The cell-autonomous mechanisms underlying the activity of metformin as an anticancer drug

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The biguanide drug metformin profoundly affects cell metabolism, causing an impairment of the cell energy balance and triggering a plethora of pleiotropic effects that vary depending on the cellular or environmental context. Interestingly, a decade ago, it was observed that metformin-treated diabetic patients have a significantly lower cancer risk. Although a variety of in vivo and in vitro observations emphasising the role of metformin as anticancer drug have been reported, the underlying mechanisms are still poorly understood. Here, we discuss our current understanding of the molecular mechanisms that are perturbed by metformin treatment and that might be relevant to understand its antitumour activities. We focus on the cell-autonomous mechanisms modulating growth and death of cancer cells.

Metformin is the first-line pharmacological treatment for type 2 diabetes (T2D) as its oral administration lowers blood glucose levels and improves insulin sensitivity of diabetic patients (Kirpichnikov et al, 2002). The antihyperglycaemic effect is mediated by different systemic adaptations including inhibition of gluconeogenesis in the liver and of glucose adsorption in the intestine combined with an increase in hexose uptake by adipose tissue and skeletal muscle (Sokolovska et al, 2010; Li et al, 2011). The observation that reduced oxygen consumption by mitochondria accompanies the hypoglycaemic effect suggested that this organelle is a metformin target (Davidoff, 1971). Indeed, in a variety of systems, metformin inhibits complex I in the mitochondrial respiratory chain (El-Mir et al, 2000; Owen et al, 2000), causing a decrease of the ATP/AMP ratio (Viollet et al, 2012). This primary perturbation, causing an impairment of the cell energy balance, triggers a plethora of pleiotropic effects that vary depending on the cellular or environmental context. The complexity of the organismal response to metformin is pictured in the four-word clouds in Figure 1 representing the co-occurrence in PubMed abstracts of the string ‘metformin’ with different terms referring to biological processes, gene names, cell types and diseases. This analysis clearly highlights the role of metformin as caloric restriction mimetics, being associated with biological processes such as glycolysis, autophagy, insulin resistance as well as with master regulators of nutrient response, such as LKB1, mTOR and AMPK1/2 (Figure 1). In agreement with its role as a caloric restriction mimetics, metformin improves lifespan in nematodes, fruit flies and mice (Anisimov, 2013). Consistently with its antiageing effect, metformin treatment promotes neurogenesis and enhances spatial memory formation by activating an atypical PKC-CBP pathway (Wang et al, 2012). In skeletal muscle, metformin attenuates damage by counteracting calcium influx triggered by cardiotoxin (Langone et al, 2014). The clinical applications of metformin have been extended from treatment of T2D to polycystic ovary syndrome, where the biguanide treatment induces a reduction of inflammatory markers (Morin-Papunen et al, 2003).

METFORMIN AS AN ANTITUMOUR DRUG

In 2005, it was reported that metformin-treated diabetic patients have a significantly lower cancer risk (Evans et al, 2005). These initial observations prompted many clinical trials in recent years.
Hyperinsulinaemia and hyperglycaemia have been associated with tumourigenesis risk and poor prognosis in several cancers. Metformin treatment exerts its anticancer role by triggering different processes: it decreases the amount of the Ki67 proliferation marker in biopsy samples of nondiabetic women with breast cancer (DeCensi et al, 2014); it suppresses metastasis formation by preferentially killing stem cells of different cancer types (Hirsch et al, 2009; Vazquez-Martin et al, 2011; Mohammed et al, 2013). The potential of the clinical use of metformin for cancer prevention and treatment have been discussed in recent reviews (Kour Elias and Siegel, 2012; Pernicova and Korbonits, 2014; Morales and Morris, 2015). Here, we consider our current understanding of the molecular mechanisms under-lying the anticancer activity of metformin, focussing on the cell-autonomous mechanisms modulating growth and death of cancer cells.

The results of most of them supported the evidence that metformin decreases the risk to develop a variety of tumours. However, some studies reached conflicting conclusions. Overall, a variety of in vivo and in vitro observations place an emphasis on metformin treatment as a promising therapeutic strategy for cancer prevention and therapy (Sui et al, 2015). Metformin treatment exerts its anticancer role by triggering different processes: it decreases the amount of the Ki67 proliferation marker in biopsy samples of nondiabetic women with breast cancer (DeCensi et al, 2014); it suppresses metastasis formation by preferentially killing stem cells of different cancer types (Hirsch et al, 2009; Vazquez-Martin et al, 2011; Mohammed et al, 2013). The potential of the clinical use of metformin for cancer prevention and treatment have been discussed in recent reviews (Kour Elias and Siegel, 2012; Pernicova and Korbonits, 2014; Morales and Morris, 2015). Here, we consider our current understanding of the molecular mechanisms under-lying the anticancer activity of metformin, focussing on the cell-autonomous mechanisms modulating growth and death of cancer cells.

Many cell-autonomous activities of metformin have been reported. Although this does not lead to a satisfactory integrated picture, here we will schematically summarise our current understanding of the molecular pathways that are modulated by metformin treatment (Figure 2).

Activation of AMPK pathway. The Ser/Thr kinase AMPK senses the unbalance in the AMP/ATP ratio and activates and modifies a well-described downstream pathway that modulates cellular metabolism and energy homeostasis. Pertinent to the anticancer role of metformin is the observation that AMPK exerts an antitumourigenic role in cancer, activating two well-known tumour suppressors, TSC2 and p53 (Faubert et al, 2015). Consistently, loss of AMPK activity has been observed in different cancer types. Different molecular mechanisms mediating the metformin-dependen-ant PK activation have been described. The first mechanism relies on the ability to act on isolated mitochondria and decrease complex I-dependent respiration and ATP production (Andrzejewski et al, 2014).AMPK senses the AMP/ATP ratio and, as a consequence, it is activated by the decrease of ATP levels following the inhibition of mitochondrial complex 1. On the same line, we recently showed that metformin also inhibits the mitochondrial respiratory complex by decreasing the protein level of complex I (NADH-ubiquinone oxidoreductase) subunits as well as mitochondrial metabolism (Andrzejewski et al, 2014). In addition, apoptosis induced by metformin in triple-negative and ER-high or HER-high breast cancer cell lines depends on AMPK but is suppressed by high concentration of glucose (25 mM) and amino acids (Silvestri et al, 2015). These observations stress the importance of cell environmental and metabolic context on response to metformin treatment. However, our understanding of the systemic anticancer effects of metformin remains limited.
as five components of complex 3 (cytochrome bc1 complex; Sacco et al, 2016). As a second mechanism, it was proposed that metformin activates AMPK by triggering the activation of the ATM–LKB1–AMPK axis (GoDarts et al, 2011). In a genome-wide association study, the authors show that inhibition of ATM in a rat cancer cell line weakens metformin-mediated activation of the metabolic enzyme AMPK.

Interestingly, after metformin treatment, the phosphoproteome profile of breast cancer cells was significantly enriched for the substrate motif of ATM, supporting the involvement of the activation of this kinase in the cell response to metformin (Sacco et al, 2016). In addition to these two mechanisms, we recently showed that metformin significantly increases the concentration of the regulatory subunit β of AMPK (PRKAB1), whose interaction with the catalytic subunit triggers the enzyme kinase activity. This last observation suggests that full activation of AMPK requires de novo transcription and translation that is consistent with the fact that metformin requires a long-term treatment for complete AMPK activation.

Besides the AMPK-dependent regulation of proteins involved in lipid and glucose metabolism (ACACA and GFPT1), the metformin-mediated activation of AMPK results in the
Inhibition of AKT–mTORC1 pathway. The impairment of target of rapamycin (mTOR) signalling pathway is one of the hallmarks of metformin treatment. The mTOR plays a key role in regulation of cell growth and metabolism, and thus the correlation between the activation of mTOR and tumour progression is not surprising. The activation of the mTOR pathway is involved in the regulation of many cancer hallmarks, including tumour growth, angiogenesis and metastasis (Hanahan and Weinberg, 2011). The mTORC1 activation is limited by metformin in several ways: by increasing the mTOR inhibitor REDD1 (regulated in development and DNA damage responses) (1); it inhibits the Regulator complex that positively regulates mTOR (2) and it mimics amino acid deprivation causing loss of colocalisation between mTOR and its activator Rheb (3) (Kalender et al, 2010; Pierotti et al, 2013). The metformin-mediated mTORC1 complex inhibition exerts a strong impact on key physiological processes, such as autophagy, protein synthesis and cell proliferation.

A deep MS-based phosphoproteomics approach revealed that metformin does not induce a mere inhibition of the whole AKT–mTOR axis, but rather rewires the whole pathway. Analysing the AKT–mTORC1 pathway in breast cancer cells MCF7 treated with metformin, we found that metformin decreases phosphorylation of two mTOR substrates, p70S6K and rpS6 but, contrary to expectation, this is not mediated by a diminished mTOR activity. We find that, in these conditions, the activity of the upstream inducer of mTORC1 complex, the Akt kinase, is increased by metformin. As a consequence, the mTOR inhibitor TSC2 is phosphorylated and therefore inhibited. There are two main logical disconnections in this pathway when perturbed by metformin: the mTOR repressor, TSC2, is inhibited but mTOR remains steadily activated, whereas its downstream effector S6K is inhibited. On the same line, in MCF7 cells treated with metformin, addition of insulin-like growth factor (IGF) triggers IGFIR and Akt phosphorylation, whereas p70S6K substrates (rpS6, IRS1) are not activated, remaining in a constitutive inactive form. We propose that IGF stimulation fails to activate p70S6K because metformin triggers the assembly and activation of the PP2A phosphatase by increasing phosphorylation of the PPP2R5C regulatory subunit (Sacco et al, 2016).

Inhibition of cell cycle progression. Cell cycle progression is often altered in cancer cells, leading to an aberrant regulation of cell division and DNA replication. Many reports demonstrated that the anticancer property of metformin is a consequence of cell cycle perturbation. Specifically, exposure to metformin induced cell cycle arrest in G0/G1 and G2/M phases in different cancer types, including breast cancer cells and oesophageal squamous cancer cells. The molecular mechanisms underlying the metformin-induced cell cycle arrest have been extensively described and involve the upregulation of cyclin-dependent kinase inhibitors (CDKIs), such as p21 or p27 proteins. Although in breast cancer cells (ER positive and negative, erbB2-overexpressing and erbB2-negative) metformin remains steadily phosphorylated and therefore inhibited, its downstream effector S6K is inhibited. The cell cycle arrest induced by metformin is more effective than that induced by staurosporin or other chemotherapeutic drugs (Sacco et al, 2010, 2011, 2015).

MAPK regulation. The mitogen-activated protein kinases (MAPKs), including the ERK1/2, p38 and JNK kinase branches, control fundamental biological processes, including proliferation, differentiation, survival and death. Although there is a general consensus about the metformin-dependent inhibition of ERK1/2 kinases in different cancer types (Memmott et al, 2010; Gou et al, 2013; Sacco et al, 2016), the modulation of JNK and p38 kinases has been less extensively reported. Metformin they become more sensitive to apoptotic stimuli such as the ones given by staurosporin or other chemotherapeutic drugs (Sacco et al, 2016).

SP1 transcription factor regulation. Metformin treatment induces a radical remodelling of the transcriptome and proteome, and it is not surprising to observe modulation of the activity of different transcription factors. Recent evidences demonstrated that metformin inhibits the SP transcription factor family members in vivo and in different cancer cell lines, such as pancreatic tumour cells or breast cancer cells (Sacco et al, 2016). Safe and colleagues (Nair et al, 2013) demonstrated that in pancreatic cancer L3.6P and Panc28 cells, metformin induced proteasome-dependent degradation of Sp1, Sp3 and Sp4 transcription factors, resulting in the downregulation of several pro-oncogenic Sp-regulated genes including bcl-2, survivin, cyclin D1, vascular endothelial growth factor with its receptor and fatty acid synthase. Interestingly, the molecular mechanism through which metformin inhibits Sp transcription factors is context dependent. The authors reported that in a different pancreatic cancer cells, Panc, metformin decreased microRNA-27a and induced the Sp repressor, ZBTB10 (Nair et al, 2013).

The analysis of metformin-induced transcriptome and proteome profiles in breast cancer cells enabled us to identify the SP1 transcription factor as the most significantly modulated, as it is equally depleted at both mRNA and protein levels. Our data, combined with the metformin-dependent phosphoproteome profile, are consistent with a model where metformin induces the SP1 degradation by increasing the phosphorylation of Ser51 that destabilises the transcription factor. We inferred that p38 kinase is responsible of the metformin-mediated SP1 phosphorylation. The decrease in the levels of SP1 is mirrored by a significant reduction of many SP1-controlled cancer and metabolic pathways. The expression of Von Hippel Lindau protein (VHL) is also diminished by metformin. The VHL is SP1 controlled and, besides its role as an E3 ligase of HIF-α in normoxia, it can repress the promoter activity of IGF1R by sequestering SP1 (Yuen et al, 2007). The SP1 also controls the expression of pyruvate kinase that is overexpressed in many tumours. We observe a downregulation of the oncogenic isofrom pyruvate kinase M2 in MCF7 and SKBR3 breast...
cancer cells treated with metformin when grown in normoglycaemic condition. On the contrary, if glucose is increased fourfold, metformin does not affect the expression levels of PKM2 (Silvestri et al, 2015).

The unfolded protein response (UPR). The UPR is triggered by a pathological increase of unfolded or misfolded proteins that is sensed by three receptors on the ER membrane. When these sensors dissociate from the ER chaperon GRP78, they activate signal transductions to stop protein synthesis, to increase proteasomal degradation and, ultimately, undergo apoptosis by overexpressing CHOP. Metformin was found to cause an AMPK-dependent downregulation of GRP78 while increasing the levels of unfolded proteins in the ER lumen. As a consequence, the cell becomes unable to adequately respond to ER stress and dies (Saito et al, 2009).

In prostate cancer cells, metformin also induces CHOP-dependent apoptosis by regulating the expression of numerous miRNAs. Among them, the tumour suppressor miR-708-5p is strongly upregulated. This miR collaborates in increasing the ER stress by suppressing the ER membrane protein neuronatin, NNAT, that controls calcium homeostasis (Yang et al, 2015). It is noteworthy that in cardiomyocytes, metformin activates the UPR but, in spite of a strong upregulation of the pro-apoptotic CHOP protein, cells are not driven to death (Quentin et al, 2012), stressing once more that metformin modulates cell death and survival in a cell-specific manner.

CONCLUSIONS

The observation that metformin reduces cancer risk in diabetic patients has raised considerable interest and has stimulated a variety of studies. Despite the wealth of information, we are still far from a clear consistent picture that could support rational strategies for cancer prevention and treatment. Metformin has a profound impact on the organism energy balance and metabolism, and the cells in the different organs, by sensing these signals, respond differently, depending on the molecular and cellular context. Tumour cell growth is affected by both changes in the environmental cues and a direct action of metformin on the molecular pathways that regulate cell growth and death. Here we have discussed the cell-autonomous mechanisms that are affected by metformin treatment combining the results of a high-content genome-wide study on a breast cancer cell line with more focused reports on different tumour systems. After metformin treatment, the transcriptome and proteome of MCF7 breast cancer cells are remodelled and the signalling pathways are rewired. Transcription, translation and post-translational modifications are profoundly affected. The resulting picture is revealing and complex at the same time and partly explains why metformin has such pleiotropic effects depending on context (Figure 2). These studies have opened the path to a systems understanding of the molecular mechanisms underlying metformin effects, but at the same time call for more such studies in different systems and in different conditions. Only such a genome-wide understanding of the subtle differences in the response of different systems in different conditions will eventually offer a rational basis for designing new strategies to potentiate the action of metformin by combining it with different antitumour treatments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.
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