Studies have demonstrated that $CD133^+$ HCC CSCs show a significant enhancement of FAO rate and glycolysis, as well as a significant decrease in mitochondrial OXPHOS capacity (66,89).

In addition, inhibiting the prolongation of FAs in HCC CSCs results in a reduction in the content of polyunsaturated FAs, which is critical for HCC CSC ferroptosis resistance (66). NANOG is a critical regulator of HCC CSC lipid metabolic reprogramming. Knockdown of NANOG in HCC CSCs promotes the expression of FASN and ACLY, which is accompanied by increased OXPHOS and inhibition of glycolysis (66). Overexpression of NANOG induces $CD133^-$ HCC cancer cell dedifferentiation to $CD133^+$ HCC CSCs and enhanced FAO activity, indicating that NANOG serves a vital role in regulating FA metabolism in liver CSCs (66). Overall, these studies show that liver CSCs suppress OXPHOS. In general, HCC CSCs favor FAO to support their stemness, self-renewal ability and therapy resistance.

Colorectal cancer (CRC). CRC is the third most frequently diagnosed cancer and one of the most lethal types of cancer

Table I. Differences and similarities among bulk cancer cells, CSCs and normal stem cells.

Pathway	Key molecules	Function	Bulk cancer cells	CSCs	Normal stem cells
FA synthesis	ACLY	Catalyze citrate converting into acetyl CoA in the cytoplasm	Elevated in gastric adenocarcinoma	Elevated in non-small cell lung carcinoma or breast cancer stem cells	Required for normal stem cells proliferation. Upregulated in mouse neural stem cells and pluripotent cells, in particular ACC and FASN activity.
	ACC	Carboxylate acetyl-CoA into malonyl-CoA	Upregulated in the breast, gastric, and lung cancers	Elevated in IPSCs	
	FASN	*De novo* lipogenesis	Elevated in liver, prostate, breast, ovarian, endometrial and pancreatic cancers	Overexpressed in IPSCs, NSPCs, GSCs	
	SCD	Catalyzes the formation of MUFAs	Higher than non-cancer adjacent tissues	Elevated in the lung, ovarian, breast, and glioblastoma cancer stem cells. SCD-dependent MUFAs could directly regulate CSCs stemness	
	SREBP1	The major transcriptional regulator of lipogenesis	Promotes invasion and migration in breast cancer and colorectal cancer	Regulates stemness through lipogenesis and MUFAs formation by inducing SCD expression	
Mevalonate pathway	HMG-CoAR	The rate-limiting enzyme in the MVA pathway and the popular cholesterol synthesis lowering agents	Integral to tumor growth and progression	Essential for correct membrane anchoring of Rho GTPases which maintains stemness.	Cholesterol biosynthesis mediated by mevalonate pathway is required for NSPC self-renewal and maintenance.
FAO	CPT family	The rate-controlling enzyme in FAO	Upregulated in less glycolytic cancer types, such as prostate adenocarcinoma and diffuse large B-cell lymphoma	Fuels multiple CSCs, such as KRAS-mutant lung cancer and MYC-driven triple-negative	Various normal stem cells rely on FAO, such as hematopoietic stem cells, neural stem cells, intestinal stem cells and skeletal muscle stem cells.

CSCs, cancer stem cells; ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FASN, FA synthase; SCD, stearoyl-CoA desaturase 1; SREBP1, sterol regulatory element binding protein 1; HMG-CoAR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; MVA, mevalonate; CPT family, carnitine palmitoyltransferase family; FAO, fatty acid; FAO, FA oxidation; IPSCs, induced pluripotent stem cells; NSPCs, neural stem and progenitor cells; GSCs, glioma stem-like cells MUFA, monounsaturated FAs; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog.

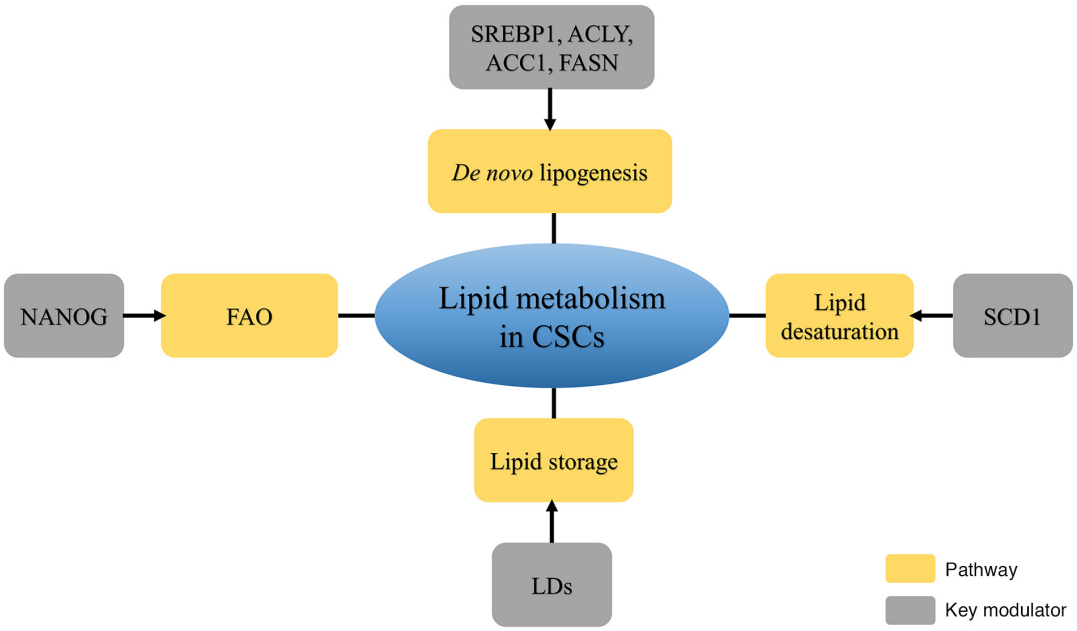

Figure 1. Diagram of four key pathways with related modulators of cancer stem cells. Increasing *de novo* lipogenesis, lipid desaturation, FAO and lipid storage participate in maintaining the properties of cancer stem cells. FAO, fatty acid oxidation; NANOG, Nanog Homeobox; LDs, lipid droplets; SCD1, stearoyl-CoA desaturase 1; SREBP1, sterol regulatory element-binding protein 1; ACLY, ATP citrate lyase; ACC1, acetyl-CoA carboxylase; FASN, fatty acid synthase; CSCs, cancer stem cells.

in both men and women worldwide (90). CRC CSCs induce tumorigenesis, proliferation, migration and metastasis of CRC. CRC CSCs are defined by a group of cell-surface markers, including CD44, CD133, CD24, epithelial cell adhesion factor molecule, leucine rich repeat containing G protein-coupled receptor 5 and Lin-28 homolog A (91). CRC CSCs also display a special lipid metabolism pathway. Genes associated with FA biosynthesis are downregulated, whereas genes involved in glycolysis, the TCA cycle and one-carbon metabolism pathway are upregulated in $CD133^{+}$ CRC CSCs, suggesting a strong preference to glycolysis but suppression of FA biosynthesis (92). Tirinato *et al* (69) found that $CD133^{+}$ CSCs contain more lipids. The lipid content in cancer cells is also positively correlated with the expression level of CD133 and Wnt/β-catenin pathway activity, which are markers of CSCs (69). $CD133^{high}$ cells possess more LDs compared with $CD133^{low}$ cells. Using the label-free Raman spectroscopy technology, researchers reported that the number of LDs in CRC CSCs was related to their tumorigenicity. The higher the number of LDs, the stronger the tumorigenicity (69). LDs may potentially open a new horizon for more specific *ex vivo* CRC CSCs diagnostics.

GBM. As the most common primary malignant brain tumor, GBM is extremely aggressive, with a median overall survival of <15 months (93). GBM CSCs contribute to the aggressive behaviors of GBM. GBM CSCs are considered to locate in a special environment, including perivascular, hypoxic and necrotic niches, as well as tumor border regions. Identified by the incorporation of ^{14}[C]-glucose and ^{14}[C]-acetate into the lipids, GBM CSCs are reported to have a higher rate of *de novo* lipogenesis compared with differentiated non-stem cancer cells (72). Increased *de novo* lipogenesis and extracellular lipid uptake result in LD accumulation in GBM CSCs (94). Moreover, GBM CSCs express a higher level of FASN protein, which facilitates the synthesis of FAs. Increased *de novo* lipogenesis may also contribute to the upregulation of FASN, thus maintaining the stemness of GBM CSCs (72). Inhibition of FASN expression decreased the expression of stemness markers and inhibited the proliferation and migration of GBM CSCs (72).

Pancreatic cancer. Pancreatic carcinoma is the fourth leading cause of mortality (95). Pancreatic CSCs were identified in 2007 (96). Metabolism reprogramming is reported as a critical factor in pancreatic CSC survival and stemness maintenance (97). Higher FA synthesis and activation of the mevalonate pathway are observed in pancreatic CSCs compared with pancreatic carcinoma non-stem cancer cells (65). Acetoacetyl-CoA transferase (ACAT2) synthesizes acetoacetyl CoA in the mevalonate pathway and leads to the elevation of cholesterol, which is significantly upregulated in pancreatic CSCs (65). Inhibition of FASN and ACAT2 reduces FA and cholesterol synthesis, which further decreases pancreatic CSC viability (65). Furthermore, the prognosis of patients with PDAC with high FASN expression levels is significantly worse and it has been proven that it depends on the induction of EGFR/ERK signaling, which is critical for pancreatic CSC maintenance (98).

6. Summary

CSCs, with their self-renewal and tumor-initiating abilities, serve an important role in metastatic dissemination, radioresistance, chemoresistance and recurrence. A review on metabolomics demonstrated the contribution of lipid metabolism to the generation and maintenance of CSCs (76). Lipid metabolism reprogramming, including *de novo* lipogenesis and the formation of LDs and FAO, is involved in CSC generation and stemness maintenance (Fig. 1).

Thus, understanding the mechanisms underlying CSC lipid metabolism reprogramming, as well as identifying the

differences in lipid metabolism between CSCs and non-stem cancer cells will be of significance for improving the current clinical treatment of cancer. Several therapeutic targets of lipid metabolism have been developed to enhance antitumor effects (99). For instance, SCD1 inhibitors, CAY10566 and A939572, targeting FA desaturation process effectively suppress cancer stemness and tumor progression (64). As CSCs have been widely investigated, the development of effective agents targeting lipid metabolism and ameliorating radioresistance or chemoresistance is important.

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YL and JG designed the structure of the review. LS revised the manuscript critically for important intellectual content. HL and ZZ wrote and reviewed the article. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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