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A nutraceutical strategy for downregulating TGFβ signalling: prospects for prevention of fibrotic disorders, including post-COVID-19 pulmonary fibrosis

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OVERVIEW OF TRANSFORMING GROWTH FACTOR-BETA SIGNALLING

Upregulated transforming growth factor-beta (TGFβ) signalling, driving mesenchymal cells to increase their production of ground substance and undergo a transition to a myofibroblast phenotype, is believed to play a pathogenic role in diverse fibrotic disorders, including benign prostatic hyperplasia, scleroderma, pulmonary fibrosis, glomerulosclerosis, tubulointerstial fibrosis, hepatic fibrosis, open angle glaucoma, Peyronie's disease and the cardiac fibrosis associated with cardiac hypertrophy and heart failure.[1–20] It should follow that safe, practical measures which downregulate such signalling may have potential for the prevention and control of these syndromes. Nutraceutical measures with this property have particular promise, as they might be employed for primary prevention. This issue is now of particular interest, as pulmonary fibrosis is emerging as a not-uncommon long-term complication of COVID-19.[21 22]

TGFβ signalling commences when this ligand binds to the type II TGFβ receptor (TβRII), inducing its association with the type I receptor (TβRI) to form a heterotrimer complex. The constitutive serine-threonine kinase activity of TβRII then phosphorylates TβRI, activating *its* dual-specificity kinase activity. Smad2 or Smad3 then bind to TβRI, which phosphorylates it on a serine. This phosphorylation enables Smad2/3 to complex with Smad4, forming a heterodimer which translates to the nucleus to serve as a transcription factor to promote expression of TGFβ-inducible genes.

However, the Smad2/3-Smad4 heterodimer quite frequently functions in concert with an AP-1 complex to mediate TGFβ-induced transcription.[23–28] Activation of AP-1 reflects concurrent TGFβ-mediated activation of the mitogen-activated protein (MAP) kinases ERK, JNK and p38.[29 30] Activation of the MAP kinase kinase kinase TAK1 is upstream from JNK and p38 MAP kinase in this signalling pathway. The E3 ubiquitin ligase TRAF6 is capable of binding to kinase-activated TβRI in the TGFβ receptor complex, and this induces the self-ubiquitination (K63) of TRAF6.[31 32] The ubiquitinated TRAF6, in turn, interacts with TAK1 and induces its K63 ubiquitination, activating its MAP kinase activity and thus resulting in downstream activation of JNK and p38 MAP kinase. (This signalling pathway is homologous to TRAF-dependent interleukin (IL)-1-mediated activation of these MAP kinases.)

TGFβ-induced activation of ERK1/2 is mediated by ShcA.[33] TβRI in the activated TGFβ receptor possesses rather weak tyrosine kinase activity; this enables its tyrosine autophosphorylation, inducing binding of ShcA. TβRI then tyrosine phosphorylates ShcA, which can then bind Grb2/Sos to stimulate GTP binding to Ras. Activated Ras, via the canonical Raf-MEK pathway, induces ERK1/2 activation.

Activated ERK1/2, JNK and p38 MAP kinase can collaborate to boost c-Fos expression and confer a serine phosphorylation on c-Jun which boosts its transactivational activity.[34] As a result, AP-1 activity is markedly induced, and this collaborates with Smad2/3-Smad4 heterodimers to promote TGFβ-mediated transcription. One of the genes whose

transcription is induced in this manner codes for NOX4, which constitutively generates superoxide/hydrogen peroxide.[35] NOX4 induction plays a key role in upregulating TGFβ signalling, as inhibitors of this enzyme notably blunt TGFβ activity.[1 36–38] This is at least partially attributable to the fact that nuclear NOX4 generates hydrogen peroxide which reversibly inhibits MAP kinase phosphatase-1.[39] This latter enzyme functions to deactivate both JNK and p38 MAP kinase; its inactivation by NOX4 hence upregulates JNK and p38 activation, thereby boosting the TGFβ signal. NOX4-mediated inhibition of tyrosine phosphatase activity (such as PTP1B) may also contribute to NOX4's impact on TGFβ signalling.[40 41]

CGMP, OESTROGEN RECEPTOR-Β, NRF2, SIRT1 AND HYDROGEN SULFIDE CAN DIMINISH TGFΒ SIGNALLING

TGFβ signalling can be opposed by cGMP, the ligand-bound oestrogen receptor-β (ERβ), activation of the nrf2 transcription factor and the Sirt1 deacetylase. The effect of cGMP in this regard is mediated by protein kinase G-1a (PKG-1a). This kinase phosphorylates the TGFβ-activated Smad3 (pSmad3) in such a way as to prevent the translocation of pSmad3/Smad4 heterodimers to the nucleus.[42 43] Once phosphorylated by PKG-1a, Smad3 has a high affinity for cytosolic beta2-tubulin, resulting in its sequestration in the cytoplasm.[44] Other research suggests that PKG activity may interfere with TGFβ signalling by promoting the proteasomal degradation of Smad3.[45] Not surprisingly, agents with boost cellular levels of cGMP have also been shown to oppose tissue fibrosis and TGFβ activity.[42 43 46–56]

Ligand-bound activated ERβ has been found to downregulate TGFβ-mediated transcription by a direct interaction with AP-1 complexes that blocks their transactivational activity.[57 58] This interaction does not involve binding of ERβ to oestrogen response elements on DNA, but rather to c-Jun. This may rationalise preclinical and epidemiological evidence that endogenous or therapeutic oestrogen provides protection from cardiac hypertrophy, hepatic fibrosis, glomerulosclerosis and primary open-angle glaucoma (POAG).[59–68] Pertinently, ERβ is expressed in hepatic stellate cells, mesangial cells, cardiac fibroblasts and prostate stroma.[59 62 69–73] Moreover, polymorphisms of the ERβ gene (but not that of the ERα gene) have been linked to increased risk for POAG.[74 75]

A number of studies show that activation of the Nrf2 transcription factor, mediator of the phase II response, can suppress TGFβ signalling.[76–81] Although Nrf2 has the potential to antagonise TGFβ signalling via promotion of glutathione synthesis and various antioxidant enzymes—thereby opposing the upregulatory impact of Nox4-produced oxidants on TGFβ activity[80]—it also does so by boosting the protein level of SMAD7, which interacts with the type 1 TGFβ receptor in such a way as to block its association with SMAD2/3, and acts in additional ways to oppose SMAD-dependent TGFβ activity.[77 81 82] This effect of Nrf2 is indirect, reflecting its ability to decrease protein expression of SMURF1, an E3 ubiquitin ligase that targets SMAD7 for proteolytic degradation.[77 81]

Many studies, though not all,[83] report that increased activity of the class III deacetylase Sirt1 downregulates TGFβ signalling and opposes pathological fibrosis.[84–92] Conversely, TGFβ activity suppresses Sirt1 expression.[93] The downregulatory effect of Sirt1 on TGFβ signalling is mediated, in part, by decreased protein expression of p300, a histone acetyltransferase which acts as a coactivator for SMAD2/3-dependent transcription; Sirt1 promotes its proteasomal degradation.[85 94 95] However, Sirt1 can deacetylate SMADs 2, 3 and 4, and this may also play a role in this effect.[91 92]

Numerous studies have demonstrated that, in vivo, exogenous hydrogen sulfide (H_2S) inhibits fibrosis in a range of tissues, and, in vitro, opposes TGFβ signalling.[96–109] That this effect is of physiological significance is suggested by the fact that genetic deficiency of enzymes that generate H_2S—for example, cystathione-β-synthase (CBS), cystathionine-γ-lyase (CSE)—as well as agents which inhibit expression of these enzymes, promote tissue fibrosis; moreover, expression of these enzymes is often decreased in fibrosis models.[97 100 109–115] In rodent models of fibrosis and in cultured cells exposed to TGFβ, H_2S suppresses SMAD2/3 phosphorylation and ERK activation.[96 97 101 101 102 116–119] This effect may be partially attributable to decreased expression of TGFβ receptors types I and II, but the possibility that H_2S intervenes in signalling by the intact receptor cannot be ruled out.[101 119] In vivo, H_2S has also been reported to decrease TGFβ expression.[101–103 105]

NUTRACEUTICALS THAT MAY DOWNREGULATE TGFΒ SIGNALLING

These considerations suggest that several nutraceuticals may have potential for downregulating TGFβ activity and thereby opposing pathological fibrosis. In regard to NOX4, it may be possible to decrease its activity via administration of spirulina or of spirulina extracts enriched in phycocyanobilin (PhyCB). The latter, a metabolic derivative and close homolog of biliverdin, has been found to share the latter's ability to inhibit certain nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complexes, including those dependent on NOX4.[120 121] Oxidative stress, via induction of heme oxygenase-1 (HO-1), promotes generation of biliverdin from heme; this biliverdin is rapidly reduced by biliverdin reductase to yield free bilirubin, which in turn quells oxidative stress by inhibiting NADPH oxidase complexes.[122–126] PhyCB, analogously, is reduced by biliverdin reductase to phycocyanorubin, a homolog of bilirubin that shares its ability to inhibit these complexes.[127] This likely explains, in large part, why oral administration of PhyCB, spirulina or phycocyanin (the spirulina protein which contains PhyCB as a covalently attached chromophore) has exerted profound antioxidant/anti-inflammatory activity in rodents in a wide variety

of contexts.[120 128 129] In particular, oral administration of spirulina/PhyCB has been shown to inhibit induction of hepatic, pulmonary and oral fibrosis, as well as glomerulosclerosis, in rodent models.[120 130–133] In vitro, exposure of two cancer cell lines to phycocyanin has been shown to inhibit TGFβ-mediated epithelial-mesenchymal transition, blocking induction of type 1 collagen, vimentin, fibronectin and snail, while preserving expression of E-cadherin.[134]

Phase II-inducing compounds activate the Nrf2 transcription factor to boost expression of a range of antioxidant enzymes; these include HO-1, which can oppose NADPH oxidase activity by giving rise to intracellular bilirubin via the heme catabolite biliverdin. These agents also oppose or reverse the modulatory impact of hydrogen peroxide on cellular signalling by increasing glutathione synthesis and boosting the expression of a range of antioxidant enzymes.[135–138] Moreover, they oppose TGFβ signalling by boosting SMAD7 levels. Perhaps the most clinically tested phase II inducer is the physiologically essential cofactor lipoic acid.[139–143] Indeed, a number of studies have reported that administration of lipoic acid can oppose TGFβ signalling and induction of pathological fibrosis in various rodent models. The utility of lipoic acid in this regard has been reported for fibrosis induced by radiation, bleomycin, laminectomy, abdominal incisions and trabeculectomy; for hepatic fibrosis induced by carbon tetrachloride, thioacetamide and bile duct ligation; and for cardiac fibrosis induced by diabetes.[144–154] Another natural agent with good clinical potential as a phase II inducer is ferulic acid, a compound widely distributed in plant foods, in free or bound form—and also long employed, as the sodium salt, for cardiovascular protection in Chinese medicine.[155] This agent has likewise shown anti-fibrotic activity in rodent studies.[156–159] Also clinically useful for phase II induction are broccoli sprout extracts, a rich, bioavailable source of the phase II inducer sulforaphane; these have been shown to exert anti-fibrotic activity in various rodent models.[160–164] Moreover, in cell culture studies, sulforaphane attenuates TFGβ signalling.[165 166]

The neurohormone melatonin, commonly employed as a nutraceutical sleep aid, can upregulate phase II induction by boosting expression of Nrf2 at the transcriptional level.[167–169] This, in turn, may reflect increased expression of the clock protein transcription factor Bmal1, which drives transcription of the Nrf2 gene.[170 171] However, Bmal1 also induces transcription of the gene coding for Sirt1.[172] Melatonin has been shown to oppose TGFβ activity and fibrosis in rodent studies and cell cultures, and this effect might reflect upregulation of both Nrf2 and Sirt1.[173–178]

Activation of AMP-activated kinase boosts Sirt1 activity in some tissues by increasing expression of nicotinamide ribosyltransferase, rate-limiting for the synthesis of Sirt1's substrate NAD+.[179 180] The phytochemical nutraceutical berberine, which activates AMPK in a matter analogous to the diabetic drug metformin, has been reported to inhibit pulmonary, cardiac, hepatic, pancreatic and renal fibrosis in rodents, likely owing to its upregulatory impact on Sirt1 activity.[181–188] Its effect in this regard would likely be complementary to that of melatonin.

Although drugs in development or in use which directly activate soluble guanylate cyclase (sGC) and potentiate its responsiveness to nitric oxide have considerable potential for control of fibrotic pathologies,[52 189–192] little consideration has been paid to the fact that, in supraphysiological but well tolerated concentrations (roughly two orders of magnitude over the physiological range), the vitamin biotin can directly activate sGC.[193–195] The maximum activation which biotin can achieve is twofold to threefold—as opposed to the 100-fold activation which NO can induce—which accounts for the fact that it has been well tolerated clinically in doses as high as 100 mg three times per day.[196 197] (Whether biotin potentiates response to concurrently applied NO, as do sGC activator drugs, has not been reported.) The ability of oral high-dose biotin to lower blood pressure and prevent stroke in stroke-prone spontaneously hypertensive rats has been shown to reflect systemic activation of sGC.[198] Favourable clinical effects of high-dose biotin on diabetes control may reflect biotin's impact on sGC.[199]

Boosting NO synthesis in tissues threatened by fibrosis could also increase cGMP production. Theoretically, uncoupling of NO synthase in such tissues could upregulate TGFβ signalling. Uncoupling mediated by asymmetric dimethylarginine (ADMA) could be offset with supplemental citrulline, whereas uncoupling reflecting oxidation of NO synthase's cofactor tetrahydrobiopterin might be reversed with high-dose folate supplementation.[200–202] In this regard, supplemental citrulline is reported to impede progression of diabetic nephropathy in rodents rendered diabetic with streptozotocin, likely reflecting a role for uncoupled endothelial nitric oxide synthase (eNOS) in this syndrome.[203] Indeed, elevated plasma ADMA predicts progression of kidney disease, and likely plays a pathogenic role in this regard.[204–206] Uncoupling of eNOS is a mediator of diastolic dysfunction in heart failure with preserved ejection fraction; hence, citrulline and/or high-dose folate might aid prevention of cardiac fibrosis in this circumstance.[207] Several studies suggest that peroxynitrite-mediated uncoupling of eNOS may play a pathogenic role in lung and pulmonary artery fibrosis associated with idiopathic pulmonary fibrosis.[208–211] An elevation of serum ADMA levels has been reported in patients with advanced POAG.[212]

Dietary or supplemental nitrates can be converted to NO (after reduction to nitrite by oral bacteria) in tissues, particularly hypoxic tissues.[213 214] Feeding of sodium nitrate or of nitrate-rich beetroot juice to diet-induced obese hypertensive rats has been shown to exert favourable effects on cardiac structure and function, including a reduction in ventricular fibrosis.[215]

With respect to ERβ, the multiple health-protective benefits of soy isoflavones have been traced to the fact that, when these agents are ingested in nutritional (as

opposed to pharmacological) amounts, the plasma levels of unconjugated genistein and equol that result are sufficient to achieve activation of ERβ, while exerting minimal impact on ERα.[216–220] For this reason, nutritional intakes of soy isoflavones can evoke the protective effects of ERβ, without the ERα-mediated feminising and pro-carcinogenic effects associated with ERα activation. Hence, soy isoflavone supplementation or a soy-rich diet may have potential for preventing and controlling fibrotic pathologies. Oral administration of genistein suppresses collagen synthesis by rat mesangial cells in vivo, and also inhibits cardiac hypertrophy and fibrosis induced by pressure overload or isoproterenol.[221–223] Oral soy isoflavones have also provided protection from hepatic fibrosis and radiation-induced pulmonary fibrosis in rodents.[224–227] A controlled study of soy isoflavone supplementation in watchful-waiting BPH showed only a trend toward benefit, but the daily dose employed (50 mg) likely was suboptimal.[228] However, a clinical evaluation of a synthetic ERβ agonist in BPH likewise had a null outcome; perhaps ERβ agonists would be more effective for prevention than for therapy of this syndrome.[229]

Recent studies indicate that the antihypertensive, antiatherosclerotic and brain-protective benefits of taurine administration may in large measure reflect increased expression of enzymes which synthesise H_2S—namely CBS and CSE.[230 231] This effect has been demonstrated to date in vascular tissues and the brain, but it may well be operative in other tissues. In light of H_2S's ability to downregulate TGFβ activity cited above, it is notable that taurine has been shown to exert anti-fibrotic effects in a number of rodent models of fibrosis, in a range of tissue, including lungs, liver, heart, kidney, pancreas and penis.[232–244] Conversely, in mice with a genetic knockout of the taurine transporter, marked cardiac fibrosis is noted.[245] An economical explanation of these findings could be that taurine controls TGFβ activity by supporting endogenous H_2S generation. In any case, in light of abundant rodent data, inclusion of taurine in nutraceutical regimens intended to oppose pathological fibrosis seems appropriate, particularly as this agent is safe and inexpensive.

Tissue cysteine levels can be rate-limiting for H_2S synthesis, and those levels tend to decline in the elderly.[246 247] Supplemental N-acetylcysteine (NAC) can also boost tissue levels of the key antioxidant glutathione, which can participate in mechanisms that reverse the pro-inflammatory effects of hydrogen peroxide on signalling pathways.[248–252] Hence, NAC supplementation has been recommended for the elderly, and might be expected to at least modestly aid control of fibrotic syndromes in this group, both by opposing the pro-fibrotic impact of Nox4-derived hydrogen peroxide, and by enhancing H_2S synthesis.[247 250 251] Consistent with this speculation, oral administration of NAC has shown favourable effects in multiple rodent models of pathogenic fibrosis.[253–267] Moreover, NAC also has been shown to downregulate TGFβ signalling in cell cultures.[268]

Box 1 Suggested dose schedules for nutraceuticals with anti-fibrotic potential in COVID-19 and other fibrotic disorders

N-acetylcysteine—600 mg two times per day.
Lipoic acid—600 mg two times per day.
Ferulic acid—250 mg two times per day.
Broccoli sprout powder—5 g one to two times per day (providing 20–40 mg of sulforaphane).
Spirulina—15 g one time per day.
Melatonin—10 mg at bedtime.
Berberine—500 mg two times per day.
Taurine—1 g two times per day.
Folate—10 mg two times per day.
Soy Isoflavones—75 mg two times per day.
Biotin—10 mg two times per day.
Vitamin D—4000 IU daily.

CONCLUSION

In summary, spirulina/PhyCB, phase II inducers such as lipoic acid, ferulic acid or broccoli sprout powder, melatonin, berberine, high-dose biotin, soy isoflavones, taurine and NAC may have potential for downregulating TGFβ signalling, and thereby decreasing risk for, or improving clinical control of, a wide range of pro-fibrotic pathologies. Suggested dose schedules for these agents are presented in box 1. With regard to post-COVID-19 syndrome specifically, the antioxidant/anti-inflammatory effects of PhyCB, phase II inducers, melatonin and NAC might address neurological aspects of this syndrome thought likely to reflect chronic inflammation of cerebrovascular endothelial cells and microglia.[269–272] Further studies are needed to confirm the benefit and safety of this potential nutraceutical strategy in COVID-19.

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