Review

The role of Wnt signaling pathway in tumor metabolic reprogramming

Yongzhen Mo[1,2,3#], Yumin Wang[1,2#], Lishen Zhang[2], Liting Yang[1], Ming Zhou[1,2,3], Xiaoling Li[2], Yong Li[4], Guiyuan Li[1,2,3], Zhaoyang Zeng[1,2,3], Wei Xiong[1,2,3], Fang Xiong[1,2,3✉], Can Guo[1,2,3✉]

1. NHC Key Laboratory of Carcinogenesis, Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410078, China
2. The Key Laboratory of Carcinogenesis and Cancer Invasion of the Chinese Ministry of Education, Cancer Research Institute and School of Basic Medical Science, Central South University, Changsha 410078, China
3. Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, The Third Xiangya Hospital, Central South University, Changsha, Hunan, China.
4. Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA

# These authors contributed equally.

✉ Corresponding authors: guocde@csu.edu.cn or xiongf@csu.edu.cn

Abstract

The occurrence and development of tumors is a complex process involving long-term multi-factor participation. In this process, tumor cells from a set of abnormal metabolic patterns that are different from normal cells. This abnormal metabolic change is called metabolic reprogramming of tumors. Wnt signaling pathway is one of the critical signaling pathways regulating cell proliferation and differentiation. In recent years, it has been found that Wnt signaling participates in the occurrence and development of malignant tumors by affecting metabolic reprogramming. This paper reviews the role of Wnt signaling in tumor metabolic reprogramming to provide crucial theoretical guidance for targeted therapy and drug response of tumors.

Key words: tumor metabolic reprogramming, Wnt signaling, targeted therapy

Introduction

The occurrence and development of tumors is a complex process involving long-term multi-factor participation [1-6]. In this process, tumor cells from a set of abnormal metabolic patterns different from normal cells, providing the energy and raw materials needed for their life activities. This abnormal metabolic change is called metabolic reprogramming of tumors [7-10]. In 1930, Warburg proposed the Warburg effect of abnormal glucose metabolism in tumors, that is, tumor cells obtain energy mainly through anaerobic glycolysis [11]. Subsequently, it was found that tumor cells also have changes in amino acid metabolism and fat metabolism, thereby providing energy and raw materials for biomacromolecule synthesis [12-14]. In recent years, it has been found that the metabolic reprogramming of tumor cells also includes pentose phosphate bypass, lipid and protein and anabolism associated with

nucleic acid synthesis, and a large number of endogenous oxygen free radicals, which are involved in the development of tumors has played an important role [15-18].

Wnt signaling pathway is one of the critical signaling pathways regulating cell proliferation and differentiation and plays an essential role in normal physiological activities such as growth and development and pathological processes including malignant tumors [19-23]. The Wnt signaling pathway is composed of various signal molecules, ligands and receptors such as Wnt protein and β-catenin, and is very conservative in evolution [24]. It mainly consists of three pathways: the classical Wnt pathway, the Wnt/Ca²⁺ pathway, and the planar cell polarity (PCP) pathway. In recent years, a large number of studies have found that the Wnt signaling pathway can affect the occurrence of obesity and diabetes by affecting the

metabolism of normal cells [25-28]. Further studies have shown that the Wnt pathway can also change the metabolism of tumor cells, thereby participating in the occurrence and development of malignant tumors by changing metabolic reprogramming [29-32].
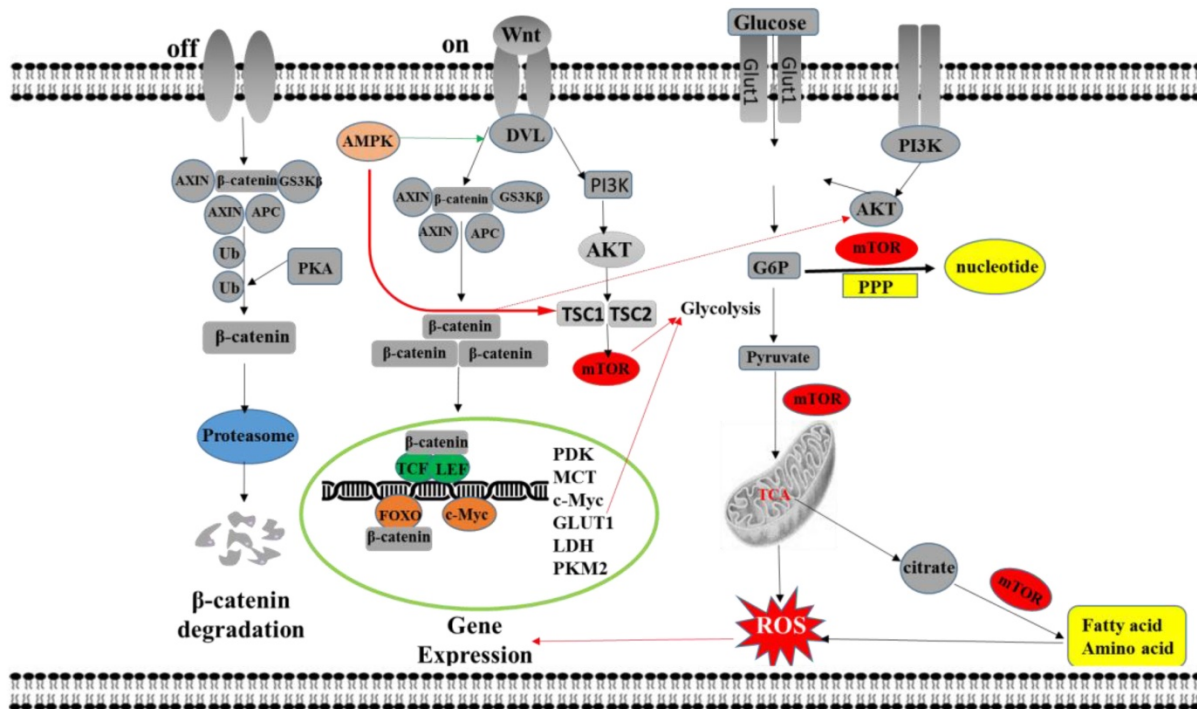
1. Tumor metabolism reprogramming is one of the characteristics of malignant tumors

Metabolic reprogramming is one of the prominent features of tumor cells, including all metabolic changes in tumor cells [33-36]. Abnormal glucose metabolism is the earliest discovered metabolic reprogramming. Under aerobic conditions, tumor cells are also mainly powered by the glycolysis pathway. This metabolic abnormality is also known as the Warburg effect [37-39]. That is, when the mitochondrial function of the tumor cells is dysfunctional, the cells obtain energy mainly by enhancing anaerobic glycolysis [40-44]. That is, after glucose is metabolized to pyruvic acid, it does not enter the tricarboxylic acid cycle for aerobic oxidation but is converted to lactic acid by lactate dehydrogenase [45]. However, because tumor cells are energy-efficient through the glycolysis pathway,

to maintain the energy required for their life activities, tumor cells, in addition to increased glucose consumption, also increase energy supply by increasing fat metabolism [46-49]. It is characterized by de novo synthesis of fatty acids and active beta-oxidation, thus providing an adequate supply of energy through increased fat metabolism [50]. In addition, due to the uncontrolled nature of tumor cell proliferation, anabolism of fatty acid synthesis and amino acid metabolism of tumor cells has also changed [51, 52]. In tumor cells, the pentose phosphate pathway, the hexose synthesis pathway, the serine/glycine synthesis pathway, and the glutamate-glutamine cycle are all increased, thereby providing the required raw materials for the synthesis of biological macromolecules such as ribonucleic acid and protein [53-59].Also, the number of oxygen free radicals (ROS) in tumor cells increased compared with normal cells, and increased ROS stimulated the proliferation of tumor cells [60-62]. The purpose of tumor metabolic reprogramming is to drive limited nutrients or intermediate metabolites to be more "effectively" utilized by tumor cells to support the vigorous metabolic demands of tumor cell development and progression [63] (Figure 1).
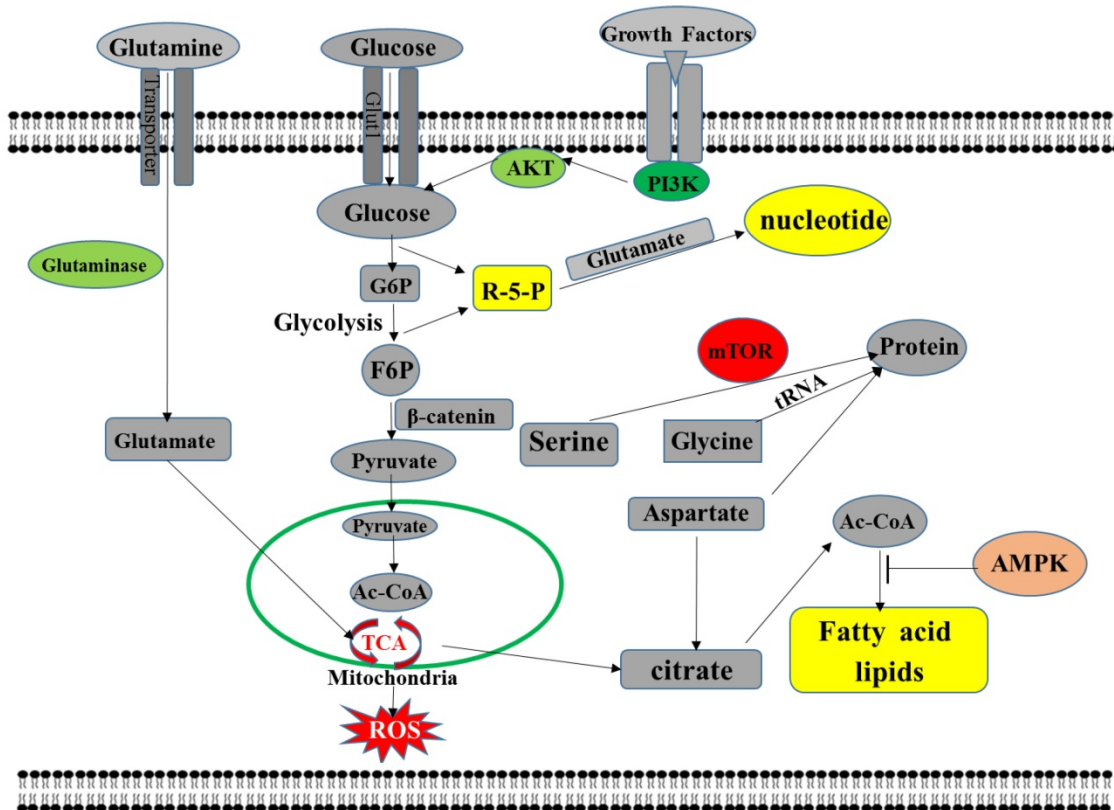
Figure 1: metabolic pathways in cancer cells. Highly proliferating cells promote glucose catabolism and glutamine catabolism by regulating key metabolic pathways, driving molecular synthesis and maintaining energy balance through molecular interactions. Cancer cells use aerobic glycolysis to produce ATP and promote pyruvate synthesis to promote glycolysis by increasing the expression of glycolytic enzymes. Tumor cells also produce macromolecules such as NADPH and 5-carbon sugar-driven nucleic acids via the pentose phosphate pathway. The citrate from the TCA cycle is exported to the cytosol and further converted to acetyl-CoA for the synthesis of lipid acids.

Figure 2: The network of Wnt signaling regulates tumor metabolism reprogramming. The activated Wnt signaling pathway promotes the up-regulation of MCT-1, CYC1 and ATP synthase by the downstream transcription factor TCF/LEF, resulting in the secretion of intracellular lactate and the occurrence of aerobic glycolysis. Wnt signaling pathway can also up-regulate the expression of GLUT-1, LDH, PKM2, SLC1A5 and other genes by c-Myc promoting glycolysis, nucleotide and fatty acid synthesis in tumor cells. The non-canonical Wnt signaling pathway promotes aerobic glycolysis by activating Akt-mTOR to stabilize the expression of mTORC1 and β-catenin. The activated mTOR pathway promotes glucose uptake by increasing glucose transporter expression. On the other hand, the mTOR pathway can also lead to an increase in fatty acid synthesis by up-regulating the expression of acetyl-CoA, resulting in an increase in fatty acid oxidative metabolism. In addition, activation of the mTOR pathway can also result in upregulation of glucose-6-phosphate dehydrogenase, resulting in enhanced pentose phosphate bypass and promotion of ribonucleic acid synthesis. ROS levels can directly affect the transcriptional activity of β-catenin. ROS can interact with TCF4, alter the binding of β-catenin to TCF, and interact with the transcriptional link factor of FOXO3a, thereby changing the gene expression of cells and promoting tumorigenesis.

2. Wnt signaling regulates tumor metabolism reprogramming

As a highly conserved signaling pathway in evolution, the Wnt signaling pathway plays an essential role in many biological processes such as growth, development, metabolism, and stem cell maintenance, while the Wnt pathway is out of control and occurs in diseases such as cancer, obesity, and diabetes [64, 65]. The Wnt signaling pathway acts as a critical regulatory pathway, similar to that involved in metabolic alterations in normal cells, and is also engaged in swollen metabolic reprogramming in tumor cells. Current research indicates that the Wnt pathway can also mediate the regulation of tumor cell metabolism, thereby participating in tumor development and progression by affecting tumor cell metabolism reprogramming [66]. The current study found that the Wnt signaling pathway can participate in the metabolic reprogramming of tumors through the regulation of multiple downstream signaling pathways such as TCF/LEF, c-myc and Akt-mTOR pathway [67-69]. The Wnt signaling pathway can also indirectly affect metabolic pathways by directly regulating the expression of rate-limiting enzymes in metabolic pathways and by regulating other

oncogenes, leading to metabolic changes in cells (Figure 2).

2.1 Wnt pathway participates in tumor metabolic reprogramming through TCF/LEF pathway

Current studies indicate that the metabolism of malignant tumor cells is mainly regulated by the canonical Wnt pathway , while the classical Wnt signaling pathway can also exert biological functions through the downstream transcription factor TCF/LEF [70-73]. When TCF/LEF is activated, the expression of MCT-1, CYC1, and ATP synthase is up-regulated, resulting in intracellular lactate secretion and aerobic glycolysis [74]. This not only leads to an increase in aerobic glycolysis but also provides essential energy for tumor cells, while a large amount of lactic acid secretion also induces secretion of factors such as VEGF, thereby promoting tumor angiogenesis [75-77]. In addition to affecting tumor cells themselves, the Wnt pathway is also involved in the formation of the tumors microenvironment [78-80]. Although alterations in fatty acid (FA) metabolism in cancer cells have received less attention compared to other metabolic alterations such as glucose or glutamine metabolism,

recent studies have uncovered the importance of lipid metabolic reprogramming in carcinogenesis [81]. By activating TCF/LEF to inhibit the expression of PPARγ and C/EBPα in adipocytes around the tumor, it promotes the fat degradation of fat cells, thus providing the necessary conditions for the fat supply of tumor cells [82, 83].

2.2 Wnt pathway participates in tumor metabolic reprogramming through the c-mycpathway

Metabolic alterations attributable to Myc are due to quantitative and not qualitative differences in its behavior, thus making it somewhat easier to understand its role in normal metabolic processes. In metabolic reprogramming, the classical Wnt signaling pathway can be involved in tumor metabolic reprogramming by over-activation of c-Myc [84, 85], c-Myc's overexpression in cancer can most likely be attributed to the fact that it is a major transcriptional integrator of most, if not all, normal and oncogenic growth factor pathways, c-Mycis activated as a transcription factor by binding to a specific gene sequence (CACGTG), the most prominent transcript families under Myc's control tend to encode proteins that supervise energy production, anabolic pathways, protein synthesis, thereby up-regulating the expression of genes such as GLUT-1, PDH, PFK1, HK, LDH, PKM2, and SLC1A5[86-90], thereby correspondingly causing cells. Increased internal glucose uptake, accelerated glycolysis, and increased glutamine-glutamate cycling. Thereby promoting the glycolysis, nucleotide and fatty acid synthesis in tumor cells, providing tumor cells with the substances and energy required for proliferation [91-94]. Also, c-myc can also up-regulate the expression of FOXOs, thereby increasing the production of reactive oxygen species and inducing autophagy in tumor cells, thereby recycling intracellular proteins and lipids through autophagy to other growth and substances required for proliferation[95-101].

2.3 Wnt pathway involved in tumor metabolic reprogramming through the Akt-mTOR pathway

Cells grow and proliferate when nutrients, growth factors and the cellular energy status trigger carbohydrate catabolism and the synthesis of essential building blocks such as proteins, nucleotides and lipids. The evolutionarily conserved Ser/Thr protein kinase target of rapamycin mTORC1 is activated by other pathways such as Wnt signalling. The Wnt signaling pathway is involved in tumor metabolic reprogramming mainly through activation of Akt -mTOR. Wnt signalling stimulate mTORC1 through

the PI3K–phosphoinositide-dependent kinase 1 (PDK1)–AKT pathway. Activated AKT phosphorylates tuberous sclerosis complex 2 (TSC2; also known as tuberin) to activate the metabolic pathways that ultimately drive cell growth [102, 103]. In comparison to mTORC1 regulation, mTORC2 regulation is poorly understood, mTORC2actived by the hydrophobic motif in a subset of AGC family kinases such as PKA, PKG, PKC , including AKT Glycogen synthase kinase 3β (GSK3β) Wnt signalling inhibits GSK3β and the TSC complex, and thus activates mTORC1 and mTORC2 [104-107]. The activated mTOR pathway promotes glucose uptake by cells by increasing the expression of glucose transporters [108]. On the other hand, the mTOR pathway can also lead to an increase in fatty acid synthesis by up-regulating the expression of acetyl-CoA, resulting in the increased oxidative metabolism of fatty acids [109-111]. Activation of the mTOR pathway can also lead to up-regulation of glucose-6-phosphate dehydrogenase, leading to enhanced pentose phosphate bypass and more feedstock for ribonucleic acid synthesis [112-116].

2.4 Wnt pathway participates in tumor metabolic reprogramming by regulating the expression of rate-limiting enzymes in metabolic pathways

Regulation of the Wnt signaling pathway also includes control of metabolic enzymes, and β-catenin-mediated c-Myc expression leads to up-regulation of several rate-limiting glycolytic genes, including those for glucose transporter 1 (GLUT-1)), LDH and pyruvate kinase, the last step in catalyzing glycolysis produces ATP and pyruvate, which promotes aerobic glycolysis in cancer cells [117-120]. When the mitochondrial function of tumor cells is dysfunctional, the cells obtain energy mainly by enhancing anaerobic glycolysis. After glucose is metabolized to pyruvic acid, it does not enter the tricarboxylic acid cycle for aerobic oxidation but is converted to lactic acid by lactate dehydrogenase [121-124]. In ovarian cancer, a large number of metabolic genes have been found to be targets of transcription, including participation in glutamine metabolism and fatty acid metabolism [125-127]. In breast cancer, Wnt/β-catenin increases the aerobic glycolysis process by reducing the expression of the cytochrome c oxidase that inhibits mitochondrial respiration [128, 129]. Also, recent studies have demonstrated that Wnt5b regulates the expression of oxidative phosphorylation-related genes, such as cytochrome C1 and ATP synthase, through the canonical Wnt pathway [130]. In colorectal cancer cells, aerobic glycolysis is promoted, pyruvate

synthesis is increased, and pyruvate dehydrogenase (PDH) activity in mitochondria is inhibited to reduce pyruvate oxidation, resulting in more conversion of pyruvate to lactic acid. The glycolytic enzyme PKM2 is a pleopoietic protein that acts as a transcriptional coactivator. In the signaling of various cancer cell types, PKM2 interacts with β-catenin to cause β-catenin transcriptional changes, resulting in up-regulation of c-myc expression [131, 132].

In addition to the above regulation, the Wnt signaling pathway is also regulated by the expression of reactive oxygen species (ROS) [133]. The phenomenon of elevated reactive oxygen species is common in tumor cell, which is mainly caused by accelerated metabolic activity, mitochondrial dysfunction, cell receptor signal enhancement, oncogene, oxidase and cyclooxygenase activity [134-136]. Low levels of ROS, by reversibly oxidizing protein sulfhydryl groups, altering protein structure and function involved in the transduction of cellular signaling pathways, also can cause DNA instability and mutations, leading to genomic instability and, ultimately, canceration of cells [137]. Mitochondria are an important source of ROS. In tumor cells, ROS levels can directly affect the transcriptional activity of β-catenin. ROS can replace the interaction between β-catenin and TCF4, and change the binding of β-catenin to TCF to transcriptional catenin with FOXO3a. The role of factors, which in turn changes the gene expression of cells, regulates the occurrence and development of tumors [138, 139]. The oxidative stress process also activates DVL levels upstream of the canonical Wnt signal, which interacts with thioredoxin family proteins to activate independent Wnt signals outside the classical Wnt signaling pathway [140-142]. Thus, oxidative stress in tumor cells regulates the canonical Wnt signaling pathway to alter gene transcriptional changes, promoting tumor cell autophagy via the mTORC1-independent pathway [143, 144]. Under nutrient pressure or other stress conditions, tumor cells can recycle cellular proteins and lipids and convert them into other substances needed for survival, helping tumor cells to pass through the harsh cellular microenvironment [145-148].

3. Prospect

Metabolic reprogramming of cells is one of the important features of tumors. And with the deepening of research, people's understanding of tumor metabolism reprogramming is no longer limited to changes in glucose metabolism such as glycolysis and tricarboxylic acid cycle, but also includes many metabolic pathways such as fatty acid metabolism, cholesterol metabolism, and amino acid metabolism change [149-152]. As one of the important signaling pathways regulating cell metabolism reprogramming, Wnt signaling pathway has been found to regulate the metabolism of tumor cells through downstream signaling pathways such as mTOR and c-myc.In addition to the pathways mentioned above, recent studies have shown that the Wnt pathway can also interact with hippo pathway regulating tumor metabolism. Wnt pathway mediates TAZ expression, upregulates IRS1 and stimulates Akt- and Glut4-mediated glucose metabolism [153].In addition Wnt pathway a key scaffolding protein Dishevelled (DVL), is responsible for nuclear export of phosphorylated YAP, DVL is also required for YAP intracellular trafficking induced metabolic stress. Note that the p53/LATS2 and LKB1/AMPK tumor suppressor axes regulating tumor metabolism reprogram [154]. Stearoyl-CoA desaturase 1 (SCD1)a central enzymatic in the conversion of saturated fatty acids, enhances the production of lipid-modified Wnt proteins that activate the canonical Wnt pathway. Activation of the Wnt pathway leads to the release of both β-catenin and YAP/TAZ from the destruction complex. This enables β-catenin and YAP/TAZ to translocate to the nucleus where, upon interaction with their transcriptional partners, they mediate the cancer metabolism reprogramming [155]. In addition, studies have shown that non-coding RNAs such as miRNA and lncRNA as well as circular RNA can regulate tumor metabolism by regulating the Wnt pathway [156-169].Also, current studies have found that abnormal changes in cellular metabolism precede tumorigenesis. Therefore, molecular markers related to tumor metabolism have important clinical value, which can provide new ideas for the development of new molecular markers and early diagnosis of tumors [170-172]. The relationship between abnormal activation of the Wnt signaling pathway and tumors and multi-level target anticancer therapy of the Wnt signaling pathway has become a new research hotspot in tumor molecular biology. These findings provide direct evidence that metabolic changes can promote tumorigenesis, and the key nodes of its regulation are also becoming potential targets in tumor diagnosis and treatment and will provide important theoretical guidance for targeted therapy and precision medicine of tumors. The tumor microenvironment is closely related to the occurrence and development of cancer [173-177]. Nutritional competition between cells can significantly affect cell growth, survival, and function. Glucose restriction caused by tumors alters the metabolism of T cells, which in turn affects their function. Studies have shown that, tumor glucose consumption metabolically limits T cells, inhibiting their mTOR activity, glycolysis, and IFN-γ

production, allowing tumors to develop further. This mechanism can help people develop more effective cancer immunotherapy, better liberate the immune system, and achieve long-lasting anti-cancer effects [178-182]. Wnt pathway regulates PDL1 to regulate tumor immune escape by regulating the expression of ALDH [183]. Tumor cells can also derived Wnt ligands stimulate M2-like polarization of TAMs through c-Myc via canonical Wnt/β-catenin signaling, which results in tumor immunosuppression [184]. In conclusion, through in-depth study of Wnt pathway and tumor metabolic reprogramming, it will further expand people's understanding of the etiology of malignant tumors and will provide an important theoretical basis for humans to overcome malignant tumors finally.

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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