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Review article

Metabolic perturbations in fibrosis disease

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ABSTRACT

Metabolic changes occur in all forms of disease but their impact on fibrosis is a relatively recent area of interest. This review provides an overview of the major metabolic pathways, glycolysis, amino acid metabolism and lipid metabolism, and highlights how they influence fibrosis at a cellular and tissue level, drawing on key discoveries in dermal, renal, pulmonary and hepatic fibrosis. The emerging influence of adipose tissue-derived cytokines is discussed and brings a link between fibrosis and systemic metabolism. To close, the concept of targeting metabolism for fibrotic therapy is reviewed, drawing on lessons from the more established field of cancer metabolism, with an emphasis on important considerations for clinical translation.

1. Introduction

The mechanisms involved in fibrosis are fundamentally similar to those in the normal wound healing response. There is an inflammatory response to tissue damage, which entails activation of local immune cells, followed by activation of local mesenchymal cells, namely fibroblasts, which deposit excessive and/or inappropriate extracellular matrix (ECM) components and further increase production of pro-inflammatory cytokines, chemokines and angiogenic factors to perpetuate the process. Scarring occurs when these mechanisms are altered and/or exaggerated, with chronic fibrosis a result of persistently abnormal ECM turnover, favouring ECM production over ECM degradation. Although other cell types make important contributions to fibrosis, fibroblasts are ultimately responsible for the excessive synthesis, deposition and remodelling of ECM and much research has been dedicated to studying their aberrances in fibrotic disease including signalling (Kendall and Feghali-Bostwick, 2014), transcription, cytoskeletal and motility changes and cell-matrix interactions (Hinz and Gabbiani, 2003). There is now a growing appreciation that a supply of building blocks and energy carriers are required to fuel these activities, provided by core metabolic biosynthetic and bioenergetic pathways, and that pathological cells in fibrosis (fibroblasts, epithelial cells, immune cells and others) undergo metabolic adaptations or reprogramming to enable their proliferative and synthetic activities. Defining and characterising these adaptations may provide new opportunities for developing effective anti-fibrotic therapies. This review discusses the core metabolic processes in the context of fibrosis and the therapeutic advances made in this regard.

2. Glycolysis and fibrosis

Glycolysis is a major metabolic process that begins with the

Abbreviations: 2-DG, 2-deoxyglucose; 3PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; ACC1, Acetyl-CoA carboxylase 1; Acetyl-CoA, Acetyl Coenzyme A; AKT, Alpha-serine-threonine protein kinase; AMP, Adenosine monophosphate; AMPK5′, AMP-activated protein kinase; ATP, Adenosine triphosphate; CCN2, Cellular Communication Network Factor 2; CHREBP, Carbohydrate-responsive element-binding protein; Cpt1, Carnitine palmitoyltransferase 1; CTGF, Connective tissue growth factor; CTRP3, C1q/TNF-related protein 3; ECM, Extracellular matrix; FASN, Fatty acid synthase; GLUT1, Glucose Transporter 1; HIF-1α, Hypoxia inducible factor 1a; HK, Hexokinase; IPF, Idiopathic pulmonary fibrosis; LDHA, Lactate dehydrogenase A; MMP, Matrix metalloproteinase; mTOR, Mechanistic target of rapamycin; NLRP3, NLR family pyrin domain containing 3; PAI1, Plasminogen activator inhibitor 1; PGC-1α, PPARγ coactivator-1α; PDGF-BB, Platelet derived growth factor BB; PDK1, Pyruvate dehydrogenase kinase 1; PFKFB3, 6-phosphofructo-2-kinase; PI3K, Phosphoinositide 3-kinase; PKM2, Pyruvate kinase M2; PPAR, Peroxisome proliferator-activated receptor; ROS, Reactive oxygen species; SMA, Smooth muscle actin; SREBP1c, Sterol regulatory element binding protein-1c; TAZ, Transcriptional co-activator with PDZ-binding motif; TCA, Tricarboxylic acid; TGFβ1, Transforming growth factor beta 1; YAP, Yes associated protein.

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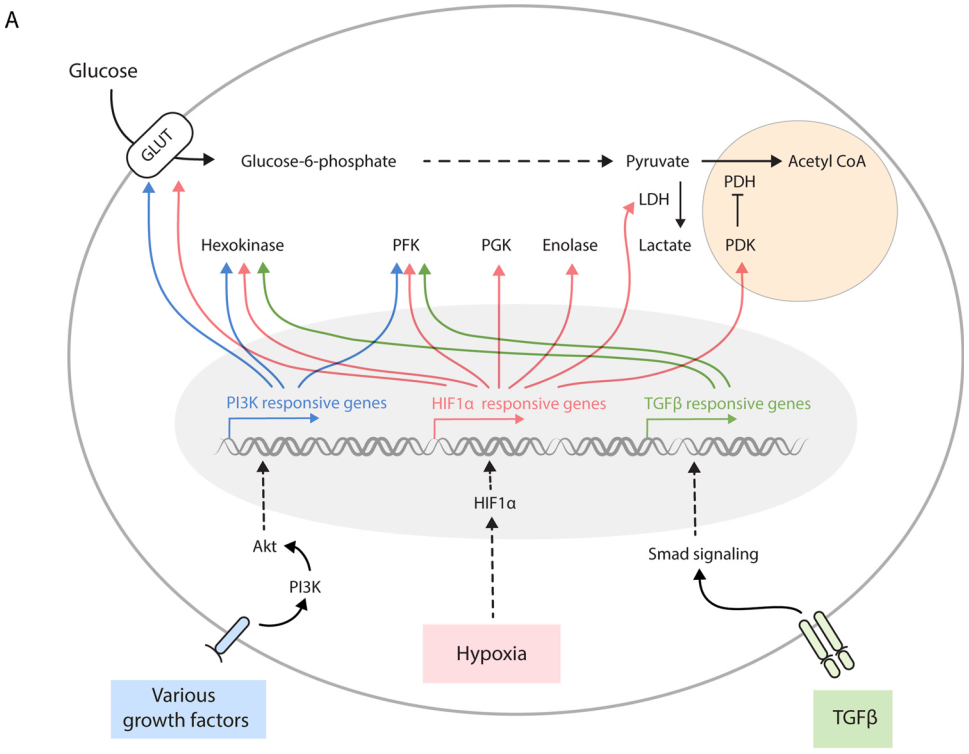
intracellular transport of glucose and ends with the production of pyruvate and two molecules of ATP per molecule of glucose. Its flux is mediated by a series of cellular enzymes with the key rate limiting ones being hexokinase, phosphofructokinase and pyruvate kinase. The final product of glycolysis, pyruvate, is converted either to lactic acid or acetyl-CoA for utilisation in the tricarboxylic acid (TCA) cycle by mitochondria. Physiologically, conversion of pyruvate to lactic acid takes place in low oxygen tension conditions. However, we are increasingly aware of situations whereby this conversion occurs despite the presence of adequate oxygen (aerobic glycolysis). This is a phenomenon known as the Warburg effect, classically described in cancer cells, where it is thought that the increase in glycolytic intermediates supply subsidiary pathways that support the activities of these proliferating cells (DeBerardinis and Chandel, 2020). However, not all cancer cells exhibit this effect and recently a "reverse Warburg" effect has been proposed whereby metabolites of aerobic glycolysis by stromal fibroblasts (rather than the cancer cells themselves) feed cancer cells and cause an upregulation of oxidative phosphorylation (Sotgia et al., 2011). In fibrosis, a similar reverse Warburg effect has been put forward whereby aerobic glycolysis takes place in the fibroblasts and the glycolytic metabolites influence the behaviour of other cell types such as epithelial cells and macrophages (or vice versa), contributing to pathogenesis (Maher, 2015).

There is significant evidence that aerobic glycolysis takes place in a wide range of fibrotic conditions, including radiation-induced skin fibrosis (Zhao et al., 2019c), renal fibrosis (Yin et al., 2018), pulmonary



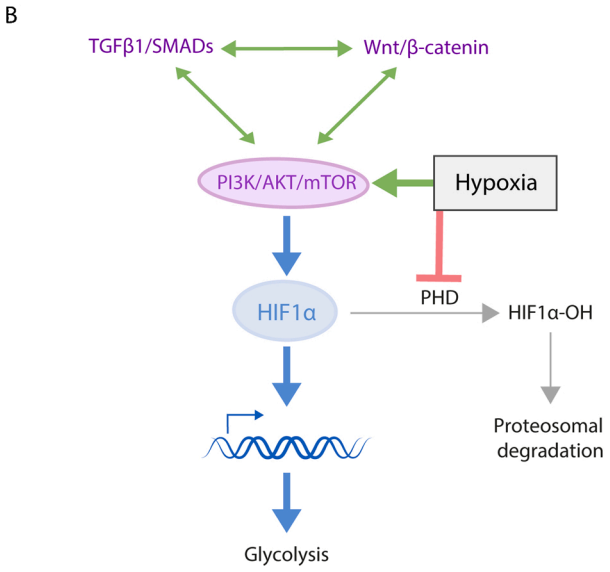


Fig. 1. **(A)** A simplified schematic showing the major pro-fibrotic factors influencing glycolysis. HIF1α stabilisation results in overexpression of glucose transporters (GLUT) and glycolytic genes including hexokinase (HK), phosphofructokinase (PFK), phosphoglycerate kinase, enolase and pyruvate kinase (PK/PKM). It also inhibits conversion of pyruvate to acetyl-CoA by inducing PDK and upregulating lactate dehydrogenase (LDH) which catalyses conversion of pyruvate to lactate. The PI3K/AKT signalling pathway leads to upregulation of GLUT, HK and PFK whereas TGFβ1 induces expression of HK and fructose-2,6-biphosphatase 3 (PFK3B) which activates PFK. **(B)** Interplay between the major pro-fibrotic pathways centring on HIF1α stabilisation. In the presence of sufficient oxygen, prolyl hydroxylases (PHD) hydroxylate HIF1α, triggering proteosomal degradation. In hypoxia, PHD is inhibited and the stabilised HIF1α enters the nucleus to create an active HIF1 complex, transcribing genes that amongst other functions, promote glycolysis. PI3K/AKT/mTOR signalling is the major pathway promoting HIF1α transcription and translation. The Wnt/β-catenin and TGFβ1/SMAD pathways cross-interact with the PI3K/AKT pathway and indirectly increase HIF1α transcription.

fibrosis (Xie et al., 2015) and cirrhosis (Lee et al., 2018). For example, renal myofibroblast activation can be induced by the overexpression of pyruvate kinase muscle isozyme M2, which increases aerobic glycolysis (Ding et al., 2017). On the other hand, suppressing glycolysis, whether by inhibition of glucose transporters (Zhao et al., 2019c) or inhibition of glycolytic enzymes (e.g. 6-phosphofructo-2-kinase (Xie et al., 2015), hexokinase (Zhao et al., 2019c), pyruvate kinase (Ding et al., 2017)), attenuated the pro-fibrotic phenotype both *in vitro* (e.g. myofibroblast differentiation (Xie et al., 2015) and fibroblast ECM production (Zhao et al., 2019c)), and *in vivo* (e.g. bleomycin-induced lung fibrosis (Xie et al., 2015) and unilateral ureteric obstruction-induced renal fibrosis (Ding et al., 2017)). This is consistent with the association of fibrosis with hyperglycaemia – patients with diabetes mellitus are afflicted by fibrosis in their end organs including kidneys, heart, liver and eyes (Ban and Twigg, 2008), and patients undergoing peritoneal dialysis are at risk of peritoneal fibrosis as a result of chronic high glucose dialysate (Chagnac et al., 1999).

Mechanistically, HIF-1α appears to be a central regulator (Fig. 1). Its stabilisation increases glycolysis by causing overexpression of glucose transporters (enabling increased glucose uptake) and activation of glycolytic enzymes such as Glut, HK2, PKM2, LDHA, and PDK1 (enabling increased glycolytic flux) (Semenza, 2010). Stabilisation of HIF-1α also inhibits the mitochondrial TCA cycle by increasing LDHA expression (promotes lactate production) and inhibiting pyruvate dehydrogenase (upregulates PDK1 which decreases conversion of pyruvate into acetyl-CoA) (Fig. 1a) (Semenza, 2010). In normoxia, HIF-1α levels are regulated through hydroxylation-triggered proteosomal degradation (Iommarini et al., 2017). Independently of oxygen availability, pathways identified in the stabilisation of HIF-1α, whether by inhibition of degradation, nuclear translocation or transcriptional activity, are numerous (Iommarini et al., 2017). The PI3K/AKT/mTOR pathway is a major pathway implicated in increasing HIF1α transcription and of particular relevance to fibrosis is its bilateral reinforcement of key pro-fibrotic pathways, including TGFβ1 and WNT/β-catenin (Vallée et al., 2017) (Fig. 1b). TGFβ1 can also directly induce the glycolytic enzyme PFKFB3 to increase phosphofructokinase-1-mediated stimulation of glycolysis (Xie et al., 2015). PFKFB3 expression has been shown to specifically correlate with the expression of α-smooth muscle actin (SMA), a marker of myofibroblast differentiation (Xie et al., 2015). However, despite the evidence implicating HIF-1α in fibrogenesis, the new HIF stabilisers that have been introduced to treat renal anaemia appear not to cause fibrosis (Kabei et al., 2020).

In addition to its contribution to pro-fibrotic pathways, glycolysis supplies amino acids for collagen synthesis. Collagen is the main structural protein found in the ECM of fibrotic tissue and the predominant amino acid constituents of collagen are glycine, proline and lysine. The collagen precursor undergoes hydroxylation, disulphide bonding and glycosylation to form the functional triple-helix collagen molecule. Following secretion into the extracellular space, peptidases cleave the amino- and carboxyl-terminals to produce insoluble collagen, which crosslinks to form microfibrils that combine to form a collagen fibre (Gelse et al., 2003). The glycolytic intermediate 3-phosphoglyceric acid is a precursor to serine which is converted to glycine, an amino acid whose presence is critical for stabilisation of the collagen helix (Nigdelioglu et al., 2016). The end-product of glycolysis, lactic acid, serves to increase collagen stability by increasing the activity of proline hydroxylase, which enhances collagen hydroxylation.

3. Amino acid metabolism and fibrosis

Amino acids are a major constituent of the cellular biomass and are involved in multiple metabolic pathways essential for cell survival. They are sources of energy, precursors for biosynthetic processes and maintain tissue homeostasis, amongst other roles (Lieu et al., 2020). Studies linking amino acid metabolism and fibrosis have mainly been on lung fibrosis although focus has also been directed at liver fibrosis and systemic sclerosis. Most evidence implicating altered amino acid metabolism in fibrosis is related to glutamine. This non-essential amino acid is the most abundant circulating free amino acid and is a precursor to numerous cellular processes, both as a carbon and nitrogen donor for macromolecular synthesis, and as an orchestrator of cellular signalling. Glutaminolysis is the process by which glutamine is converted first into glutamate by the activity of glutaminase, then into α-ketoglutarate by two divergent pathways, namely glutamine dehydrogenase and a group of transaminases including glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase and phosphoserine transaminase. At times of limited pyruvate availability such as during aerobic glycolysis, the TCA cycle is maintained by a process known as anaplerosis, metabolic reactions that replenish the required intermediates. α-ketoglutarate is the main anaplerotic substrate, although other metabolites formed from glutaminolysis such as oxaloacetate and citrate can also serve this purpose. Glutamine anaplerosis in the TCA cycle can provide precursors for the generation of other non-essential amino acids, lipids and nucleotides. Furthermore, by-products of glutaminolysis such as succinate can stabilise HIF-1α (Xie et al., 2015), which in turn augments glycolysis.

Metabolic profiling studies on patients with various fibrotic conditions including systemic sclerosis, pulmonary fibrosis and liver fibrosis have indicated alterations in glutamine-glutamate metabolism (Hasegawa et al., 2020; Kang et al., 2016; Murgia et al., 2018) and *in vitro* studies have supported this, implicating pathway enzymes such as glutamate dehydrogenase (Li et al., 2017) and glutaminase (Ge et al., 2018; Henderson et al., 2020; Li et al., 2017), amongst others. Glutaminase levels were found to be raised in TGFβ1-stimulated mouse lung fibroblasts and fibroblasts from patients with idiopathic pulmonary fibrosis (IPF). TGFβ1 was shown to stimulate glutaminolysis and induce metabolic reprogramming favouring lung myofibroblast differentiation, while lung fibroblasts grown in the absence of glutamine showed an attenuated response to TGFβ1 (Bernard et al., 2018). Further mechanistic studies showed that the expression of collagen in TGFβ1-induced lung myofibroblasts was reliant on glutaminolysis as glutaminase blockade (using specific glutaminase inhibitors CB-839 and BPTES as well as using glutaminase gene knockdown) was shown to decrease the expression of type I and III collagens, whereas glutaminase overexpression had the opposite effect (Ge et al., 2018; Hamanaka et al., 2019). Mechanistically, Ge et al. (2018) reported the importance of α-ketoglutarate (the mitochondrial end product of glutaminolysis)-dependent mTOR signalling in promoting collagen (proline) hydroxylation whereas Hamanaka et al. (2019) focused on the need for the cytoplasmic glutamate-consuming enzymes phosphoserine aminotransferase 1 and aldehyde-dehydrogenase 18A1 in producing glycine and proline, respectively.

As the main constituents of collagen, it is of no surprise that both proline and glycine are independently gaining interest, particularly in the fields of pulmonary (Gaugg et al., 2019; Kang et al., 2016) and liver (Hasegawa et al., 2020; Sanchez-Antolín et al., 2015) fibrosis, respectively. Not only serving collagen biosynthetic roles, proline in particular has been found to be a HIF-1α stabiliser in skin fibroblasts although this effect is blunted in the presence of glutamine (Szoka et al., 2017). As larger and more detailed exploratory studies are performed, it is likely that more interconnections between pathways will be discovered.

4. Lipid metabolism and fibrosis

It is important to consider that metabolically dysfunctional adipose tissue in obesity is characterised by fibrosis (Sun et al., 2013). Here, chronic positive energy balance promotes adipose tissue hypertrophy and hyperplasia, accumulation of immune cells and neovascularisation, leading to pathological ECM remodelling, largely by pre-adipocytes (Sun et al., 2013). There is also a growing appreciation that the adipose tissue ECM can feedback to resident cells, modulating, for example, adipocyte metabolism including response to insulin and lipolysis (Baker

et al., 2017).

Fatty acid (beta) oxidation is the catabolic process where fatty acids are broken down to generate ATP. Free fatty acids are first activated in the cytosol to form acyl-CoA by conjugation with coenzyme A, then converted to acylcarnitine for transport across the mitochondrial membrane and conversion back to acyl-CoA for beta oxidation to take place. A repeated sequence of four enzymes is involved in beta oxidation resulting in the release of an acetyl-CoA unit that enters the TCA cycle (Houten and Wanders, 2010). Due to its energy efficiency, it is not surprising that fatty acid oxidation is an important source of energy for cellular functions. Impaired fatty acid oxidation is associated with renal fibrosis (Kang et al., 2015), pulmonary fibrosis (Zhang et al., 2020) and radiation-induced skin fibrosis (Zhao et al., 2019b) and differences in the lipid composition of fibrotic keloid skin have also been reported (Louw and Dannhauser, 2000), although the pathophysiological significance of this is not clear.

The PPAR signalling pathway is a major regulator of fatty acid oxidation. PPARs are a family of transcription factors that exist as three main isoforms (α, δ and γ). They have variable tissue expression and divergent roles in lipid metabolism. PPARα is an activator of mitochondrial and peroxisomal fatty acid beta oxidation in the liver, PPARδ is a regulator of fatty acid oxidation in muscle and PPARγ is an activator of fatty acid synthesis and storage, most abundantly expressed in adipose tissue (Varga et al., 2011). Another main regulator of fatty acid oxidation is the transcriptional coactivator PGC-1α which binds to and increases the activity of PPARs but also directly modulates the activity of transcription factors that can increase the expression of proteins involved not only in fatty acid beta-oxidation but also the TCA and the electron transport chain. PGC-1α in turn is regulated by AMPK, which senses cellular energy status, becoming activated when the AMP/ATP ratio is high and triggers a wide range of catabolic pathways to restore ATP (Hardie, 2011).

There may be several means by which lipid metabolism influences fibrogenesis and generally, it appears that fibrogenesis is associated with an increase in fatty acid synthesis and a decrease in fatty acid oxidation (Fig. 2). As exemplified in diabetes-induced renal fibrosis, levels of key enzymes in fatty acid synthesis pathways (induced by the transcription factors SREBP1c and CHREBP) are increased and this corresponds with a decrease in fatty acid oxidation (Proctor et al., 2006). The increase in fatty acid synthesis was shown to raise levels of TGFβ1 and decrease ECM degradation via the serine protease inhibitor, PAI1, which regulates the activity of MMPs that mediate extracellular collagen degradation. Consistent with this, most fibrotic tissues have been shown to have downregulated PPAR signalling (generally indicating downregulated fatty acid oxidation) in response to TGFβ1 (Lakshmi et al., 2017; Qian et al., 2012; Wei et al., 2010; Zheng et al., 2002). A further link between fatty acid oxidation and ECM regulation was provided when in a recent study, CD36, a PPAR signalling-responsive fatty acid transporter which mediates type I collagen internalisation and degradation, was found to be reduced in both human and murine skin fibrosis (Zhao et al., 2019b). This phenotype was rescued by enhancing PPAR signalling using caffeic acid and its bioactive derivative, thereby restoring fatty acid oxidation. Upstream of PPAR signalling, it is interesting to note that PGC-1α deficiency leads to mitochondrial degradation, inflammation, and renal fibrosis (Fontecha-Barriuso et al., 2019). In pulmonary fibrosis, levels of the master cellular metabolism regulator, AMPK, are decreased. As well as promoting fatty acid oxidation, AMPK normally inhibits fatty acid synthesis via ACC1 phosphorylation and SREBP1c. In their study, Rangarajan et al. (2018) demonstrated a reversal of fibrosis in a bleomycin lung fibrosis model by activation of AMPK using metformin.

The cholesterol biosynthesis pathway, also known as the mevalonate pathway, deserves specific mention. Its intermediates, the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are involved in post-translational modifications of proteins known as protein prenylation (Hooff et al., 2010). The function of small monomeric GTPases such as Rho and Ras, signal transducers that mediate various profibrotic sequelae, require prenylation to function, whether by increasing protein hydrophobicity for associating with cell membranes or by stabilising protein-protein interactions (Distefano et al., 2006). Notable downstream pathways are the CTGF/CCN2/TGFβ1 and the Hippo signalling pathways. RhoA isoprenylation was required for the CTGF/CCN2 induction by TGFβ1 in human lung fibroblasts (Watts and Spiteri, 2004) as well as the activation of YAP/TAZ (Santos et al., 2020; Sorrentino et al., 2014), transcriptional co-activators of the Hippo

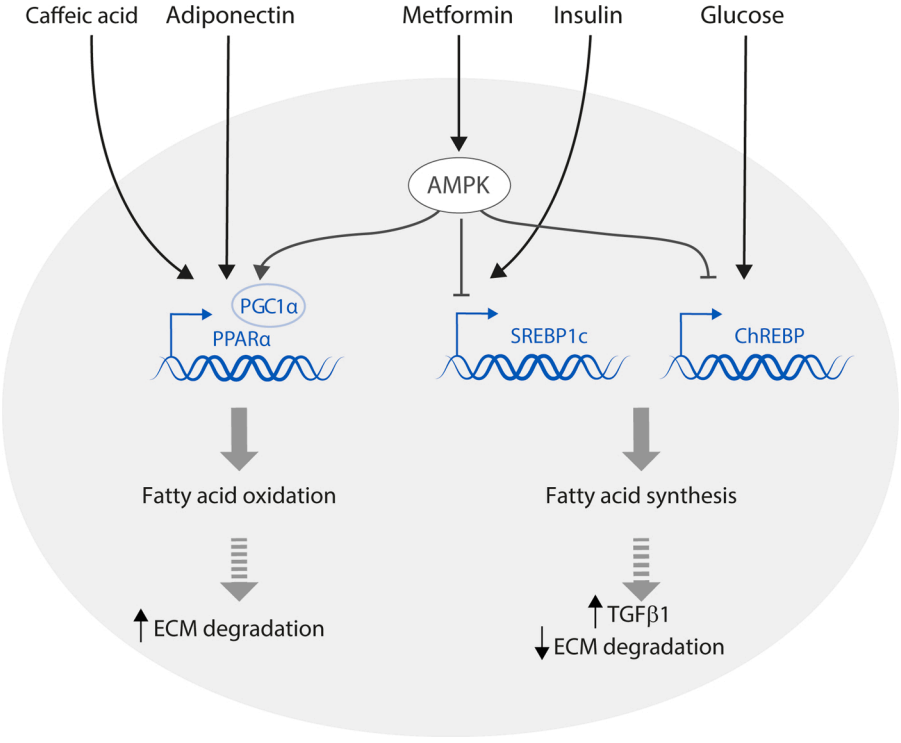


Fig. 2. Some key factors influencing fatty acid metabolism and links to fibrogenesis. Upon sensing energy shortage, AMPK causes activation of transcription factors including PPAR and its transcriptional coactivator PGC1α, whilst inhibiting the transcription factors SREBP1c and ChREBP. This results in a switch from fatty acid synthesis to fatty acid oxidation, which is associated with ECM degradation. In hyperinsulinaemic states with surplus glucose, SREBP1c and ChREBP are induced, in turn promoting fatty acid synthesis and this has been shown to be associated with increased TGFβ1 expression and decreased ECM degradation.

signalling pathway which are induced in hepatic (Mannaerts et al., 2015) and pulmonary fibrosis (Liu et al., 2015). Consistent with these observations, using statins as a proxy for inhibiting isoprenoid synthesis had promising anti-fibrotic results (Santos et al., 2020; Watts and Spiteri, 2004).

Lipids have also been implicated in fibrosis in the context of inflammation. Specifically, anti-inflammatory lipid mediators (lipoxins, resolvins, protectins) can attenuate experimental fibrosis (Serhan et al., 2015); secondary messenger diacylglycerol (binding to protein kinase C) promotes fibroblast proliferation (Weigel et al., 2016); and lipid rafts (e.g. caveolae) influence relevant signalling pathways, including β1 integrin-mediated mechanotransduction (Radel et al., 2007).

5. Mitochondrial dysfunction and fibrosis

Beyond their role in bioenergetic pathways (namely the TCA cycle and oxidative phosphorylation), mitochondria contribute to numerous cellular processes including biosynthetic pathways, cellular signalling, anti-oxidant defence and apoptosis (Herst et al., 2017). Through these processes, evidence is increasing for the interplay between mitochondrial dysfunction and fibrogenesis and approaches to restore mitochondrial quality have been shown to reverse fibrosis (Li et al., 2020; Rangarajan et al., 2017).

A key link between mitochondrial dysfunction and fibrosis is oxidative injury, manifesting as increased reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) release. A byproduct of oxygen metabolism, ROS can directly regulate ECM production and degradation (Siwik and Colucci, 2004), is required for TGFβ1-induced myofibroblast differentiation (Hecker et al., 2009), and can induce NLRP3 inflammasome activation, which in turn can set off signalling cascades that promote fibrosis (e.g. interleukin-1β secretion that enhances production of PDGF) (Stout-Delgado et al., 2016). On the other hand, mtDNA release can serve as a Damage-Associated Molecular Pattern, which when bound to toll-like receptor 9, can lead to TGFβ1 production, release, and activation (Fang et al., 2016). Consistent with this is the finding that IPF fibroblasts produce more mtDNA and normal fibroblasts have increased mtDNA production when stimulated with TGFβ1 (Ryu et al., 2017). Of interest, the increased mtDNA production by the TGFβ1-treated fibroblasts in this study were accompanied by enhanced glycolysis.

Mitochondrial stress is also accompanied by the mitochondrial unfolded protein response (mitoUPR), which induces transcription of genes that promote mitochondrial recovery. However, persistent mitoUPR activation can lead to irreversible mitochondrial dysfunction and upregulation of mitoUPR markers has been observed in lung fibrosis (Cuevas-Mora et al., 2021; Jiang et al., 2020). It is important to refer to the growing body of research suggesting cross-talk between mitochondria and the mevalonate pathway – a key finding is that mitoUPR signalling upregulates the mevalonate pathway and sustains protein prenylation, which is antagonized by statins (Oks et al., 2018; Rauthan et al., 2013). In the context of these studies, it is thought that protein prenylation confers cellular protection and its inhibition underlies some of the non-cholesterol (adverse) effects of statins such as muscle pain. However, one is reminded that these non-cholesterol effects also include inhibition of fibrosis, as discussed above (Santos et al., 2020; Watts and Spiteri, 2004).

6. Adipokines and fibrosis

Adipose tissue is now recognized as an endocrine organ that regulates glucose and lipid metabolic homeostasis, and numerous adipose tissue-derived secretory products (adipokines) have been identified as important mediators (Stern et al., 2016). Shortly after the discovery of leptin as the product of the mouse *obese* gene in 1994, adiponectin was identified as an adipokine whose secretion was enhanced by insulin, spurring larger scale profiling efforts to identify hundreds of novel adipokines for further study (Lehr et al., 2012). Of the numerous adipokines, adiponectin is probably the most frequently studied for its effects on expanding healthy adipose tissue. It has been shown to be a potent insulin sensitiser and it regulates the expression of key glycolysis genes (Liu et al., 2012). It activates AMPK, an important regulator of energy balance, which amongst its other functions, induces PPARα transcription to stimulate fatty acid oxidation. Of relevance to this review is the recent finding that adiponectin has an antifibrogenic effect on fibroblasts. Human skin biopsies of patients with systemic sclerosis show decreased phosphorylated AMPK (reflecting adiponectin activity) and augmentation of adiponectin signalling mitigated skin fibrosis in mice (Marangoni et al., 2017). A similar result was demonstrated in keloid disease where reduced adiponectin expression was noted and *in vitro* treatment of keloid fibroblasts with adiponectin suppressed CTGF/CCN2-induced proliferation, migration and ECM production (Luo et al., 2017). A few other adipokines have been indicated to have antifibrotic potential – visfatin is a proinflammatory adipokine that has been associated with obesity and myocardial fibrosis, but in late stage diffuse cutaneous systemic sclerosis, increased visfatin levels in serum was accompanied by regression of fibrotic skin lesions (Żółkiewicz et al., 2019). Apelin is a novel adipokine that has recently been shown to alleviate renal, myocardial and lung fibrosis (Huang et al., 2016) as well as TGFβ1-induced skin fibrosis (Yokoyama et al., 2018). CTRP3 is another lesser known adipokine with a molecular structure and function resembling adiponectin which exerted antifibrotic activity by targeting CTGF/CCN2, TGFβ1 and type I collagen production in colonic fibroblasts (Hofmann et al., 2011). Adipolin is a recently identified insulin-sensitising adipokine that was shown to be protective against pathological vascular remodelling by reducing PDGF-BB stimulated proliferation of vascular smooth muscle cells (Ogawa et al., 2019).

7. Targeting metabolic pathways for fibrosis therapy

Elucidating metabolic perturbations in fibrosis has highlighted some promising targets for fibrosis therapy. This development is discussed in detail by Zhao et al. (2019a). Most of the attempts to address specific metabolic alterations to treat fibrosis have been limited to the preclinical stages and it is important to consider what makes a good metabolic target in human disease. There are lessons to be learnt from the more established field of cancer metabolism therapy, particularly whether manipulation of metabolic pathways can be tolerated by normal tissues. Antimetabolites such as antifolates (methotrexate, pemetrexed), purine analogues (6-mercaptopurine, 6-thioguanine) and pyrimidine analogues (5-fluorouracil) are successful chemotherapeutics but are accompanied by prominent toxic side-effects on normal rapidly proliferating cells (e.g. bone marrow, intestinal crypts and hair follicles).

The glycolysis pathway has been targeted at several points in antifibrotic studies. The expression of GLUT1 correlates with increased glycolysis and its inhibition has shown anti-fibrotic effects on lung fibroblasts (Cho et al., 2017) and cardiac myoblasts (Ying et al., 2018). 2-DG is a compound which competitively inhibits HK and slows glycolysis. Ding et al. (2017) showed that treating renal fibroblasts with 2-DG decreased TGFβ1-associated fibrosis markers (fibronectin and α-SMA) whilst increasing environmental pH with reduced lactate accumulation. This process was tested in a mouse model of renal fibrosis (using unilateral ureteric obstruction) and showed therapeutic efficacy, as did shikonin, an alternative rate-limiting inhibitor of glycolysis that targets PKM2 (Ding et al., 2017). Similarly, in lung myofibroblasts, 2-DG treatment was associated with antifibrotic changes to cell phenotype (differentiation, contraction, collagen deposition) (Xie et al., 2015).

The approach of targeting glycolysis therapeutically has long been studied in cancer (Pelicano et al., 2006); however, its use in patients was limited by unacceptable systemic hypoglycaemia when doses sufficient to limit glucose metabolism in cancer cells were used. Although lower doses were better tolerated by patients, efficacy was limited and the question of whether there exists a sufficient therapeutic window to inhibit glycolysis enzymes remains to be determined (Dwarakanath

et al., 2009; Landau et al., 1958). It is worth noting the challenges faced when targeting glucose metabolism in the cancer therapeutics field and pre-empt the alternative approaches being considered for use in fibrotic conditions. One such approach is isoform-selective targeting of glycolytic enzymes. Some cancers are specifically dependent on the HK2 isoform of HK, an isoform that is normally expressed in skeletal and adipose tissue, rather than being constitutively expressed. This specificity provided a rationale for development of selective HK2 inhibitors as viable anticancer agents (Garcia et al., 2018). Whether cells involved in fibrosis exhibit metabolic enzyme isoform-selective dependency is a question worth pursuing. Another finding in cancer glucose metabolism is that partial and transient reduction of glycolysis rather than completely blocking it (e.g. using 3PO rather than 2-DG), is sufficient to impair pathologic angiogenesis (Schoors et al., 2014), offering an alternative approach to address the issue of toxicity.

In general, fatty acid oxidation is thought to be impaired in fibrosis (Zhang et al., 2020) and several therapeutic discoveries have supported this. The synthetic compound C75, which inhibits FASN and increases fatty acid oxidation (via the rate limiting enzyme Cpt1), was found to attenuate both renal and lung fibrosis (Jung et al., 2018; Kang et al., 2015). Zhao et al. (2019c) provided evidence that PPAR activation (using caffeic acid) functionally enhanced fatty acid oxidation and suppressed glycolysis, whilst downregulating ECM components fibronectin and type 1 collagen. Again, there are lessons from cancer therapeutics but also important differences. Whilst increased fatty acid synthesis is common to both cancer and fibrosis, fatty acid oxidation is seen to promote cancer cell survival (Harjes et al., 2016). In this field, efforts are being made for pharmacological blockade of fatty acid oxidation. For example, Cpt1 inhibitors show tumour inhibitory effects (Melone et al., 2018) and are suggested as potential druggable agents (Schlaepfer et al., 2014). However, they are associated with increased fibrosis markers in mice (Kang et al., 2015) and it is interesting to note that a clinical trial using the Cpt1 inhibitor etomoxir in patients with heart failure was stopped due to hepatotoxicity (Holubarsch et al., 2007).

PPARγ agonists have long attracted attention as regulators of adipocyte differentiation (promote fibroblast conversion to adipocytes) (Tontonoz et al., 1994) that increase insulin sensitivity in patients with diabetes mellitus. Beyond their antidiabetic effects, PPARγ agonists have been found to have antifibrotic actions on various models of fibrosis including the lung (Burgess et al., 2005), cornea (Jeon et al., 2017), and skin (Wu et al., 2009), with mechanistic studies showing that their action is by antagonizing TGFβ-induced responses through both PPARγ-dependent and PPARγ-independent pathways (Dantas et al., 2015; Jeon et al., 2014; Kuriyan et al., 2012). In considering the PPARγ-independent effects, it is noteworthy that several PPARγ ligands can inhibit mitochondrial pyruvate carrier activity (Divakaruni et al., 2013), and in so doing potentially attenuate fibrosis (McCommis et al., 2017). Using IPF fibroblasts, Oruqaj et al. (2015) found that PPARα activators (ciprofibrate or WY14643) also reduced TGFβ-induced myofibroblast differentiation and collagen production and hypothesised that this occurred through increased peroxisomal biogenesis. Previous studies had provided evidence that peroxisomes are important in diminishing ROS production and inflammatory reactions, and a well-known peroxisomal disorder with absent or reduced peroxisomes, Zellweger syndrome, manifests with hepatic fibrosis (Oruqaj et al., 2015).

It is exciting that a number PPAR agonists have reached clinical trials as potential anti-fibrotic agents, namely in treating non-alcoholic steatohepatitis, including lanifibranor, a pan-PPAR agonist (NCT03008070, NCT03459079), elanfibranor, a dual PPARα/δ agonist for non-alcoholic steatohepatitis (NCT02704403) and obeticholic acid, a nuclear receptor that transcriptionally increases PPARα and PPARδ (NCT02548351). It is important to note however, that lanifibranor was first developed to treat systemic sclerosis but the Phase 2b trial showed that its primary efficacy end point to alleviate skin fibrosis was not met (Denton et al., 2020). An important caveat in drugs targeting the PPAR signalling pathway is that there are complex interactions between the different isoforms that remain incompletely understood.

Another noteworthy metabolic target is the signalling protein mTOR. A serine/threonine protein kinase in the PI3K-related kinase family, mTOR is an orchestrator of metabolic reprogramming and influences glucose metabolism, lipid metabolism and glutamine metabolism through the induction HIF1α (glycolytic shift), SREBP (fatty acid synthesis) and glutaminase (glutaminolysis), respectively (Mossmann et al., 2018; Saxton and Sabatini, 2017). Rapamycin/sirolimus, an allosteric inhibitor of mTOR, has shown promise in inhibiting fibrosis in laryngotracheal stenosis (Namba et al., 2015), renal fibrosis (Chen et al., 2012) and cardiac fibrosis (Yu et al., 2013). This is postulated to be a result of reduced fibroblast proliferation and synthesis, attenuated epithelial-mesenchymal transition and suppression of inflammation-induced fibroblast stimulation (Hillel and Gelbard, 2015). One of the newer classes of antidiabetics, the sodium-glucose cotransporter 2 inhibitors, also act to inhibit mTOR and have recently been shown to reduce renal fibrosis (Kogot-Levin et al., 2020). However, it is necessary to be aware that a different allosteric inhibitor of mTOR, everolimus, used in the management of several cancers, is associated with the development of pulmonary fibrosis, possibly through the induction of the profibrotic protein CTGF/CCN2 (Eren et al., 2020; Leask, 2019).

Finally, it is important to consider the role epigenetic mechanisms play. DNA hypomethylation is already well known to associate with fibrogenic gene activation (Moran-Salvador and Mann, 2017). Barcena-Varela et al. (2020) recently provided evidence linking epigenetic effectors, fibrogenic activation and metabolic reprogramming. Using novel dual small molecule inhibitors against the H3K9 methyltransferase G9a and DNA-methyltransferase, they showed that pro-fibrogenic responses to TGFβ1 and hypoxia were dependent on epigenetic factors. Of particular interest, TGFβ1-induced glycolysis and lactate production were attenuated whereas the metabolic regulator, PGC-1α, reversed by TGβ1, was reactivated (Barcena-Varela et al., 2020). As described earlier, PGC-1α is a transcriptional coactivator that increases fatty acid oxidation, amongst other metabolic activities.

8. Summary and future perspectives

Although there is promise for clinical translation, efficacy and tolerability of emerging therapies are variable and reasons for discrepancies in relative effectiveness within drug classes are poorly understood. Furthermore, there exist incompletely understood mechanisms acting indirectly on metabolism to influence fibrosis. For example, glucagon-like peptide 1 agonists, which are another class of newer antidiabetic agents, are increasingly investigated for their anti-fibrotic effects (Warren et al., 2019; Zhang et al., 2015). As insulin sensitisers, it would have been reasonable to postulate that their effects involved the activation of glycolysis, although Almutairi et al. (2021) showed that this was not the case.

Although the effects of metabolic dysregulation on fibroblasts have been the focus of this review, using therapeutic agents to alter metabolism would affect all cell types in the body. Within the fibroblast population, there is substantial diversity within tissues, as well as between organ systems and tissue states (Philippeos et al., 2018; Shaw and Rognoni, 2020). Their respective phenotypes are an area of intense research and dissecting the metabolic profiles of these subpopulations is anticipated to be instructive. Inflammation is another major factor driving fibrosis and its association with metabolism was only briefly touched on in this review. Immunometabolism is a field with growing momentum, and it is likely new discoveries here will have relevance to fibrosis. Cells outside of the traditional wound healing repertoire are also coming into light. Shook et al. (2020) reported that adipocytes can alter their identity and become wound bed myofibroblasts. Interestingly, they found that adipocyte lipolysis regulates inflammatory

macrophage infiltration and thereby contributes to the wound healing response. It would be interesting to know whether the metabolism of adipocytes in the vicinity of scars/fibrosis is relevant.

To conclude, metabolic dysregulation is not merely a consequence of fibrotic tissue changes but makes significant functional contributions to disease processes, which justifies antifibrotic drug development or repurposing focusing on the manipulation of metabolic targets.

Author contributions

CYU: coordination, writing original draft. **All authors**: conceptualisation, writing - reviewing & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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