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mTORC1 activity as a determinant of cancer risk – Rationalizing the cancer-preventive effects of adiponectin, metformin, rapamycin, and low-protein vegan diets

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ABSTRACT

Increased plasma levels of adiponectin, metformin therapy of diabetes, rapamycin administration in transplant patients, and lifelong consumption of low-protein plant-based diets have all been linked to decreased risk for various cancers. These benefits may be mediated, at least in part, by down-regulated activity of the mTORC1 complex, a key regulator of protein translation. By boosting the effective availability of the translation initiator eIF4E, mTORC1 activity promotes the translation of a number of "weak" mRNAs that code for proteins, often up-regulated in cancer, that promote cellular proliferation, invasiveness, and angiogenesis, and that abet cancer promotion and chemoresistance by opposing apoptosis. Measures which inhibit eIF4E activity, either directly or indirectly, may have utility not only for cancer prevention, but also for the treatment of many cancers in which eIF4E drives malignancy. Since eIF4E is overexpressed in many cancers, strategies which target eIF4E directly – some of which are now being assessed clinically – may have the broadest efficacy in this regard. Many of the "weak" mRNAs coding for proteins that promote malignant behavior or chemoresistance are regulated transcriptionally by NF-kappaB and/or Stat3, which are active in a high proportion of cancers; thus, regimens concurrently targeting eIF4E, NF-kappaB, and Stat3 may suppress these proteins at both the transcriptional and translational levels, potentially achieving a very marked reduction in their expression.

mTORC1 as a central target for cancer prevention

Increased plasma levels of adiponectin have been linked to decreased risk for a number of cancers (breast, prostate, colorectal, endometrial, pancreatic, gastric, renal cell, as well as melanoma and multiple myeloma) in prospective and case-control studies; reduced adiponectin levels are suspected to mediate a portion of the increase in cancer risk associated with obesity [1–5]. Diabetics treated with metformin have been found to be at decidedly lower cancer risk than those treated with insulin or sulfonylureas [6–9]. Administration of rapamycin or its analogs to renal transplant patients – typically at high cancer risk owing to immunosuppression – has been associated with reduced new cancer incidence [10–12]. Plant-based diets may be largely responsible for the lower risk for many "Western" cancers characteristically observed in the rural Third World throughout the last century [13–16]. There is reason to suspect that down-regulation of the kinase activity of mTORC1 in pre-cancerous lesions plays a mediating role in each of these phenomena.

Regulation of mTORC1

The mTORC1 complex is a heterotrimer comprised of mTOR, raptor, and mLST8 [17,18]. The latter protein is not crucial to the kinase activity of this complex; its participation is an epiphenomenon reflecting the fact that mLST8 is required for the kinase activity of the alternative kinase complex mTORC2 [19]. The kinase activity of the activated complex is mediated by mTOR. Raptor promotes interaction between mTOR and its key substrates, S6 kinase and 4E-BP1, each of which bind to raptor; raptor also enables recruitment of mTORC1 to endosomal membranes where the kinase activity of mTOR can be most efficiently activated [20].

The regulation of mTORC1 kinase activity is complex and subtle, integrating a variety of signals that reflect nutritional and bioenergy status, as well as exogenous growth factor availability. Activation requires interaction between mTOR and the G protein Rheb in its GTP-activated conformation. The tuberous sclerosis complex (TSC), a dimer consisting of TSC1 and TSC2, functions to "turn off" Rheb by stimulating its GTPase activity. The protein kinase Akt, a key downstream mediator of growth factor signaling, catalyzes a phosphorylation of TSC2 that inhibits the GTPase-activating function of TSC, indirectly activating mTOR by sustaining the GTP-bound conformation of Rheb [21]. (An independent

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mechanism whereby Akt boosts mTORC1 activity is by phosphorylation of PRAS40; the unphosphorylated form of this protein binds to raptor and inhibits mTORC1 activity [22].) AMP-activated kinase (AMPK), whose activity is stimulated when cellular bioenergetics are impaired (and hence AMP levels are elevated), likewise phosphorylates TSC2, but does so in a way that boosts TSC activity, thereby indirectly suppressing mTOR activity [23]. Akt and AMPK thus have a "yin-yang" relationship with respect to Rheb – and hence mTOR – activation. In addition to its direct impact on the kinase activity of mTOR, GTP-bound Rheb promotes this activity indirectly by activating a phospholipase D that generates phosphatidic acid, a membrane lipid that facilitates the Rheb-mediated activation of mTOR [24].

Amino acid availability does not appear to influence the GTP-charging of Rheb; rather, it promotes migration of mTOR to Rab7-rich endosomal membranes where Rheb is chiefly found [18,20]. For reasons that remain obscure, amino acids – particularly leucine – induce GTP binding by Rag G proteins which, like Rheb, are localized to endosomal membranes. In their GTP-bound configurations, Rag GTPases avidly bind raptor, and thus attract the mTORC1 complex to endosomal membranes, facilitating the interaction of mTOR and GTP-bound Rheb.

mTORC1 promotes and drives malignancy

Chronic activation of the mTORC1 complex is often seen in cancer, most commonly reflecting upstream activation of the PI3K-Akt pathway attributable to excessive growth factor signaling and/or loss of PTEN function. In contrast, overexpression or mutation of mTOR is rarely seen. The chief functional targets of mTORC1's kinase activity are believed to be S6 kinase and 4E-BP1 [17]. (mTORC1 also phosphorylates and thereby inhibits a heterotrimer required for initiation of macroautophagy [25] – a process whose increased activity is thought to mediate much of the pro-longevity benefit of calorie or protein restriction [26]. The down-regulation of mTORC1 activity induced by amino acid deficit thus acts to correct this deficit by promoting proteolysis.) Activation of S6 kinase by mTORC1 boosts the ability of ribosomes to translate ribosomal proteins, and hence promotes ribosomal neogenesis; chronic overactivation of S6 kinase has an anabolic impact on cell growth, but does not by itself induce cell transformation [17]. In contrast, phosphorylation of 4E-BP1 can play a key role in cellular transformation. 4E-BP1 functions to sequester the translation initiation factor eIF4E in an inactive complex; mTORC1-mediated phosphorylation of 4E-BP1 leads to dissociation of this complex, enabling eIF4E to promote cap-dependent translation of mRNA [27]. (Optimal activity of eIF4E also requires a phosphorylation catalyzed by Mnk1, a downstream mediator of the Ras-Erk pathway [28].) Rather minimal concentrations of eIF4E appear to be sufficient for efficient translation of many mRNAs, but the increased availability of eIF4E made possible by mTORC1 activity enables translation of a subset of "weak" mRNAs with long 5′ UTRs that form complex hairpin secondary structures, and that are thus more difficult to translate. Another set of "weak" RNAs are characterized by a specific nucleotide structure in their 3′ UTR, and require eIF4E binding for extranuclear transport, prior to translation [29]. Intriguingly, a number of these "weak" mRNAs code for proteins that promote proliferation (cyclin D1, c-myc, and ODC), angiogenesis (VEGF, FGF-2), or aggressive behavior (HIF-1alpha, MMP-9, and heparanase), or that inhibit apoptosis (survivin, Bcl-2, Bcl-xL, Mcl-2, and dad1) [30]. Indeed, in a high proportion of cancers, these proteins are overexpressed, often owing either to increased expression of eIF-4E, and/or chronic activation of mTORC1; these proteins can contribute importantly to aggressive cancer growth and spread, as well as to chemoresistance.

Chronic activation or overexpression of eIF4E has been found sufficient to induce malignant transformation in fibroblasts and other cell lines; moreover, overexpression of this factor has been described in a wide range of cancers, and such overexpression tends to correlate with aggressive cancer behavior and poor prognosis [30–33]. Evidently, the promotional impact of elevated growth factor exposure is mediated in part by increased eIF4E activity. Conversely, inhibition of eIF4E expression, or overexpression of its functional antagonist 4E-BP1, tends to block cellular transformation in vitro [34,35]. Moreover, inhibition of mTORC1 with rapamycin or its analogs has been shown to suppress cancer induction in vivo in various rodent models [36,37] – whereas constitutively active Rheb is oncogenic [38]. In aggregate, these findings suggest that mTORC1-mediated activation of eIF4E is often a key driver of cellular transformation, and also helps to sustain the aggressive behavior of transformed cells.

The regulatory impact of mTORC1 on autophagy may also influence cancer risk, as rodents with a genetically-impaired capacity for autophagy have been found to be at increased cancer risk [39]. Autophagy plays a key role in antigen presentation, and thus may be important for immune scavenging of nascent cancers. Autophagy also can decrease potentially mutagenic oxidative stress by clearing aging mitochondria that generate excess superoxide.

Down-regulating mTORC1 for cancer prevention

The anti-diabetic drug metformin, as well as the adipokine adiponectin (whose levels tend to be suppressed in individuals with metabolic syndrome and visceral obesity), are activators of AMPK, and thus function to inhibit mTORC1 activity [40,41]. This provides a satisfying explanation for epidemiology pointing to lower cancer risks in diabetics who use metformin or in individuals who enjoy relatively high plasma levels of adiponectin. Rapamycin and its "rapalog" analogs inhibit the kinase activity of mTORC1 by binding to it in a complex with the protein FKBP12 [42]; it is thus not surprising that the relatively high cancer risk in immunosuppressed transplant patients is substantially ameliorated in patients receiving these drugs. Decreased risk for non-Hodgkin lymphoma in regular alcohol drinkers has recently been rationalized by evidence that ethanol selectively suppresses mTORC1 activity in lymphoid tissue [43].

As noted above, relatively low risks for "Western" cancers noted in many rural Third World populations throughout the twentieth century have been attributed to the quasi-vegan traditional diets of these populations, often complemented by regular physical activity. Reduced activity of mTORC1 in cancer-prone epithelia may be a key mediator of this benefit, reflecting, at least in part, a reduction in Akt activation. In the many tissues that are responsive to insulin and/or IGF-I, circulating levels of insulin and of free IGF-I promote Akt activation – and hence mTORC1 activation – via the IRS-PI3K pathway. In individuals who habitually consume a moderate protein quasi-vegan diet, hepatic production of IGF-I tends to be down-regulated, presumably owing to the fact that limited availability of certain essential amino acids exerts an inhibitory impact on hepatocyte IGF-I synthesis [14,15,44,45]. Moreover, such a diet, especially if accompanied by regular physical activity, tends to be associated with leanness and good insulin sensitivity of skeletal muscle and the liver (in large part owing to the low saturated fat content of such diets), leading to a compensatory down-regulation of insulin secretion and an up-regulation of hepatic insulin clearance [46]. Low dietary protein may also tend to decrease postprandial insulin levels, since co-ingested protein can markedly potentiate the insulin secretion evoked by carbohydrate [47]. Furthermore, relatively low circulating insulin levels tend to

decrease IGF-I bioactivity by up-regulating hepatic production of IGFBP-1, a plasma protein which binds to IGF-I and inhibits its interaction with its receptor [48]. Hence, a "Third World lifestyle" tends to be associated with low plasma levels of both insulin and free IGF-I; a straightforward consequence of this should be decreased GTP-charging of Rheb in tissues responsive to these hormones. (Increased plasma levels of adiponectin in lean populations would also be expected to contribute to this effect, via activation of AMPK.) It should be noted that the associated reduction in Akt activity may have cancer-preventive potential independent of mTOR modulation, as Akt exerts a variety of anti-apoptotic effects not dependent on mTOR [49].

The quality and quality of dietary protein also has the potential to influence mTORC1 activity by modulating Rag GTP binding and hence the subcellular localization of mTORC1. In vitro, intracellular amino acid deficiency – most notably, deficiency of leucine – compromises the GTP-charging of Rags [18,20,50]. Whether a vegan diet of modest protein (and leucine) content can down-regulate Rag GTP-binding in vivo during fasting metabolism has not yet been clarified. However, there is recent evidence that a the temporary increase in plasma leucine levels following a protein-rich meal boosts mTORC1 signaling in the skeletal muscle of rats – a finding paralleled by the clinical demonstration that leucine-rich meals can acutely increase muscle protein synthesis following exercise in humans [51]. Moreover, hypothalamic injections of leucine in rats suppress feeding behavior by boosting hypothalamic mTORC1 activity [52]. These findings suggest that, in at least some tissues, a super-abundance of leucine can achieve a further increase in Rag GTP charging and thus mTORC1 activation. It will be of particular interest to determine whether vegan diets of moderate protein and leucine content can chronically or episodically down-regulate Rag GTP charging in cancer-prone epithelia, and thereby reduce cancer risk, independent of their down-regulatory impact on Rheb activity.

Quasi-vegan diets of modest protein content tend to be relatively low in leucine, if only because total protein content is low relative to most omnivore diets. Although plant proteins as a class do not appear to be notably lower in leucine than are flesh foods or eggs, dairy protein is exceptionally rich in this amino acid – possibly reflecting the desirability of an anabolic stimulus in growing infants. Thus, whereas the leucine content of most plant protein falls into the range 400–500 mg per gram nitrogen, the corresponding value in cows' milk protein is around 680 mg/g N [53]. As noted, there is recent evidence that meals of adequate protein content tend to boost the mTORC1 activity of skeletal muscle; the degree of activation tends to be proportionate to the leucine content of the meal. For example, a meal containing whey protein was found to increase muscle mTORC1 activity more notably than a meal containing a comparable amount of wheat protein [54]. Even though the impact of leucine-rich meals on mTORC1 activity is transitory, many of the proteins whose synthesis would be boosted by a temporary increase in this activity would presumably outlive the mTORC1 activation, and thus would have a more durable impact on cellular function.

Milk protein, for reasons that remain to be clarified, is highly insulinogenic (thus accounting for the low glycemic index of milk products); moreover, diets high in dairy protein tend to be associated with elevated plasma IGF-I levels [55,56]. When one further takes into account the exceptionally high leucine content of milk protein – capable of boosting postprandial mTORC1 activity – it is clear that dairy products have notable anabolic activity. While this may be physiologically appropriate for growing infants, the Western tradition of consuming ample amounts of dairy protein throughout adulthood is of questionable wisdom when diseases of overnutrition such as cancer are gaining increased prominence throughout the world [56]. On the other hand, temporary ingestion of dairy protein might be indicated when increased anabolic activity could be clinically beneficial – as during wound healing or serious infections.

Therapeutic implications

As noted, elevated cellular levels of free eIF4E can make cancers more aggressive and more chemoresistant by boosting the translation of mRNAs coding for proteins that promote proliferation, angiogenesis, and survival. Increased sequestration of eIF4E can be induced by measures which, directly or indirectly, suppress mTORC1 activity. In cancers which retain sensitivity to insulin and/or IGF-I, a vegan diet of moderate protein content, complemented by physical training and leanness, may be useful in this regard [14,57]. Direct inhibition of mTORC1 with rapamycin analog drugs, or indirect inhibition via the AMPK activator metformin (which has the ancillary benefit of down-regulating systemic levels of insulin and free IGF-I via its effects on the liver and skeletal muscle [58]) are now receiving considerable attention as strategies for cancer management [59–61]. While these agents can be administered chronically, they can also be administered episodically as adjuvants to concurrent chemotherapy; presumably owing to the multiple anti-apoptotic effects of mTORC1 activity, rapalogs as well as metformin have been shown to potentiate the cytocidal response to chemotherapy drugs in cell culture and rodent studies [61–63], and, in diabetics receiving neoadjuvant chemotherapy for breast cancer, concurrent metformin therapy is associated with a higher rate of pathologic complete response [60].

Each of these strategies, however, has potential drawbacks. mTORC1 activates S6 kinase, which in turn phosphorylates the immediate target of insulin/IGF-I receptors, IRS1. This phosphorylation promotes the proteolytic degradation of IRS1, and thus achieves a feedback down-regulation of insulin/IGF-I signaling. Inhibition of mTORC1 breaks this feedback loop, increasing the capacity of these hormones to activate Akt [64]. Such an effect may be clinically beneficial when the intent is to promote tissue insulin sensitivity (it has been suggested that epidemiological associations of high-protein diets with increased diabetes risk may reflect increased S6 kinase-mediated phosphorylation of IRS1 [65]), but in some cancers the associated increase in Akt activity can be counterproductive. As noted, Akt exerts a number of anti-apoptotic effects, independent of its impact on mTORC1, that could promote chemoresistance; these include inhibitory phosphorylations of BAD and caspase-9, suppression of the activity of forkhead transcription factors (which induce expression of various pro-apoptotic proteins), and activation of NF-kappaB and CREB (the latter boosting transcription of bcl-2 and mcl-1) [49]. These considerations need to be taken into account when rapalogs or metformin are employed as chemosensitizers.

However, recent studies show that metformin has the potential to inhibit activation of Akt, since AMPK can catalyze a phosphorylation of IRS-1 (on Ser789) that reduces the efficiency of IGF-I signaling; metformin has been reported to lessen Akt activation in vascular smooth muscle cells and a breast cancer cell line, and, in vivo, to impede IGF-I signaling in the muscle of rats [66,67]. Moreover, metformin tends to down-regulate plasma levels of free IGF-I modestly [58]. As might be expected, a very large number of studies have linked IGF-I signaling to decreased chemo- or radiosensitivity in cancer cells [68–72]. And there is now evidence that metformin may specifically alleviate the chemoresistance of cancer stem cells, for reasons that remain to be clarified [61].

On the negative side, the impact of metformin on angiogenesis may be equivocal. While AMPK-mediated inhibition of mTORC1 would be expected to decrease the efficiency with which the mRNA for VEGF is translated, AMPK also acts to enhance the stability of

VEGF mRNA [73]. In some cancers, the balance of these effects favors VEGF synthesis. Thus, metformin administration has been shown to amplify the growth and spread of a human mammary cancer in nude mice by increasing the cancer's production of VEGF – despite the fact that this drug inhibits the proliferation of this cell line in vitro [74]. (From a homeostatic standpoint, it is hardly surprising that a kinase which signals cellular energy deficit would work in certain ways to promote angiogenesis and thus enhanced substrate delivery.)

The up-regulatory impact of mTORC1 inhibition on autophagy can influence response of cancer to cytotoxic therapies; however, the nature of this influence appears to vary as a function of the agent used and the genetics of the cancer. Potentially, induction of autophagy can help cancer cells to survive a pro-apoptotic assault; however, autophagy can sometimes mediate cytotoxin-induced cell death when cancer cells express defective apoptotic machinery [75,76]. On balance, present evidence seems to incriminate chemotherapy-induced autophagy as a common cause of chemoresistance [77,78]. Hence, when metformin or rapalogs are used in conjunction with chemotherapy, concurrent suppression of autophagy, as with the antimalarial drug hydroxychloroquine, might be expected to improve therapeutic response.

Direct targeting of eIF4E

Theoretically, measures which target eIF4E directly should have the greatest potential in cancer therapy, since they will leave intact the down-regulatory impact of S6 kinase on IRS-1. Moreover, the expression of this protein is amplified in many cancers; suppressing the phosphorylation of its sequestrant 4E-BP1 via mTORC1 inhibition may not always be sufficient to minimize free eIF4E levels unless 4E-BP1 levels are commensurately high. In some cancers, the overexpression of eIF4E may reflect a positive feedback loop whereby c-myc, by interacting with an E-box in the eIF4E promoter, boosts transcription of the eIF4E gene; the resulting increase in translational initiation would be expected to increase the synthesis of c-myc, completing the loop [79]. (Loss of p53 may up-regulate this loop, since p53 intervenes in it by binding c-myc [80].) Increased levels of eIF4E can also reflect gene amplification; other factors being equal, such amplification would be apt to promote proliferation and survival, and thus be selected for. Another reason why direct targeting of eIF4E activity may be more consistently effective than mTORC1 inhibition is that Pim-2 kinase (and possibly other kinases) can promote inhibitory phosphorylation of 4E-BP1, independent of mTORC1 activity; indeed, initiation of protein translation is insensitive to rapamycin in acute myelogenous leukemia, reflecting increased activity of Pim-2 [81]. And underexpression of 4E-BP1 may also limit the therapeutic efficacy of mTORC1 inhibition; PI3K activity has the potential to decrease transcription of the 4E-BP1 gene, possibly owing to Akt-mediated inhibition of the FOXO1 transcription factor [82].

Measures for directly targeting eIF4E are now being evaluated. Antisense agents capable of blocking eIF4E synthesis have shown striking dose-dependent tumor retardant effects in xenograft models, in doses that do not cause notable weight loss or other signs of overt toxicity; synthesis of "housekeeping proteins" in healthy tissues appears to be relatively well preserved even when eIF4E levels are notably diminished [83]. One of these antisense agents is currently in phase I clinical trials. Whether it will induce the range of side effects seen in clinical trials with rapamycin analogs [84] remains to be seen. Another research group has developed a DNA vector, containing a survivin promoter, that may enable tumor-selective expression of interfering RNAs that inhibit translation of eIF4E; breast cancer cells transfected with this vector grow more slowly in nude mice, and are more sensitive to the cytotoxicity of cisplatin [85].

There are also reports that, in clinically feasible low micromolar concentrations, the antiviral drug ribavirin can bind to eIF4E by mimicking the structure of the 7-methyl guanosine cap structure of mRNA, thereby competitively inhibiting eIF4E's ability to interact with mRNA [33]. In cell culture studies, micromolar levels of ribavirin have indeed been found to inhibit extranuclear transport and/or translation of "weak" mRNAs, to inhibit eIF4E-mediated transformation of fibroblasts, and to suppress proliferation of acute myelogenous leukemia cells, known to be eIF4E-dependent [33]. Moreover, well tolerated oral doses of ribavirin markedly inhibited the growth of a human head and neck squamous cell carcinoma implanted in nude mice [33]. These encouraging finding prompted a phases I/II clinical trial with ribavirin in acute myeloid leukemia, a type of cancer frequently characterized by eIF4E overexpression; 9 of 11 patients achieved objective response or stable disease [86]. A clinical trial of ribavirin in head and neck cancer is also being planned [87]. The ability of ribavirin to bind eIF4E as a mimic of mRNA cap structure has been called into question by two research groups [88,89], however, they used cell-free assays which might not adequately replicate the intracellular environment [90]. Clearly, eIF4E antagonists may have potential for chronic use in the management of the high proportion of cancers in which mTORC1/eIF4E activity is elevated; they might also be administered episodically to alleviate chemoresistance in such cancers.

Targeting the transcription of oncogenic "weak" mRNAs

Curiously, a number of the "weak" mRNAs coding for proteins that promote malignant behavior or chemoresistance are regulated at the transcriptional level by NF-kappaB – including those that code for Bcl-2, Bcl-xL, survivin, cyclin D1, c-myc, HIF-1alpha, MMP-9, and VEGF [91,92]. In a high proportion of aggressive cancers, NF-kappaB activity is constitutively active or up-regulated [91,93]; fortunately, agents such as salsalate or silibinin, in clinically feasible doses, have the potential to suppress NF-kappaB activity [92,94]. These considerations suggest that treatment regimens which target eIF4E and NF-kappaB simultaneously may be able to decrease synthesis of a number of key oncogenic proteins at both the transcriptional and translational levels, potentially down-regulating them quite markedly.

Similarly, the Stat3 transcription factor, whose activity is up-regulated in a high proportion of cancers, in which it promotes malignant behavior and chemoresistance, likewise boosts transcription of a number of "weak" mRNAs which code for oncogenic proteins, including Bcl-2, Bcl-xL, survivin, cyclin D1, c-myc, HIF-1alpha, and VEGF [95]; the parallel to the activity of NF-kappaB in this regard is indeed striking [96]. Although small molecule inhibitors of Stat3 activation are currently being developed as potential drugs [97], a number of phytochemicals have been shown to inhibit Stat3 activation in cancer cell cultures [95]. Cucurbitacin has received considerable attention in this regard, but is not clinically available [98]. Aggarwal et al. have shown that a range of phytochemicals can inhibit Stat3 activity by inducing increased expression of the tyrosine phosphatase SHP-1 [99–101]. Perhaps the most interesting of these is the Z-isomer of guggulsterone, a key component of the Ayurvedic remedy sallai guggul – a.k.a. guggulipid; this is commercially available, and has been shown to slow proliferation and induce apoptosis in various cancer cell lines [102,103]. Moreover, guggulipid, which is considered nontoxic, has inhibited the growth of human prostate, colorectal, and head and neck squamous cell cancer xenografts in nude mice [103,104]. And, for unknown reasons, guggulsterone also can sup-

press NF-kappaB activity in some cancer cells [105]. Another natural agent with potential for targeting both NF-kappaB and Stat3 is silibinin [106,107], which likewise can inhibit growth of a number of types of human cancer in nude mice [108,109].

These considerations thus suggest that a regimen in which ribavarin is complemented with sufficient oral doses of salsalate, guggulipid, and/or silibinin – preferably used in conjunction with lifestyle measures which down-regulate systemic insulin and IGF-I activity – has the potential to down-regulate the expression of a number of key oncoproteins at both the transcriptional and translational levels in a high proportion of cancers, thereby slowing tumor growth and spread while boosting chemosensitivity. Conceivably, such a strategy could be even more effective if coupled with feasible epigenetic measures designed to boost the expression of tumor suppressor genes silenced by promoter methylation [110].

Conflict of interest

The author has no conflicts of interest.

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