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Anti-cancer Activities of ω-6 Polyunsaturated Fatty Acids

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Abstract

The ω-3 and ω-6 polyunsaturated fatty acids (PUFAs) are two major families of PUFAs present as essential cellular components which possess diverse bioactivities. The ω-3s, mainly found in seafood, are associated with many beneficial effects on human health, while the ω-6s are more abundant in our daily diet and could be implicated in many pathological processes including cancer development. Increasing evidence suggests that the adverse effects of ω-6s may be largely attributed to arachidonic acid (AA, a downstream ω-6) and the metabolite prostaglandin E2 (PGE2) that stems from its cyclooxygenase (COX)-catalyzed lipid peroxidation. On the other hand, two of AA's upstream ω-6s, γ-linolenic acid (GLA) and dihomo-γ-linolenic acid (DGLA), are shown to possess certain anti-cancer activities, including inducing cell apoptosis and inhibiting cell proliferation. In this paper, we review the documented anti-cancer activities of ω-6 PUFAs, including the recent findings regarding the anti-cancer effects of free radical-mediated DGLA peroxidation. The possible mechanisms and applications of DGLA (and other ω-6s) in inducing anti-cancer activity are also discussed. Considering the wide availability of ω-6s in our daily diet, the study of the potential beneficial effect of ω-6 PUFAs may guide us to develop an ω-6–based diet care strategy for cancer prevention and treatment.

Keywords

anti-cancer activity; apoptosis; cyclooxygenase-catalyzed lipid peroxidation; dihomo-γ-linolenic acid; free radicals; ω-6 polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are long-chain fatty acids with more than one C–C double bond in their backbones. According to the position of the first double bond in the structure, PUFAs can be classified into two major categories, namely ω-3 and ω-6, which are present as essential cellular components and possess diverse biofunctions. There is a great deal of variation in the sources and bioactivities between these two different classes of PUFAs. For example, the ω-3s, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are mainly found in seafood and have been shown to be associated with several beneficial effects in human health, including cancer suppression, cardiovascular disease prevention, and cognitive ability improvement.[1–10] On the other hand, the ω-6s, especially arachidonic acid (AA, a downstream ω-6), are much more abundant in our daily diet and are

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generally associated with many adverse effects on the human body, including cancer promotion. For instance, the high intake of ω-6s was found to correlate with a high risk of breast, prostate, and colon cancer incidence in many animal and human studies, and the ratio of ω-6s to ω-3s was suggested to be a predictor for cancer progression.[11–22] The pro-cancer effects may be mainly due to AA, the downstream and pro-cancer ω-6.[17–23] Given these differences, the bioactivities from ω-3s have been extensively studied for health improvement purposes, whereas the potential beneficial effects from ω-6s have received much less research attention.

Increasing evidence suggests that unlike the downstream ω AA, which has been associated with cancer development, the upstream ω-6s, such as linoleic acid (LA), γ-linolenic acid (GLA), and dihomo-γ-linolenic acid (DGLA), may possess anti-cancer effects, and thus could be a promising dietary source for cancer prevention and therapy.[24–39] However, the upstream ω-6s can be effectively converted into AA by a series of fatty acid metabolism enzymes. Upon uptake, LA (the precursor of ω-6s) will be converted into GLA in the presence of Δ-6 desaturase (D6D), followed by a two-carbon chain elongation by elongase to become DGLA, and finally be de-saturated by Δ-5 desaturase (D5D) to form AA [Figure 1]. Such a conversion could greatly restrict the availability and anti-cancer effects of upstream ω-6s. Thus, it seems critical to control ω-6 metabolism to favor upstream ω-6 synthesis while limiting AA production in order to elicit the anti-cancer activities from upstream ω-6s such as DGLA.

Through catalysis by cyclooxygenase (COX), a major lipid peroxidizing enzyme, ω-6s can undergo a free radical–mediated lipid peroxidation and produce various PUFA-derived metabolites. For instance, DGLA and AA, both major substrates for COX, can produce 1-series prostaglandins (PGs-1) and 2-series prostaglandins (PGs-2), respectively, during COX-catalyzed lipid peroxidation. Recent studies found that DGLA and AA could go through different free radical pathways during lipid peroxidation and produce distinct free radical metabolites.[40–42] It was recently proposed and demonstrated that the adverse effects from ω-6s may be mainly attributed to AA and its metabolite prostaglandin E2 (PGE2), while DGLA may exert an anti-cancer effect via the production of prostaglandin E1 (PGE1) and the exclusive free radical metabolites from its COX-catalyzed lipid peroxidation.[17–23,38,39,43–45]

In this paper, we will review the documented anti-cancer activities of ω-6 PUFAs, including the recent findings of the anti-cancer effect from COX-catalyzed DGLA peroxidation. The possible mechanisms and applications of anti-cancer effects induced by the ω-6s (especially DGLA) will also be briefly discussed.

Implications of *ω*-6s in cancer

LA and conjugated linoleic acid

Although all the ω-6s can be directly consumed from the daily diet, LA, the precursor of ω-6s, is more abundant in plant seeds and oils, and thus is considered to be the main dietary source of all ω-6s [Figure 1]. Research evidence shows that LA can be involved in both pro- and anti-cancer activities. For example, LA stimulates cell proliferation in the human breast

cancer cell line BT-474 and the human lung cancer cell line A549 *in vitro*, and promotes colon and prostate tumorigenesis and tumor growth in animal models.[15,46–49] On the other hand, a high dose of LA inhibits proliferation of the colon cancer cell line Caco-2,[24] while a high intake of LA also shows a protective effect against cancer development.[50] LA is endogenously converted into various downstream ω-6 PUFAs and the corresponding metabolites by the enzymes D6D, elongase, and D5D. Thus, the observed effects of LA on cancer growth could actually be derived from a mixture of effects of its downstream products. In fact, various studies show that the lipid peroxidizing enzyme COX and the lipid peroxidation metabolite PGE2 are indeed involved in LA-induced cancer development.[46,51–56] The role of pure LA in cancer growth still remains to be investigated in the context of controlling PUFA metabolism.

Conjugated linoleic acids (CLAs) are a series of isomers of LA (mainly cis-9, trans-11 and trans-10, cis-12) with conjugated double bonds in their structures. Although chemically not belonging to the ω-6 family, CLAs can originate from the endogenous biohydrogenation of LA by gastrointestinal tract bacteria [Figure 1].[57–59] CLAs have been extensively studied and shown to possess anti-cancer effects in a number of cancer types both *in vitro* and *in vivo*. For instance, *in vitro* studies showed that CLA isomers could inhibit cell growth in diverse cancer cell lines including the breast cancer cell line MCF-7,[60–62] the colon cancer cell lines HT-29, DLD-1, and Caco-2,[63,64] the prostate cancer cell lines PC-3 and DU-145,[62,64–66] and the gastric cancer cell line SGC-7901.[67] Consistently, animal studies also show that a CLA-enriched diet reduces mammary epithelial mass, suppresses terminal end bud cell proliferation, and decreases premalignant lesions and tumor incidence in a methylnitrosourea-induced mammary tumor rat model.[68–71] A CLA supplement was also shown to reduce the tumor incidence and diameters in mice bearing forestomach tumors.[72] Although the anti-cancer effects varied among different CLA isomers and different cancer types, most of the existing evidence consistently indicates that CLAs could inhibit cancer development both *in vitro* and *in vivo*.

γ-Linolenic acid

LA can be desaturated and converted into GLA which is catalyzed by D6D enzyme [Figure 1]. Evidence shows that GLA is also associated with anti-cancer activities both *in vitro* and *in vivo*. For example, GLA inhibited cell growth of the human neuroblastoma cell lines GOTO, SK-N-DZ, NKP, and NCG, a rat C6 glioma cell line, and the rat carcinosarcoma cell line LLC-WRC256 *in vitro*.[25–27] A dietary supplement of GLA also reduced tumor growth in an implanted WRC256 rat model.[28] More interestingly, GLA-induced cytotoxicity was shown to exhibit high selectivity toward cancer cells with no significant effect on normal cell growth. For instance, a series of studies suggested that 3–7 days of incubation with GLA could selectively induce cell death in various human cancer cell lines, including the human breast cancer cell ZR-75–1, the lung cancer cell A549, and the prostatic cancer cell PC-3, without affecting normal cell growth.[29–36] GLA was shown to be cytotoxic to the malignant rat astrocytoma cell line 36B10 without affecting normal astrocytes. GLA also enhanced the radiation sensitivity of astrocytoma cells, but not normal astrocytes.[37] In the *in vivo* C6 glioma rat model, the infusion of GLA was shown to increase the frequency of cell apoptosis and regression in tumors, without influencing normal neural tissue and

vasculature.[26] Therefore, GLA seems to be a promising cancer therapeutic agent with desirable characteristics, although the reason for the high selectivity in GLA-induced anti-tumor effect still remains to be investigated.

DGLA versus AA

Given the anti-cancer effects of GLA, it is anticipated that DGLA, the direct downstream ω-6 of GLA, may also possess similar anti-tumor effects [Figure 1]. In fact, it was observed that both GLA and DGLA inhibited cell proliferation in human cervical carcinoma cells (KB-3–1) in a dose-dependent manner. The potency of the cytotoxic effect of DGLA was shown to be equal to that of GLA.[38] In rats with 7,12-dimethylbenz(α) anthracene-induced mammary tumors, the ratio of tumor-bearing rats to total number of rats was lowest after 12 weeks of DGLA administration (by oral intubation, 0.15 g, twice a week) compared to groups treated with GLA and corn oil (which contains mainly LA).[39] However, some research groups also reported that DGLA may not influence or even promote cancer development. For instance, low doses of DGLA were shown to stimulate human breast carcinoma cell growth.[73] In a rat mammary tumor model, the tumor multiplicity in the DGLA treatment group was higher than the GLA and corn oil treatment groups.[39] The potential pro-cancer activity of DGLA observed in some studies may be due to the readily conversion of DGLA to AA (a downstream and pro-cancer ω-6) in cells, catalyzed by D5D. Such conversion could greatly restrict DGLA's availability and its associated anti-cancer activity. So far, much less research attention has been paid to the implications of DGLA and D5D in cancer prevention and treatment.

Unlike upstream ω-6s, the downstream ω-6 AA, produced directly from DGLA by D5D, is commonly associated with many adverse effects to human health [Figure 1]. Most results have built a substantial correlation between COX-catalyzed AA peroxidation (as well as AA metabolites, e.g. PGE2) and cancer development, including prostate, colon, and breast cancers.[17–23] For a long time, controlling COX-catalyzed AA metabolism by COX inhibition has received much research attention and become a conventional strategy for cancer therapy. There is only a little evidence to show that AA could inhibit cell proliferation in the human colon cancer cell line Caco-2 and in the human cervical carcinoma cell line KB-3-1.[24,38]

Given the contrasting activities in cancer development and the rapid conversion from DGLA to AA, it seems that the ratio of DGLA to AA is crucial in dictating their effects on cancer growth, and it is possible that preventing the conversion from DGLA to AA may represent an effective strategy for eliciting the anti-cancer activity of DGLA *in vivo.* Unfortunately, there have been very limited studies focusing on this topic. Recent research from Qian's group found that DGLA's free radical derivatives from lipid peroxidation could inhibit human colon cancer cell growth,[43] while direct treatment with DGLA had no effect on cell proliferation, probably due to effective D5D-catalyzed conversion of DGLA to AA. However, when this conversion was limited by D5D knockdown via siRNA transfection, DGLA treatment led to a significant inhibition in cell growth (unpublished research result from Qian's group).

Mechanisms of the anti-cancer effects of ω-6 PUFAs

Inducing cell apoptosis and altering cellular fatty acid composition by ω-6s

The ω-6s have been shown to exert their anti-cancer proliferation effects by influencing gene and protein expression, thereby disrupting cell cycle progression and inducing apoptosis. For example, in rat carcinosarcoma cells (LLC-WRC256), GLA triggered cytochrome *c* release associated with changes in mitochondrial metabolism and increased caspase 3 activity, thereby finally leading to cell apoptosis.[27] In an implanted WRC256 rat model, GLA altered mitochondrial metabolism and structure by influencing mitochondrial membrane composition and decreasing hexokinase and carnitine palmitoyltransferase I activities, thus eventually leading to apoptosis.[28] Exogenous GLA treatment was also reported to induce apoptosis in human and rat glioma cell lines *in vitro*, while in the *in vivo* C6 glioma rat model, infusion of GLA increased the frequency of cell apoptosis, cell death, and regression in tumors.[26]

Treatment with CLAs, the derivatives of LA, caused G1 arrest in the DU-145 and HT-29 cell lines by up-regulating the protein expression of the cell cycle inhibitor p21 and decreasing the expression of cyclins A and D.[65,74] CLAs were also shown to promote cell apoptosis in various cancer cell lines, including Caco-2, HT-29, PC-3, SGC-7901, and dRLH-84, probably by increasing the expression and activity of pro-apoptotic proteins (e.g. caspase 3, caspase 9, and Fas), while decreasing the expression of pro-growth and anti-apoptotic proteins (e.g. ErbB3, phosphorylated Akt, bcl-2, c-myc, and Ki-67).[63–67,75–77]

Supplementation with ω-6s could also alter the lipid composition in cell membranes and lead to cell membrane dysfunction. For example, GLA was found to increase the triacylglycerol content in a WRC256 rat tumor model and alter the quantity of ω-6s in a triacylglycerol fraction.[28] In human neuroblastoma cell lines, GLA-induced cytotoxic effects were found to be associated with a significant increase in triglycerides and polyenoic acids in cell membrane phospholipids and decrease in monoenoic acids, suggesting that the anti-tumor effect of GLA may be attributed to fatty acid modification-induced cellular dysfunction.[25,78]

Involvement of PGs from COX-catalyzed lipid peroxidation

Through a free radical–mediated lipid peroxidation, COX can catalyze ω-6s to produce two types of PGs, the 1-series and 2-series PGs, which have been shown to possess diverse activities and are proposed to be responsible for the bioactivities of ω-6s. In fact, a number of studies suggest that ω-6s could regulate cancer cell growth depending on the COX level. For example, LA and AA are shown to dose-dependently decrease cell proliferation in cancer cell lines with high COX expression (e.g. Caco cells), but not in those with low COX expression (e.g. HT-29).[24] Other evidence, moreover, shows that the ω-6–induced cytotoxicity in cancer cells can be partially inhibited by a COX inhibitor, suggesting that COX-catalyzed lipid peroxidation and its corresponding metabolites may contribute to the anti-cancer bioactivity of ω-6s.[79]

Two major PGs, PGE1 and PGE2, derived from DGLA and AA, respectively, have been the most extensively studied due to their diverse implications in physio-pathological conditions.

Interestingly, PGE2 is shown to promote inflammation and cancer development, while PGE1 is now accepted to exert beneficial effects on human health, including anti-cancer activity. For example, PGE1 was found to inhibit the growth of Hela cells *in vitro*.[44,79] In highly metastatic murine B16-F10 melanoma cells, 48 h and 72 h treatment with PGE1 inhibited cell growth and invasion, stimulated cell differentiation, and decreased matrix metalloproteinase (MMP)-2 and MMP-9 levels.[45] Infusion of PGE1 into the tail vein of peritoneal tumor–bearing rats was shown to increase the anti-cancer effect of cisplatin by increasing the platinum concentration in tumor masses while reducing the renal cytotoxicity.[80]

There is also other evidence that COX inhibitors do not influence the GLA-induced anti-proliferation effect in some cancer cell lines, while CLAs may exert an anti-cancer effect by inhibiting COX activity.[59,79] This is probably because the inhibition of COX could limit the production of PGE2, a pro-cancer factor derived from AA peroxidation. Thus, the opposing bioactivities from PGE1 versus PGE2 imply that COX-catalyzed lipid peroxidation in cancer diseases is indeed complicated, and the ratio of anti-cancer metabolites (PGE1) to pro-cancer metabolites (PGE2) is rather critical.

Implications of ω-6 free radicals from COX-catalyzed peroxidation in cancer

In addition to the PGs, a series of PUFA-derived free radical intermediates produced from COX-catalyzed lipid peroxidation may also be associated with the anti-cancer activity of ω-6s. In fact, evidence shows that the ω-6-induced inhibition of cell proliferation in Hela cells is a free radical–dependent process and can be blocked by the antioxidant vitamin E.[44] The dose-dependent inhibition of cell proliferation induced by GLA in rat carcinosarcoma LLC-WRC256 cells was correlated with an increase in lipid peroxide and reactive oxygen species.[27,28] In 36B10 cells, GLA treatment resulted in an increase in the cellular level of 8-isoprostane (which is an indicator of oxidative stress), whereas the antioxidant trolox blocked the GLA-induced inhibition of growth and enhanced the sensitivity to radiation.[37] In human neuroblastoma cell lines, treatment with antioxidants (e.g. coenzyme Q, alpha-tocopherol, and butylated hydroxytoluene) partially reduced the GLA-induced inhibitory effect on cell growth.[25] All these evidences indicate that the reactive PUFA-derived free radicals from COX-catalyzed lipid peroxidation are somehow responsible for the ω-6s' anti-cancer activities. However, the individual PUFA-derived free radical species was not identified and studied for a long time due to the lack of an appropriate method.

With the use of a novel liquid chromatography/mass spectrometry/electron spin resonance (LC/MS/ESR) combined system along with spin-trapping technique, a recent series of studies by Qian's group has successfully detected, identified, and characterized major free radical intermediates produced from COX-catalyzed DGLA versus AA peroxidation.[40–43,81,82] The contribution to the study on lipid peroxidation enables us for the first time to investigate the effect of individual ω-6 free radical metabolites and pathways in cancer development. These studies showed that in addition to a C-15 oxygenation shared by both DGLA and AA, there is a unique C-8 oxygenation pathway present during COX-catalyzed DGLA peroxidation, which can give rise to exclusive DGLA free radicals.[40–42]

These studies also demonstrated that the exclusive DGLA free radical derivatives could induce significant inhibition of cell growth and significant cell cycle arrest and apoptosis in the human colon cancer cell line HCA-7 colony 29.[43] Interestingly, in a comparison experiment, PGE1 and PGE2 did not affect cell proliferation at the same concentration, suggesting that the free radicals, rather than PGs, may be more responsible for DGLA's anti-cancer activity under physiological conditions.

A further mechanistic study from the Qian group suggests that the anti-cancer effect of the exclusive DGLA free radical derivatives may be due to the regulation of molecular targets involved in the cell cycle progression and the cell apoptotic pathway, such as p27, pro-caspase 9, and p53.[43] This work provided the first evidence suggesting that the distinct free radical pathway and metabolites from COX-catalyzed DGLA peroxidation are more likely than the PGs to account for the ω-6s' anti-cancer activities under physiological conditions.

Potential applications of ω-6s in combination with other therapeutic drugs

Co-treatment with ω-6s and/or their metabolites was shown to enhance the efficacy of other chemo-drugs. For example, concurrent supplementation with GLA and paclitaxel or docetaxel inhibited cell growth in the human breast cancer cell lines MDA-MB-231, T47D, SK-Br3, and MCF-7, additively and/or synergistically.[83] The combination of DGLA and vincristine was shown to significantly enhance cell death in vincristine-resistant cells (KB-Ch^{R}-8–5) compared to DGLA or vincristine treatment alone.[38] Infusion of PGE1 into the tail vein of peritoneal tumor-bearing rats was shown to increase the anti-cancer effect of cisplatin while reducing the renal cytotoxicity.[80] Although they still remain unclear, the mechanisms by which ω-6s enhance the anti-cancer effects of chemo-drugs may include regulating the genes and proteins involved in apoptosis, modifying membrane composition, and altering drug uptake and efflux.[38,43,80,83]

A recent study from Qian's group found that the exclusive DGLA free radical derivatives enhanced the cytotoxicity of 5-fluorouracil (5-FU) toward the human colon cancer cell line HCA-7 colony 29, probably by further promoting apoptosis triggered by pro-caspase 9 activation.[43] More interestingly, direct treatment with DGLA was found to further decrease the IC50 of 5-FU in HCA-7 cells in which D5D was knocked down via siRNA transfection (unpublished data from Qian's group). These promising results suggest that regulating D5D to favor DGLA synthesis represents a potential novel strategy for cancer therapy in combination with other chemo-drugs. This strategy takes advantage of the high COX levels in colon cancer cells during cancer treatment. Thus, it might change the paradigm and outlook on COX inhibition and peroxidation in cancer biology.

Conclusions

The ω-6 PUFAs, widely available in the daily diet, are essential cellular components that play important roles in diverse physio-pathological processes. Although some studies have suggested that a high intake of ω-6s could be deleterious and promote cancer development, increasing evidence indicates that the upstream ω-6s are actually associated with anti-cancer growth effects. It is noteworthy that recent studies from Qian's group show that the DGLA

free radical metabolites from COX-catalyzed lipid peroxidation can induce cell growth inhibition, cell cycle arrest, and apoptosis in the human colon cancer cell line HCA-7 colony 29. These results provide a novel insight into the implications of COX-catalyzed lipid peroxidation in cancer prevention and treatment. It was also demonstrated in their studies that the regulation of PUFA metabolism enzymes (e.g. D5D) is an effective way to prevent beneficial upstream ω-6s (e.g. DGLA) from converting into AA, thus helping to elicit DGLA's anti-cancer effect. In addition, ω-6 PUFAs and their metabolites (e.g. PGs and free radicals) were also shown to enhance the efficacy of various commonly used chemo-drugs in cancer cells, while preventing their cytotoxicity toward normal cells.

Given their wide availability and diverse anti-tumor effects, the ω-6 PUFAs, especially DGLA (the most under-investigated ω-6), should be able to become a promising and more common dietary source for cancer prevention and treatment. Regulating the ω-6 metabolic enzymes and taking advantage of the high COX levels in cancer cells to allow DGLA and the related beneficial free radical metabolites to accumulate may represent a potentially novel ω-6–based diet care strategy for cancer therapy and may challenge the current paradigm of COX inhibition in cancer treatment.

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Biography

Dr. Steven Y. Qian

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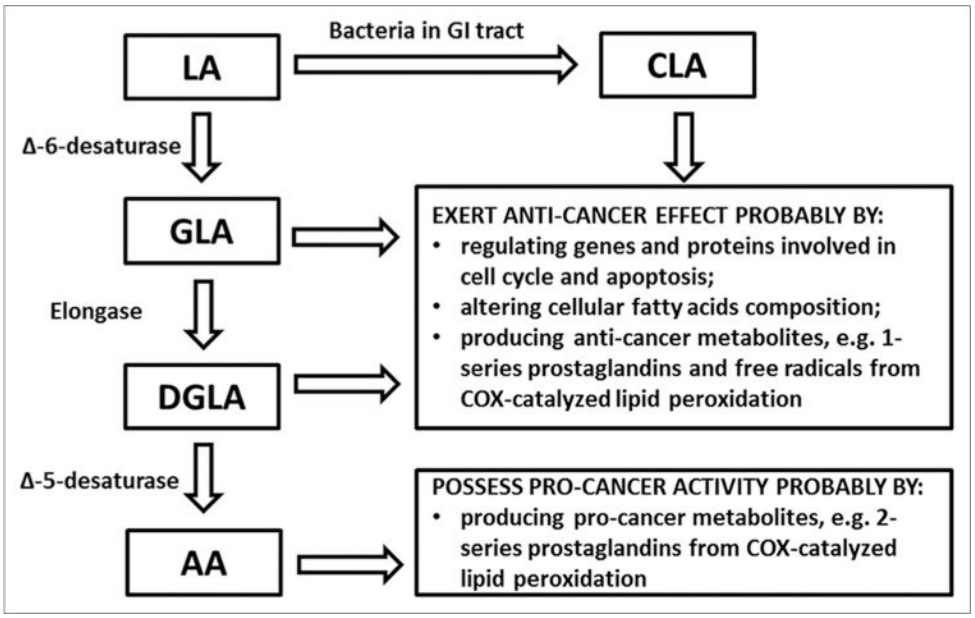

Figure 1.

Overview of the metabolism of ω-6 PUFAs and their implications in cancer. Abbreviations: LA: Linoleic acid; GLA: γ-Linolenic acid; DGLA: Dihomo-γ-linolenic acid; AA: Arachidonic acid; CLA: Conjugated linoleic acid.