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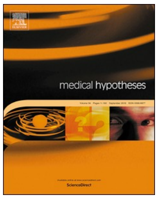

Nutraceutical targeting of TLR4 signaling has potential for prevention of cancer cachexia

Mark F. McCarty[a,*], Simon Iloki-Assanga[b], Lidianys Maria Lewis Lujany[b]

[a] Catalytic Longevity, San Diego, California, USA
[b] Departamento de Ciencias Quimico Biologicas, Universidad de Sonora, Mexico

ABSTRACT

The mechanisms underlying cancer cachexia – the proximate cause of at least 20% of cancer-related deaths – have until recently remained rather obscure. New research, however, clarifies that cancers evoking cachexia release microvesicles rich in heat shock proteins 70 and 90, and that these extracellular heat shock proteins induce cachexia by serving as agonists for toll-like receptor 4 (TLR4) in skeletal muscle, macrophages, and adipocytes. Hence, safe nutraceutical measures which can down-regulate TLR4 signaling can be expected to aid prevention and control of cancer cachexia. There is reason to suspect that phycocyanobilin, ferulic acid, glycine, long-chain omega-3s, green tea catechins, β-hydroxy-β-methylbutyrate, carnitine, and high-dose biotin may have some utility in this regard.

Toll-like receptor 4 is the key mediator of cancer cachexia

A recent study by Zhang and colleagues provides strong evidence that, at least in a high proportion of instances, cancers induce cachexia by releasing microvesicles rich in heat shock proteins 70 and 90; each of 5 cancer cell lines known to induce cachexia in rodents released ample amounts of such microvesicles, whereas a non-cachexigenic cancer cell line and several non-tumorigenic cell lines failed to do so [1]. These microvesicles were shown to activate toll-like receptor 4 (TLR4) on skeletal muscle fibers – promoting cachexic muscle catabolism - and on macrophages and adipocytes to induce release of pro-inflammatory cytokines responsible for the systemic inflammation associated with cancer cachexia [1]. These circulating cytokines, including tumor necrosis factor-α and interleukin-1, can then act on skeletal muscle to potentiate muscle catabolism, and on the hypothalamus to suppress appetite. The resistance of TLR4 knockout mice to cancer cachexia is consistent with this model [2,3].

Other research concludes that signaling by myostatin – a member of the transforming growth factor family produced by muscle fibers that acts in an autocrine fashion on activin receptors – is likewise necessary for development of cancer cachexia. Hence, myostatin knockout mice, or mice treated with activin receptor (ActRII) antagonists, are resistant to cancer-induced loss of muscle mass [4–7]. Conversely, forced overexpression of myostatin induces muscle atrophy [8,9]. However, muscle expression of myostatin was found not to increase in mice developing cancer cachexia, and plasma levels of myostatin tend to be lower in cachectic cancer patients than in non-cachectic cancer patients [5,10]. This suggests that constitutive myostatin signaling may support responsiveness to TLR4 stimulation in muscle; indeed, muscle expression of TRAF6, a key mediator of TLR4 signaling, was found to be markedly diminished in myostatin knockout mice [5]. Activin, a chemical relative of myostatin that likewise activates ActRII receptors, can be produced by some cancers, and its plasma levels tend to be moderately elevated in cachectic cancer patients; hence it seems likely that activin plays at least a co-factor role in some cases of cancer cachexia [10,11].

It follows that practical clinical measures which suppress TLR4 signaling should have value for controlling cancer cachexia – which is the proximal cause of death in about 20% of cancer deaths. Nutraceuticals which may have potential in this regard include phycocyanobilin, ferulic acid, glycine, long-chain omega-3 fatty acids, methylated green tea catechins, and high-dose biotin.

How TLR4 signaling promotes loss of muscle mass

Although the details of TLR4 signaling in skeletal muscle fibers has been little studied, this signaling is likely homologous to that characterized in other cell types. TLR4-mediated activation of p38β MAP kinase and subsequent activating phosphorylation of the transcription factor C/EBPβ is crucial to induction of the E3 ubiquitin ligases – atrogin1 and UBR2 – which contribute importantly to the accelerated proteasomal degradation of muscle contractile proteins that causes muscle catabolism in cancer cachexia [12,13]. Additionally, TLR4 stimulates the transcriptional activity of NF-κB, which promotes increased expression of another E3 ubiquitin ligase, MuRF1, that contributes to loss of contractile proteins during cancer cachexia [14].

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[*] Corresponding author.
E-mail address: markfmccarty@gmail.com (M.F. McCarty).

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In various immune cells, TLR4-mediated activation of p38β is downstream from TRAF6-ASK1 activation, which in turn requires increased production of oxidants via NADPH oxidase activity [15]. Apparently, TLR4 activation induces production of hydrogen peroxide in the microenvironment of the TLR4 signaling complex, which includes TRAF6. This hydrogen peroxide oxidizes thioredoxin, releasing it from its inhibitory interaction with ASK1 [16]. ASK1 is then free to bind with TRAF6, which positions ASK1 such that it can form homo-oligomers that *trans*-autophosphorylate, fully activating ASK1′s kinase activity [17]. ASK1 is a MAP3K that can activate p38 MAPK via MKK3 and MKK6 [18].

There is reason to suspect that NADPH oxidase-mediated oxidant production may also play a role in catalyzing the integration of TRAF6 into the TLR4 signaling complex; it appears to play this role in interleukin-1 signaling, which is likewise MyD88 dependent [19]. If this is the case, then oxidant production may also catalyze an alternative pathway of TLR4-mediated activation of p38β, mediated by TAK1. TAK1 also activates NF-κB via IKKβ [20].

How nutraceuticals can oppose TLR4 signaling

These considerations suggest that phycocyanobilin (PhyCB), a biliverdin metabolite that functions to harvest light energy in cyanobacteria (such as spirulina) and certain blue-green algae, and that shares the ability of unconjugated bilirubin to inhibit Nox2- and Nox4-dependent NADPH oxidase activity, may have the potential to oppose TLR4 signaling in skeletal muscle [21–23].

The antioxidant phytochemical ferulic acid has been shown to inhibit TLR4 signaling in various cell types – albeit this has not been studied in skeletal muscle [24]. Some recent evidence suggests that this inhibitory effect reflects targeting of the MyD88 adaptor protein, which is upstream from the TRAF6-ASK1-p38 pathway [24,25].

The anti-inflammatory and insulin sensitizing effects of the long-chain omega-3 fatty acids EPA and DHA are now known to be mediated largely by the ability of these compounds to act as agonists for GPR120, a G-protein-coupled receptor expressed by macrophages and adipocytes, but not skeletal muscle [26,27]. These omega-3 s, via activation of GPR120, have been shown to oppose the pro-inflammatory effects of TLR4 signaling; the mechanism responsible for this effect has recently been unraveled [28]. Activated GPR120 binds to β-arrestin2; this enables the latter to bind the TAK1-binding protein-1 (TAB1) [26,27]. This sequesters TAB1 away from TAK1, preventing the TLR4 signaling complex from inducing activating phosphorylation of TAK1. Hence, the ability of TAK1 to stimulate the activities of the JNK and p38 MAP kinases, as well of IKKβ and NF-kappaB, is blunted. The anti-cachexic activity of dietary omega-3-rich fish oil has been documented both clinically and in rodents [29,30]. This presumably reflects down-regulation of inflammation in macrophages and adipocytes; the protein-sparing effect on skeletal muscle is not direct, but rather a function of decreased muscle exposure to pro-inflammatory cytokines produced by macrophages and adipocytes.

Some of the metabolic effects of green tea catechins have recently been traced to the interaction of EGCG and of its methylated derivative EGCG3″ Me with a cell surface laminin receptor, 67LR [31,32]. In a range of cell types, this interaction has been shown to oppose TLR4 signaling by inducing the toll-interacting protein (Tollip) as well as an E3 ubiquitin ligase, RNF216, which promotes proteasomal degradation of TLR4 [33–39]. Green tea cultivars relatively rich in methylated catechins – such as benifuuke tea – may have superior clinical utility, as orally administered EGCG3″Me achieves far higher plasma concentrations than comparable intakes of EGCG [40,41].

These effects of 67LR are mediated by stimulation of endothelial nitric oxide synthase (eNOS), which in turn boosts cGMP production via soluble guanylate cyclase (sGC) [37,42]. Indeed, drugs which directly activate sGC have been shown to mimic the ability of EGCG and 67LR to oppose TLR4 signaling [37,42]. Since the B vitamin biotin, in concentrations two orders of magnitude higher than its ordinary physiological concentration, can directly activate sGC, high-dose biotin – currently being safely employed in management of multiple sclerosis – may also have potential for control of cancer cachexia [43–48].

In cells which express strychnine-inhibitable glycine receptors, glycine exerts antioxidant and anti-inflammatory effects, possibly via suppression of NADPH oxidase activity [49,50]. In particular, glycine has been shown to suppress TLR4 signaling [51–53]. Although it is not known whether skeletal muscle fibers express glycine receptors, supplemental glycine has been found to aid maintenance of skeletal muscle mass in a rodent model of cancer cachexia, and in lipopolysaccharide-injected pigs, glycine administration blocked induction of atrogin1 and down-regulated mRNA expression of TLR4 [53–55]. Hence, while its mechanism of action may be somewhat obscure, the impact of supplemental glycine on cancer cachexia merits more study.

There are also multiple reports that the leucine catabolite β-hydroxy-β-methylbutyrate (HMB), used to potentiate the gains of muscle mass achieved with exercise, can diminish loss of muscle mass in rodent models of cancer cachexia or LPS-induced sepsis [56–61]. Two clinical trials have addressed the utility of a regimen providing HMB (3 g daily), arginine and glutamine in cachectic cancer patients; one of the two reported a favorable result, with a null result in the other [62–64]. The anti-cachectic effects of HMB may reflect, in part, its targeting of double-stranded RNA-dependent protein kinase (PKR). Although this kinase is activated by infection with certain viruses, it can also be stimulated by the activated TLR4 receptor, likely via interaction with TIRAP/MyD88 [65,66]. PKR suppresses protein synthesis by conferring inhibitory phosphorylations on eIF2α and eEF2 [66,67]. Concurrently, PKR boosts proteasomal protein degradation by enhancing the expression of proteasomes and their constituent proteins [66]. For reasons that remain obscure, HMB, although it does not directly inhibit PKR, interferes with activation of this kinase induced by cachectic stimuli, including LPS and cancer [61,66,68–70]. Hence, in rodent models of cancer cachexia or sepsis, HMB has been reported to suppress PKR activation and proteasomal activity, while counteracting inhibition of protein synthesis [60,61,66].

There is limited evidence that the ketone body beta-hydroxybutyrate (BHB) may have anti-catabolic and anti-inflammatory activity in cancer cachexia [71–73]. In particular, when myotubes were exposed *in vitro* to conditioned medium from two cancer cell lines that evoke cachexia, concurrent exposure to this compound dose-dependently inhibited expression of both atrogin1 and MuRF1 [71]. BHB is known to function as a physiological agonist for the G-protein-coupled receptor GPR109A (a.k.a. HCA2); this is likely expressed in skeletal muscle, as the mRNA coding for this receptor has been found in skeletal muscle of rats and cattle [74–76]. Activation of GPR109A is known to oppose TLR4 signaling in monocytes, associated with inhibition of NF-kappaB signaling [77]. Curiously, the activated GPR109A receptor binds to beta-arrestin, just as the GPR120 receptor does [78]. If GPR109A likewise interferes with TLR4 signaling at the level of TAK1, this could explain the inhibition of both atrogin1 and MuRF1 induction achieved by BHB in myotubes. Although it is now feasible to raise plasma ketone levels with ketone ester preparations, nicotinic acid also serves as an agonist for GPR109A; indeed, this receptor is believed to mediate niacin's hypolipidemic effects [79,80]. These considerations suggest that the impact of time-release nicotinic acid should be studied in rodent models of cancer cachexia. Indeed, this possibility was suggested some years ago, but never followed up [81].

Several reports suggest that muscle carnitine levels are sub-normal in rodents or humans with cancer cachexia [82,83]. It would be of interest to determine whether TLR4 signaling or sepsis decreases the expression of the carnitine transporter OCTN2 in skeletal muscle [84]. Conversely, carnitine supplementation has been found to blunt loss of muscle mass in rodent cancer models and in a controlled study with pancreatic cancer patients – albeit another controlled clinical trial failed to observe a favorable impact of supplemental carnitine on fatigue in cancer patients [85–89]. Muscle carnitine levels tend to fall in the elderly, and carnitine supplementation has been found to lessen tiredness and increase lean mass in elderly subjects complaining of fatigue [90–92]. How carnitine might influence muscle mass remains unclear. However, in the low mM concentrations that prevail in healthy skeletal muscle, carnitine has been shown to act as a histone deacetylase (HDAC) inhibitor [93]. HDAC activity has been shown to play a role in muscle wasting syndromes, and the HDAC inhibitor valproic acid has been found to alleviate muscle wasting in rodents models of cancer cachexia, and in myotubes exposed to conditioned medium from cachexia-inducing cell lines [94–97]. Notably, valproic acid prevented an up-regulation of muscle C/EPBβ expression in these models. Hence, correction of subnormal muscle carnitine levels via supplementation may have a favorable impact on the progression of cancer cachexia via modulation of HDAC activity.

Inasmuch as TLR4 activation in macrophages, microglia, and adipocytes is believed to play a key pathogenic role in metabolic syndrome,[28,98–101] it is notable that each of the agents suggested here, aside from HMB, has been shown to ameliorate this syndrome in rodents, and in some instances clinically [102–128].

Fig. 1 summarizes the postulated mechanisms whereby the nutraceuticals discussed here may suppress TLR4 signaling.

Some of These nutraceuticals may also slow cancer growth

It may be noted that glycine, PhyCB, ferulic acid, long-chain omega-3s, and HMB have been reported to slow cancer growth in certain rodent models. Glycine and omega-3s exert an anti-angiogenic effect, and PhyCB may slow the growth of cancers in which NADPH oxidase-mediated oxidant production up-regulates growth factor signaling [129–134]. Ferulic acid has been shown to inhibit the growth of a human breast adenocarcinoma in nude mice; its mechanism of action in this regard is unclear [135]. A modest but significant retardation of the growth of MAC16 mammary adenocarcinoma in mice and of Walker carcinoma in rats has been reported with HMB [56,60].

With regard to use of nutraceuticals in cancer cachexia, it should be noted that some recent evidence indicates that zinc may play a co-factor role in this syndrome. Upregulation of the ZIP4 zinc transporter in skeletal muscle fibers has been found to be a feature of cancer cachexia, and the consequent increase in intracellular zinc potentiates the loss of muscle mass [136]. Since an increase of zinc in healthy muscle does not precipitate cachexia, it seems likely that zinc somehow potentiates TLR4 signaling in muscle. Moreover, increased uptake of zinc by the ZIP14 transporter enhances the propensity of at least some pancreatic cancers to release microvesicles rich in hsp70 and 90, by boosting expression of a G protein, RAB27B, required for microvesicle release [137]. Hence, zinc supplementation may be contraindicated in the context of cancer cachexia.

While anti-cancer measures which directly address cancer cells are often doomed to ultimate failure owing to selection for mutations that promote resistance, it is reasonable to expect that a practical strategy for countering cancer cachexia will have durable efficacy. Moreover, if TLR4 is indeed the mediator of most cases of cancer cachexia, a strategy targeting TLR4 signaling should be useful for most patients at risk for

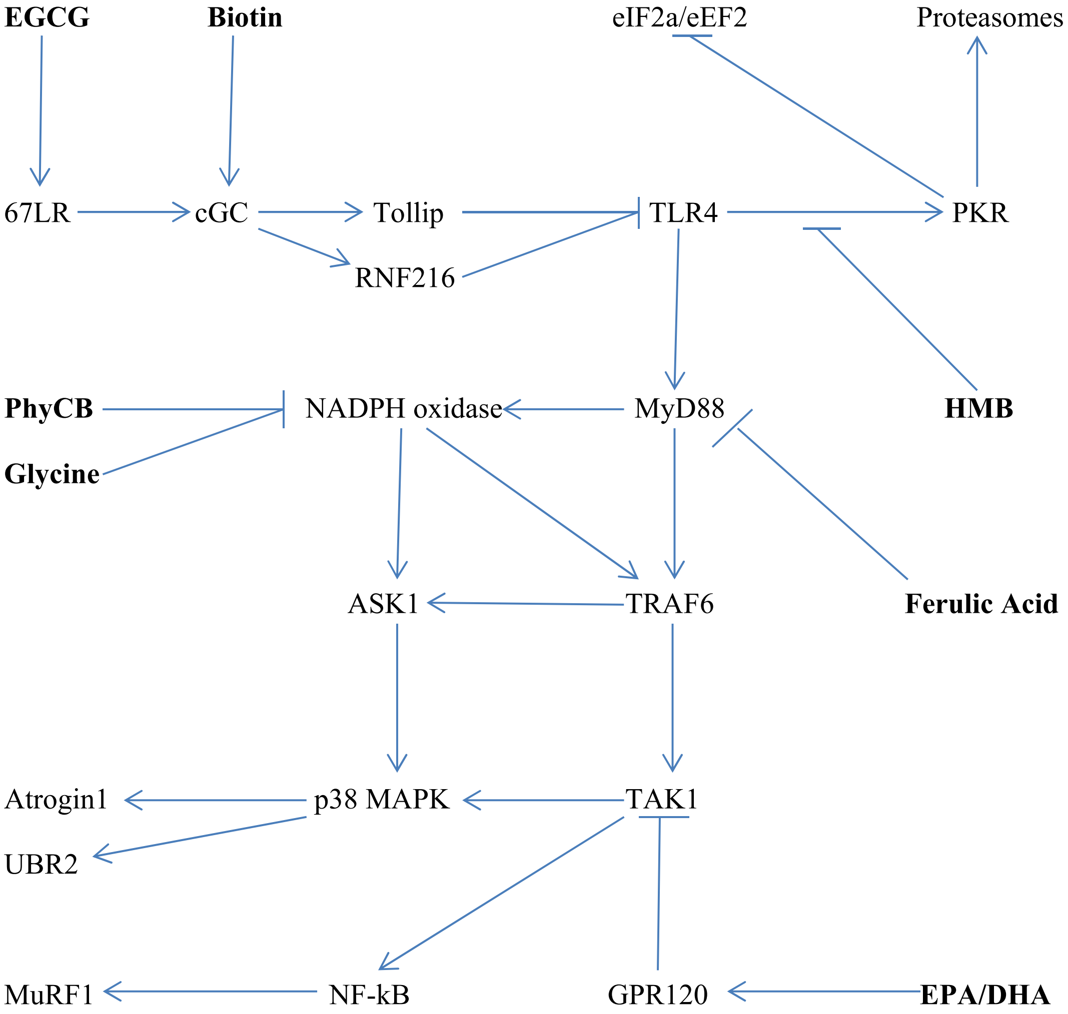

Fig. 1. Postulated mechanisms for nutraceutical suppression of TLR4 signaling.

this complication. Hence, rodent studies and ultimately clinical studies are needed to assess what combination and dose schedule of the measures suggested here might provide important protection from cancer cachexia.

Declaration of Competing Interest

Mark McCarty is co-inventor and co-owner of a US patent covering nutraceutical uses of phycocyanobilin oligopeptides.

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