REVIEW ARTICLE

The remodel of the "central dogma": a metabolomics interaction perspective

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Abstract

Background In 1957, Francis Crick drew a linear diagram on a blackboard. This diagram is often called the "central dogma." Subsequently, the relationships between different steps of the "central dogma" have been shown to be considerably complex, mostly because of the emerging world of small molecules. It is noteworthy that metabolites can be generated from the diet through gut microbiome metabolism, serve as substrates for epigenetic modifications, destabilize DNA quadruplexes, and follow Lamarckian inheritance. Small molecules were once considered the missing link in the "central dogma"; however, recently they have acquired a central role, and their general perception as downstream products has become reductionist. Metabolomics is a large-scale analysis of metabolites, and this emerging field has been shown to be the closest omics associated with the phenotype and concomitantly, the basis for all omics.

Aim of review Herein, we propose a broad updated perspective for the flux of information diagram centered in metabolomics, including the influence of other factors, such as epigenomics, diet, nutrition, and the gut- microbiome.

Key scientific concepts of review Metabolites are the beginning and the end of the flux of information.

Keywords Metabolomics · Central dogma · Small molecules · Metabolites

1 Introduction

Sixty-three years ago, Francis Crick gave a lecture in which he presented the diagram called the "central dogma." This dogma states that the transfer of information from DNA to DNA/RNA, or from nucleic acid to protein, may be possible, but the transfer from protein to protein or protein to nucleic acid is impossible (Cobb, 2017; CRICK, 1957).

The flux of information attained another dimension when small molecules advanced to the forefront of chemical

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biology. In 2005, Dr. Schreiber was the first to describe small molecules as the missing link in the central dogma and as the central elements of life (Schreiber, 2005). Consequently, the perception of small molecules as only downstream products became reductionist, as they have been shown to modulate all steps in the flux of information, including the phenotype (Chang et al., 2008; Guijas et al., 2018; Kondratov et al., 2001; Mathew & Padmanaban, 2013; Patti et al., 2012; Rabinowitz & Silhavy, 2013; Yugi & Kuroda, 2018). In 2016, for the first time, a white paper provided recommendations to include metabolomics in precision medicine (Beger et al., 2016). In recent years, several papers have described an integrative data analysis with metabolomics (Ahmed et al., 2021; Damiani et al. 2020; Hou et al., 2020; Long et al., 2020; Mussap et al., 2021; Xie et al., 2021). In the last 20 years, the advance of important analytical tools, such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS), has led to the advocacy of small molecules, by the large-scale analysis called metabolomics. These exceptional omics techniques have made it possible to build the Human Metabolome Database (Wishart et al., 2018) and the Biological Magnetic Resonance Data Bank (Ulrich et al., 2007). The assignment of several metabolites

has been extremely important for revealing distinct metabolic pathway shifts related to the phenotype, such as the polyol pathway detour under vitamin D intake (Santos et al., 2017), enhanced lipid metabolism in oral cancer (Sant'Anna-Silva, 2018), glycerol metabolism in osteoarthritis (de Sousa et al., 2017a, 2017b, 2019), glutaminolysis in cancer (DeBerardinis et al., 2007; Koczula et al., 2016; Rodrigues et al., 2016; Yang et al., 2016), tumor microenvironments (Costa Dos Santos et al., 2021), and COVID-19 (Costa dos Santos Junior et al., 2020).

Metabolites are the substrates and products of molecular mechanisms linked to the steps in the flux of information. Molecular modulation can start outside the host organism, as metabolites can come from the metabolism of microorganisms, diet, and other exogenous sources (Johnson et al., 2012; Martin et al., 2007; Tang et al., 2015). One good example of a metabolite is trimethylamine N-oxide (TMAO), commonly found in urine; it can be generated directly from the diet by ingestion of fish, or indirectly from gut-microbiome choline metabolism (Thøgersen et al., 2020; Thomas & Fernandez, 2021; Ufnal et al., 2015).

TMAO can affect the proteome, as MAP kinase and nuclear factor-κB (NF-κB) proteins can be activated by TMAO in endothelial cells, and high levels of this metabolite are associated with cardiovascular diseases (Bennett et al., 2013; Gibson et al., 2020; Seldin et al., 2016; Zeisel & Warrier, 2017). The mechanism of interaction of TMAO with proteins is still unknown; however, there is evidence that it can influence enzyme activity and protein stability (Hu et al., 2010; Mashino & Fridovich, 1987). TMAO can affect the genome, epigenome, and transcriptome by stabilizing DNA G-quadruplex structures (Knop et al., 2018; Ueda et al., 2016), altering levels of DNA methylation (Knight et al., 2018), and stabilizing RNA tertiary structures (Denning et al., 2013; Lambert et al., 2010), respectively. In addition, other factors can affect TMAO levels, such as age and sex (Rossner et al., 2017).

Herein, we discuss various pieces of evidence to shed light on the main role of metabolites shaping the other omics levels, such as the epigenome, genome, transcriptome, and proteome (Adamski & Suhre, 2013; Anders et al., 2014; Bhaduri et al., 2018; Choi et al., 2018; Dervan, 2001; Etchegaray & Mostoslavsky, 2016; Francisco & Paulo, 2018; Gao et al., 2016; Kimball & Vondriska, 2020; Neidle, 2001; Padmanabhan et al., 2013; Pogribny et al., 2008; Reid et al., 2017; Rodriguez & Miller, 2014; Tzika et al., 2018; Usanov et al., 2018; Wilson & Li, 2012), as shown in Fig. 1. In addition, this evidence is particularly important in the multiomics era, because it can reveal the modes of action of small molecules, accelerate drug development (Patel-Murray et al., 2020), reveal gut-microbiome alterations (Li et al., 2020a, 2020b), and link with machine learning for diagnoses, such as COVID-19 (Delafiori et al., 2021).
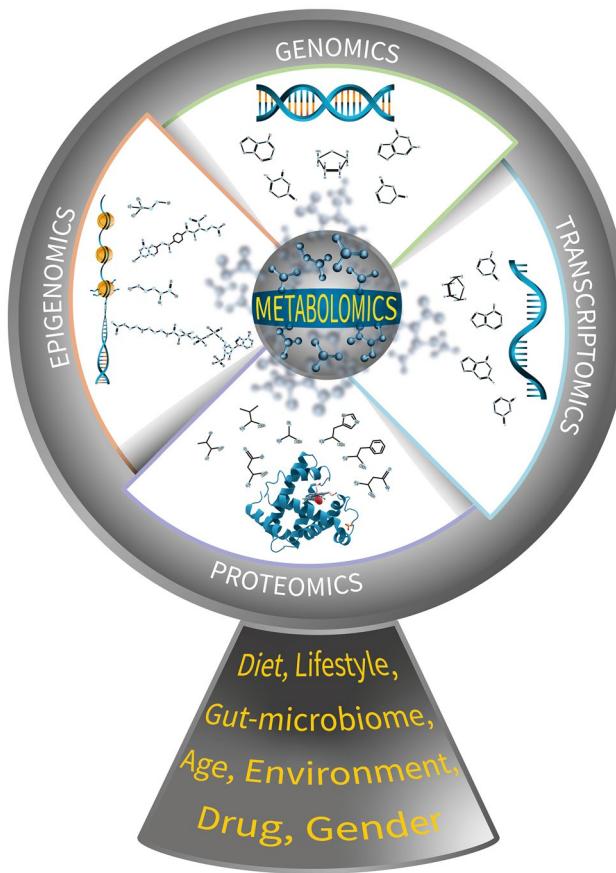
Fig. 1 Small molecules are the center of life. A multiinteraction dynamic perspective of the flux of information centered on metabolomics. The small molecules drive all other omics, as a rotor drives the blades in the turbine of a windmill. External factors such as diet, lifestyle, gut-microbiome, age, drug, and sex will affect the metabolomics, e.g. the center of the flux of the information, and consequently affect all other omics

2 Metabolite–macromolecules interactions and modifications

Metabolites can interact with macromolecules through competitive and allosteric binding to the active site of enzymes, leading to alterations in enzyme activity. This is not exclusive to enzymes; it occurs in other signaling proteins, such as G protein-coupled receptors (GPCRs). The succinate receptor (*SUCNR1*/GPR91), a cell-surface sensor for extracellular succinate, was shown to be upregulated in mice-activated macrophages, which function as an autocrine and paracrine sensor for extracellular succinate to enhance interleukin 1β (IL-1β) production (Littlewood-Evans et al., 2016). The GPCR (GPR132), which can sense and respond to lactate, was shown to promote an M2-like protumoral phenotype in mice macrophages, stimulating cancer metastasis (Chen et al., 2017). Lactate controls muscle regeneration

by inducing M2-like macrophage polarization (Zhang et al., 2020). Some GPCRs (GPR40 and GPR120), which are activated by several fatty acids, including palmitic acid esters of hydroxystearic acids (PAHSAs) in mice and human models, are targets of type II diabetes therapies (Syed et al., 2018; Yore et al., 2014). In neutrophils, short-chain fatty acids engage with GPR43, inducing chemotaxis (Vinolo et al., 2011). Thus, the binding of metabolites to proteins, such as receptors, induces specific cellular responses, leading to the activation of specific signaling pathways.

Additionally, metabolites are related to prions. The cellular prion protein, PrP^c is a cell-surface glycoprotein anchored to the plasma membrane via glycosylphosphatidylinositol (GPI). PrP^c is found in mammalian tissues, mostly in neuronal cells, despite some evidence of its involvement in signal transduction (Bate et al., 2016; Mouillet-Richard et al., 2000), memory formation, peripheral myelin maintenance, circadian rhythm neuroprotection, and immune system activation (Dearmond et al., 1999; Ermonval, Mouillet-Richard, Codogno, Kellermann, & Botti, 2003). Although the exact role of PrP^c is not well defined, it is well known that PrP^c is the pathology of its misfolded isoform related to disease, PrP^{sc}. This isoform can aggregate with other PrP molecules, causing a fatal neurodegenerative process (Ermonval et al., 2003). Glycosylation is strongly related to glucose and glutamine metabolism (Carvalho-cruz et al., 2018): it is the most important posttranslational modification of PrP. Unglycosylated PrP has been reported to induce apoptosis in oral squamous cell carcinoma and colon adenocarcinoma (Yap & Say, 2011). Another study reported that glycosylation is important for determining the PrP location on the membrane, to inhibit its aggregation and diminish its cytotoxicity by lowering the intracellular levels of reactive oxygen species (ROS) (Yi et al., 2018).

In 2012, Koonin refuted the "central dogma" idea that information cannot be transferred from proteins to the genome. This refutation is based on the genetic assimilation of prion-dependent phenotypic heredity, which is mediated by epigenetic mechanisms. He named it the "general look-ahead effect" (Koonin, 2012). Conventionally, epigenetic modifications comprise all aspects of the chromatin structure, histone posttranslational modifications, RNA, DNA methylation, or hydroxymethylation, and metabolites act as the substrates for these modifications (Carrer & Wellen, 2014; Gerhäuser, 2012; Janke et al., 2015; Johnson et al., 2015; Petersen et al., 2014; Roberti et al., 2021). In 1942, Waddington introduced the concept of epigenetics. He defined internal and external interactions between genes and their products, leading to the development of phenotypes (Waddington, 1942). In recent years, this concept has been slightly updated to the most accepted definition: "the study of mitotically and/or meiotically heritable changes in

gene function that cannot be explained by changes in DNA sequence" (Robertson, 2005).

Posttranslational modifications of histones are involved in the repression or activation of gene transcriptions and can be linked to DNA methylation. One good example is histone acetylation, through an acetyl donor, the metabolite acetyl-CoA, which modifies the chromatin structure and creates an accessible structure that is beneficial for transcription. The availability of the metabolite acetate and its pathway is important for maintaining acetylation levels (Di Cerbo & Schneider, 2013; Pogo et al., 1966; Turner & O'Neill, 1995; Wolfe, 2005). In addition, histone acetylation is responsible for generating binding sites that are recognized by bromodomain-containing regulators, promoting gene activation (Filippakopoulos & Knapp, 2014; Shogren-Knaak et al., 2006). Acetate supplementation restored chromatin accessibility in a neuroblastoma differentiation model (Li et al., 2020a, 2020b). Lauterbach et al. observed that in macrophages, lipopolysaccharide (LPS) signaling promotes the incorporation of acetyl-CoA into histones through an increased glycolytic flux and ATP-citrate lyase activity. This histone acetylation induces specific gene sets associated with proinflammatory responses (Lauterbach et al., 2019).

In addition to acetyl-CoA, there are other metabolites responsible for posttranslational modifications, such as succinyl-CoA (succinylation) and sugar molecules, such as uridine 5'-diphosphoglucose (UDP-glucose) (glycosylation and GlcNAcylation). Succinylation was observed to mediate the mitochondrial translocation of pyruvate kinase M2 (PKM2), thereby playing a role in switching the cellular machinery from proliferation to cell survival mode and vice versa in cancer cells (Qi et al., 2019). In macrophages, Lys311 is a key succinylated site in the regulation of PKM2 activity, promoting inflammation (Wang et al., 2017). O-GlcNAcylation plays an important role in the regulation of cellular signaling, translation, and transcription in response to nutrients and stresses (Li et al., 2019; Ong et al., 2018); glycosylation is important in the correct folding and trafficking of proteins, such as Relmα, CD206, and CD301, which are destined for secretion or exportation to the cell surface in anti-inflammatory macrophages (Jha et al., 2015).

In addition, α-ketoglutarate and flavin adenine dinucleotide (FAD) from the tricarboxylic acid cycle (TCA) increase DNA demethylase, while succinate and fumarate function as antagonists to inhibit such demethylases, thus demonstrating the pivotal role of TCA in epigenetic reprogramming (Xiao et al., 2012) and tumorigenesis (Kaelin & McKnight, 2013; Martínez-Reyes & Chandel, 2020; Soga, 2013). Previous studies have demonstrated that mutations in metabolic enzymes, such as succinate dehydrogenase, fumarate hydratase, and NADP+-dependent isocitrate dehydrogenase (both cytosolic and mitochondrial) favor the generation of oncometabolites through the accumulation of succinate and

fumarate, triggering hypermethylation of DNA (Eijkelen-kamp et al., 2020; Mohammad et al., 2020; Parsons et al., 2008; Ward et al., 2010; Zhu et al., 2020).

Methylation and demethylation are key modifications of histones, DNA, and RNA; they play an important role in the regulation of gene expression and are essential for cell differentiation and embryonic development (Bachman et al., 2014; Petkovich et al., 2017). In this process, the methyl group of the metabolite, S-adenosylmethionine (SAM), is donated to the methyl transferase enzymes (Warth et al., 2017). DNA methylation is strongly associated with histone deacetylases (HDACs), leading to chromatin inactivation (Tiwari et al., 2008). In addition, methylation turnover can differ within the genome (Ginno et al., 2020).

Epitranscriptomics has been shown to be extremely important. Among 170 epigenetic modifications in coding and noncoding RNAs (Boccaletto et al., 2018), N^6-methyl-adenosine methylation (m^6A) is the most studied (Zaccara et al., 2019b). Some proteins recognize this RNA modification and mediate several functions, such as mRNA splicing, stability, microRNA processing, and translation (Meyer & Jaffrey, 2017; Shi et al., 2019; Zaccara et al., 2019a). In addition, m^6A is linked to diverse biological functions, such as cancer (Sun et al., 2019), T cell differentiation (Furlan et al., 2019), and skin morphogenesis (Xi et al., 2020).

The association of metabolites with metabolic states can enable the formation of metabolic signatures. Furthermore, the identification of the relationships between metabolites and enzyme activity, nutrient import, and posttranslational modifications (Table 1) reinforces their role in phenotype acquisition.

3 Diet microbiome, metabolites, and epigenetic changes

Changes in the extracellular environment, such as food deprivation, caloric restriction, and intense exercise, modify intracellular nutrient-responsive pathways that promote adaptation and epigenetic changes (Dai et al., 2020; Gut & Verdin, 2013; Pizzorusso & Tognini, 2020).

Diet and lifestyle are important external factors that can affect metabolomics and, consequently, the phenotype. Vitamin D is mainly produced through endogenous production; however, through the lifestyle factor, solar ultraviolet-B radiation (UV-B) irradiates 7-dehydrocholesterol present in the skin to generate cholecalciferol (Pilz et al., 2013), which is subsequently activated in the liver and kidney. The other source of vitamin D is dietary intake, which includes supplementation with ergocalciferol or cholecalciferol. Most of the biological functions of the active metabolite of vitamin D are mediated through the regulation of gene expression. The 1,25 dihydroxyvitamin D ($1,25(OH)_2D_3$) binds to its nuclear receptor (nVDR) with high affinity and specificity, forming a heterodimer with the retinoid X receptor. Thus, this complex can repress or amplify the transcription of target genes. This occurs through its binding to vitamin D-responsive elements in DNA (Pilz et al., 2013). nVDR is found in some immune cells, such as monocytes and macrophages (Neve et al., 2014). Thus, the active metabolite of vitamin D has an anti-inflammatory effect on macrophages, modifying the phenotype, and downregulating the expression and production of several proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8 (Giulietti et al., 2007), in different diseases, such as COVID-19 (Jain et al., 2020), hepatic inflammation and steatosis (Dong et al., 2020).

Folate, choline, and methionine are essential metabolites related to methylation through the conversion of homocysteine to SAM. These metabolites are dietary requirements for maintaining methylation levels (Elango, 2020; Niculescu & Zeisel, 2002; Pizzorusso & Tognini, 2020). A methyl-deficient diet reduces one-third of the remethylation of one-carbon cycle metabolites (Farias et al., 2015; Ferrari & Pasini, 2013; Gerhäuser, 2012; Townsend, Davis, Mackey, & Gregory, 2004) and leads to aberrant DNA-methyltransferase activity, abnormal DNA methylation in liver tumors (Lopatina, 1998), and RNA methylation (Mosca et al., 2019). In addition to dietary sources, folate can be synthesized by small intestine flora, and most of it is absorbed by the host (Camilo et al., 1996). Betaine supplementation can enhance the levels of mRNA methylation and decrease fat mass and obesity-associated (FTO) expression in mice on a high-fat diet (Zhou et al., 2015). The presence of selenium in the culture media affects the methylation levels of selenocysteine tRNAs (Diamond et al., 1993).

Among the metabolites, β-hydroxybutyrate (β-OHB), a ketone body delivered by the liver during fasting or prolonged exercise, reshapes DNA by inhibiting HDACs (Mikami et al., 2020; Shimazu et al., 2013). After 12 h of fasting, the intake of ketogenic diets, or prolonged intense exercises, high circulation levels of β-OHB reach 1–2 mM (Koeslag, Noakes, & Sloan, 1980). β-OHB acts through GPR109, a GPCR that binds short-chain fatty acids. Such actions inhibit class I HDACs, which regulate gene expression through the deacetylation of lysine residues on histone and nonhistone proteins (Newman & Verdin, 2014).

β-OHB increases the intracellular content of acetyl-CoA, indirectly altering histone acetylation by promoting acetyltransferase activity via an acetyl-CoA flux (Ku et al., 2020; Xie et al., 2012). Furthermore, histone hyperacetylation triggered by β-OHB results in the increased expression of forkhead box O3 (FOXO3) (Kenyon, 2010). The increase in FOXO3 and metallothionein promoted by the hyperacetylation of histone H3 on lysine 9 (H3K9) offers resistance to oxidative stress (Shimazu et al., 2013; Xie et al., 2016).

Tanegashima et al. demonstrated that fasting induces H3K9 acetylation in the enhancer region of the Slc2a1 gene

Table 1 Metabolites as modulators of enzymes, posttranslational modifications, and nutrient transport expressions

Metabolites as modulators of enzymes

Metabolite	Effect/modulated enzyme	Product	References
Accumulation of 2-oxoglutarate (2OG) with a concomitant decrease in citrate	Activation of isocitrate dehydrogenase (IDH) toward the reductive carboxylation of 2OG HBO	Generation of citrate	Mullen et al. (2014)
Fructose-1,6- bisphosphate (Fru-1,6-BP) and high levels of serine	Activation of the M2 isoform of pyruvate kinase (PKM2); increase in the activity of PKM2 for phosphoenolpyruvate (PEP)	Conversion of phosphoenolpyruvate to pyruvate with the generation of ATP	Chaneton et al. (2012), Israelsen and Vander Heiden (2015)
PEP	Major allosteric regulation of PKM	Regulation of PKM activity promoting tetramerization and stabilization in the active state	Chaneton et al. (2012), Israelsen and Vander Heiden (2015)
Low levels of serine	Allosteric activation of PKM2 generating reduced activity	Shuttle of glucose-derived carbons to serine biosynthesis	Chaneton et al. (2012)
AMP	Allosteric activation of AMP-activated protein kinase (PKM2) favoring its phosphorylation	AMPK phosphorylates its targets modulating metabolic fluxes: induction of energy-producing processes and repression of energy-consuming processes. Exphosphorylation of Acetyl-CoA-carboxykinase (ACC) generating malonyl-CoA, which in turn inhibits carnitine palmitoyltransferase (CPT)	Gowans et al. (2013), Wegner et al. (2015)
High concentrations of succinate, fumarate, 2OG, and 2-hydrox-ylglutarate (2HG)	Inhibition of 2-hydrox-Prolyl hydroxylase 2 (PHD2)	Hydroxylation of hypoxia-inducible factor-1α (HIF-1α) inhibiting its proteasomal degradation and stabilization, independent of the oxygen supply	Chaneton et al. (2012), Wegner et al. (2015), Xu et al. (2011)
Ceramides	Allosteric activation of protein phosphatase 2A (PP2A)	Dephosphorylation of AKT at Thr308 and Ser473 triggering insulin resistance	Blouin et al. (2010)
Resveratrol metabolites: resveratrol-3'-O-sulfate (R3S) and resveratrol-4'-O-sulfate (R4S)	Inhibition of COX-1	Anti-inflammatory effects	Luca et al. (2020)
R4S	Activation of SIRT1	Deacetylation of histones	Luca et al. (2020)
Tetrahydrocurcumin	Activation of glutathione peroxidase (GPX), glutathione S-transferase (GST), and NADPH: quinone reductase	Antioxidant effects	Luca et al. (2020)

Table 1 (continued)

Metabolites and posttranslational modifications

Metabolite	Effect	Product	References
Saturated fatty acids (SFA)	Provide substrates for the synthesis of lipids, such as diacylglycerol (DAG) and ceramides; TLR4 mediated activation of inhibitors of nuclear factor-kβ (NF- kβ) kinase subunit-β (IKKβ) and Jun N-terminal kinase (JNK)	Impairment of insulin sensitivity through IKKβ and JNK-mediated phosphorylation of IRS1 on Ser307; increased production of proinflammatory cytokines	Yang et al. (2018)
Polyunsaturated fatty acids (PUFAs)	Activation of GPCR120	Recruitment of β-arrestin 2, which sequesters TAK1-binding protein (TAB1), triggering the inhibition of MAP3K7 to prevent JNK and IKKβ activity and resulting in anti-inflammatory effects	Yang et al. (2018)
Palmitic acid esters of hydroxystearic acid (PAHSAs)	Activation of the long form of GPCR120	Enhanced insulin-stimulated GLUT4 translocation to membrane	Yore et al. (2014)
Acetyl-CoA	Acetylation of IRS proteins in lysine residues by the histone acetyltransferase, p300	Impaired insulin signaling	Cao et al. (2017)
	Acetylation of AKT at lys14 and lys20 by p300 and the p300/CBP-associated factor (P/CAF)	Blockage of AKT binding to phosphatidylinositol (3,4,5)-triphosphate (PIP3) at the plasma membrane	Sundaresan et al. (2011)
	Deacetylation of AKT at lys14 and lys20 by SIRT1	AKT activation through AKT-PIP₃ binding	Sundaresan et al. (2011)
	Acetylation of glucosamine-6-phosphate	Synthesis of uridine-diphosphate-GlcNac	Yang and Qian (2017)
Palmitate	Palmitoylation of GLUT4 at Cy223	Insulin-stimulated GLUT4 translocation to membrane	Du et al. (2017)
β-OHB	Inhibition of HDAC1 and HDAC2 activity	Increase in histone acetylation at promoters of FOXO3 and met-allothionein 2 resulting in protection against oxidative stress	Shimazu et al. (2013)

Metabolites and solute carrier transporters

Metabolite condition	Transporter modulation	Cellular effect	References
Glucose starvation	Induction of SLC7A11 expression	Uptake of cystine by SLC7A11 transporters depleting intracellular NADPH and inducing ROS, triggering cancer cell death under glucose starvation	Koppula et al. (2017), Shin et al. (2017)
Cystine deprivation, oxidative stress	Induction of SLC7A11 expression via nuclear factor erythroid 2-related factor 2 (NRF2) and activating transcription factor 4 (ATF4)	Import of cystine and reestablishment of redox balance	Koppula et al. (2018)

Table 1 (continued)

Metabolites and solute carrier transporters

Metabolite condition	Transporter modulation	Cellular effect	References
Loss of lactate transport	Decreased expression of SLC5A8	Decreased transport of butyrate	Zhang et al. (2019)
Low levels of butyric acid in the gut	Downregulation of SLC16A1	Decreased transport of butyric acid	Thibault et al. (2007)
mTORC complex	Increased GLUT1 expression	Downstream aerobic glycolysis in T cells to support their proliferation and effector function	Song et al. (2020)

in neuronal and endothelial cells, due to increased levels of β-OHB. This further maintains a constant glucose concentration in the brain during fasting (Tanegashima et al., 2017). In contrast, supplementation with ketone esters has recently been shown to inhibit glycolysis in the brains of nonfasted mice (Suissa et al., 2021).

In addition to β-OHB, other metabolites are required for enzymes capable of modifying DNA or histones, and during fasting or energy scarcity, the intracellular levels of nicotinamide adenine nucleotide (NAD+), an energy carrier, increase. This metabolite is a cofactor for sirtuin and poly (ADP-ribose) polymerases (PARP), which regulate cellular functions ranging from gene expression to fatty acid metabolism. Once NAD+ levels increase during fasting or energy scarcity, this reflects the potential of such metabolites to regulate intracellular processes in response to environmental changes (Katsyuba et al., 2020; Verdin, 2015).

It was previously demonstrated that food bioactive compounds, such as sulforaphane, a thiocyanate particularly found in broccoli, increase VDR expression (Apprato et al., 2020), inhibit HDAC activity (Tortorella et al., 2015), and increase histone H3 and H4 acetylation (Juge et al., 2007). Furthermore, sulforane cysteine, sulforane *N*-acetyl-cysteine, allyl mercaptan, and diallyl disulfide, the metabolites produced by microbial metabolism of cruciferous vegetables and garlic induce epigenetic changes by inhibiting histone deacetyl transferase enzymes (Kim et al., 2010).

It is well known that the intestinal microbiota is sensitive to environmental changes, such as high-fat diets (David et al., 2014; Peng et al., 2021), micronutrient deficiency (Hibberd et al., 2017), obesity (Aron-Wisnewsky et al., 2021; Turnbaugh et al., 2009), and chronic inflammation (Couto et al., 2020; Round & Mazmanian, 2009). Therefore, modulating the microbiome maintains and/or improves health through the metabolites produced by intestinal microorganisms in response to the components of the diet, thus resulting in the production of short-chain fatty acids (SCFA), such as butyrate, acetate, and propionate (Guilloteau et al., 2010). In addition, SCFAs are produced through the fermentation of nondigestible carbohydrates, such as dietary fibers, which activate GPCRs, such as GPR41 and GPR43, leading to the inhibition of HDACs (Bhat & Kapila, 2017).

Food bioactive compounds can interact directly with DNA, and dietary behavior can affect DNA structure, leading to a different phenotype. For example, three flavonoids, quercetin, kaempferol, and delphinidin can bind to adenine and guanine (major groove), and thymine (minor groove) (Kanakis et al., 2005), and saffron derivate metabolites can interact with DNA guanine-quadruplexes (G4) (Hoshyar et al., 2012). These G4 motifs are stable structures related to gene promoter regulation and DNA methylation (Hardin et al., 1993; Mao et al., 2018); they can be dysregulated by aberrant DNA methylation due to folate deprivation

(Tavakoli Shirazi et al., 2018). Upon interfering with the genome, all other steps of the flux of information will be affected, including the phenotype.

4 Conclusion

Metabolites can induce macromolecule activity and control phenotypes. It has been shown that omics-scale techniques provide better correlation than single approaches, which indicates that the "central dogma" is a wide integration of information (Piras et al., 2012). Recently, Bar et al. analyzed 1251 metabolites from the serum of 491 individuals and by machine learning deduced that the diet and microbiome both represent 50% of an individual's metabolic profile (Bar et al., 2020). This concept is a paradigm shift in that it reshapes the conventional thinking about the molecular linear "central dogma," placing metabolomics at the center, not only providing a simple readout to other omics, but also acting as a master regulator of the whole system (Guijas et al., 2018).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Research involving human participants and/or animals GCS, MRM and NMB complied with Springer's ethical policies. This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent to participate Not applicable.

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