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Hypothesis: Spirulina may Slow the Growth and Spread of Ovarian Cancer by Interfering with Growth Factor Activity of Lysophophatidic Acid

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Abstract

Lysophosphatidic acid (LPA) has emerged as a key autocrine growth factor for most ovarian cancers, promoting their proliferation, survival, invasiveness, dissemination within the peritoneal cavity, and angiogenic capacity. Effective LPA signaling requires activation of endosomal NADPH oxidase activity. Free bilirubin is now known to function intracellularly as a potent inhibitor of NADPH oxidase complexes. The cyanobacterial chromophore phycocyanobilin (PhyCB), via intracellular conversion to the bilirubin homolog phycocyanorubin, can likewise inhibit NADPH oxidase activity, and is orally active in this regard. The cell wall polysaccharides of cyanobacteria may also aid cancer control by activating innate immunity and inhibiting angiogenesis. Hence, consumption of edible cyanobacteria such as spirulina may have potential for slowing the growth and spread of ovarian cancer – as it has recently been shown to do with a human pancreatic adenocarcinoma.

Keywords: Lysophosphatidic acid; Ovarian cancer; NADPH oxidase; Spirulina; Phycocaynobilin

Lysophosphatidic Acid – a Key Autocrine Growth Factor for Ovarian Cancer

Lysophosphatic acid (LPA) is produced by most ovarian cancer cells lines, and acts as an autocrine growth factor via its receptors LPA2 and LPA3 [1-5]. Stimulation of these receptors, linked to several heterotrimeric G proteins, promotes the phosphorylation of Akt1, ERK, EGFR, and STAT3, cox-2 expression, and the transcriptional activity of NF-kappaB and HIF-1alpha [6-11]. These effects stimulate proliferation, inhibit apoptosis, enable release of ovarian cancer cells into the peritoneal fluid by suppressing E-cadherin expression, promote invasion by inducing matrix proteases, and enhance angiogenesis by increasing the production of VEGF [5,12-19]. Studies with human ovarian cancers xenografted in nude mice demonstrate that interference with LPA signaling (via silent RNA knockdown of LPA receptors, or via transfection with an enzyme that cleaves LPA) markedly slows the spread of these cancers [13,20] – implying that LPA is an important growth factor for ovarian cancer in vivo. Levels of LPA in plasma and in peritoneal fluid are markedly higher in ovarian cancer patients than in healthy controls [21-23]. Intraperitoneal levels are highest – in part because peritoneal mesothelium also can make LPA [24] – and likely promote the formation of malignant ascites.

NADPH Oxidase Mediates LPA Signaling

Recent research indicates that stimulation of NADPH oxidase activity within endosomes plays a critical role in transmitting the signals triggered by LPA receptors [25,26]. Thus, the NADPH oxidase inhibitor DPI blocks the ability of LPA to promote phosphorylation of Akt and ERK, to activate NF-kappaB, and to stimulate proliferation [25]. Interaction of LPA with its receptors induces the internalization of these receptors into endosomes, and the activated receptors stimulate local NADPH oxidase activity that generates hydrogen peroxide within these endosomes; this leads to cysteine sulfenic acid formation in neighboring proteins that may be required for optimal LPA receptor activity [26]. N-acetylcysteine mimics the inhibitory effects of DPI [25], presumably by reversing the oxidation of protein cysteine groups [26-28]. The NADPH oxidase inhibitor apocynin, as well as a cell permeable form of catalase, likewise inhibited LPA-mediated Akt phosphorylation [25]. Other studies with ovarian cancer cells lines have found that DPI promotes apoptosis, and decreases expression of HIF-1alpha and of VEGF [29,30]. Knockdown of the NADPH oxidase component Nox4 – the expression of which is increased in many of these cell lines – exerts similar effects [29].

Phycocyanobilin May Aid Ovarian Cancer Control by Suppressing NADPH Oxidase Activity

These considerations suggest that agents which can safely inhibit NADPH oxidase activity may have important potential for slowing the growth and spread of many ovarian cancers. Free intracellular bilirubin, generated via heme oxygenase activity, functions physiologically as an inhibitor of NAPDH oxidase complexes [31-34]. Although bilirubin is too insoluble to be useful as an orally administrable drug, its chemical relative phycocyanobilin (PhyCB), a prominent light-harvesting chromophore in edible cyanobacteria such as spirulina, shares the ability of bilirubin to inhibit NADPH oxidase activity [35,36]. This likely reflects the fact that PhyCB, a metabolite of biliverdin, can be converted intracellularly by biliverdin reductase to the bilirubin homolog phycocynorubin [35,37]. Moreover, spirulina and PhyCB-enriched spirulina extracts exert marked anti-inflammatory/antioxidant effects in rodent studies, suggesting that PhyCB can inhibit NADPH oxidase after oral administration [38]. Hence, oral consumption of adequate amounts of spirulina, or of PhyCB-enriched spirulina extracts, may have clinical potential for treatment of ovarian cancers. In this regard, dietary spirulina has been reported to slow the growth of a human pancreatic cancer in nude

mice by about 60% [39]; notably, NADPH oxidase activity has been found to be elevated and to exert pro-growth, pro-survival effects in pancreatic cancer cells lines [40-44].

The cell wall polysaccharides of spirulina also may have potential for aiding cancer control, as they can interact with toll receptors to boost innate immunity, while also impeding angiogenesis [45,46].

As a proviso, it should be noted that spirulina probably should not be administered in conjunction with taxane chemotherapy, as the killing mechanism of these drugs appears to be contingent on NADPH oxidase activation [47-50]. On the other hand, in light of evidence that LPA signaling renders ovarian cancer cells relatively resistant to apoptosis induction by platinum drugs and doxorubicin, it is conceivable that NADPH oxidase inhibition could boost responsiveness to these drugs; however, there appears to be no direct evidence for this [51-54]. In rodents, dietary spirulina has been reported to provide protection from the cardiotoxicity of doxorubicin and the nephrotoxicity of cisplatin [55,56].

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