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Lipidomic Therapy to Cancer: A Novel Drug Designing Strategy – A Research Note

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WARBURGS HYPOTHESIS

Warburgs [1-3] findings on the origin of cancer cells was based on the impairment in the respiratory metabolism of normal cells. According to his hypothesis normal cells when deprived off thirty three percent of their oxygen requirement will turn into cancer cells by switching over to anaerobic glycolysis and the production of lactic acid. The production of lactic acid is a specific diagnostic feature of all cancer cells of any type of cancer and also the cells of all cancer types [1-3]. In fact visualized that the metabolic switch in respiratory cancer cell's aerobic metabolism from the oxidative phase to anaerobic phase may be the causative factor for carcinogenesis.

CANCER ETIOLOGY

However research investigations beyond 1953, consequent to the revelation of DNA molecules being the crucial regions for the transformation of normal cells into cancer cells, proved beyond doubt that tumorigenesis or carcinogenesis is possible only due to various mutagenic factors. Oncological studies have revealed that multifarious chemical compounds in the environment, back ground radiations of the environment or the radio nuclides, microbial infections and food contaminants can effect/bring crucial mutations in such critical genes as proto-oncogenes and tumor suppressor genes as well as single nucleotide polymorphic changes in the down line genes of the core critical genes. The cumulative effects of such mutations are only attributed as the cause for cancer cells formation [2].

CANCER METABOLISM

The very long latent period that the cancer disease takes for its manifestation (15-20 years), stand as evidence to document the above accumulation of changes or mutations in the base composition of DNA or genes. The fermentation process of energy production in cancer or the Warburg effect may represent one of the after effects of transformation in their metabolism and may not be considered as the etiologic reason for origin of cancer cells or the transformation of normal cells into cancer cells. In this context, it is of interest to note that muscle cells of all higher organisms suffer a small bout of anoxic condition at times of hyper activity and create an oxygen debt by the production of the fatigue poison namely the lactic acid. However these muscle cells reinstate their normal condition as and when the O_2 supply is restored. It is also a functional adaptation of all cancer cells to thrive with a minimal energy production through Warburg effect. Recent studies have revealed that cancer cells maintain a micro environmental niche wherein several pro-inflammatory cytokines/proteins, growth factors synthesized from within as well as obtained from without enable their survival and aberrant growth through proliferation.

In this context, researchers optimism that absence of sulfhydryl groups and a fatty acid partner produce a low oxygen environment and encourage cancer cells to proliferate may be indicating the metabolic profile of cancer cells. His view gives a cue that all normal cells undergo some changes at the plasma membrane level and thus transform into a malignant form where in the membrane compounds play a crucial metabolic role as well as an immunological unresponsive potential to the host immune surveillance.

FATTY ACIDS DILEMMA

Cancer being an epigenetic as well as a genetic disease

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involving many genes and either their expression or suppression, it may be a daunting task and a cumbersome procedure to rectify all these genetic changes through gene therapy. It is also very difficult to construct a road map to follow the pathway of cancer cells and to undertake the treatment modalities or interventional procedures at the midst of their pathway because each individual cancer cell is different from the other cancer cells in its pursuit of metabolism. However the recent studies on the lipid constituents in normal cells versus cancer cells give an insightful hope towards cancer/cure. Recent studies have revealed that n3-PUFA like α-linolenic acid and long chain omega fatty acids like eicosapentaenoic acid (EPA), docosapentaenoic acid (DHA) may play important role DHA in normal cells, both prevention and cure of cancer [5-7].

In our school of oncological research and thought, it has been construed that different essential fatty acids play a role either in enhancing or suppressing cancer as visualized previously. For instance the synthesis of prostaglandins of D, E and F series/through arachidonic acid induced enzyme pathway and eicosanoids and the tilt of balance between n-3 and n-6 PUFAs towards more n-6 categories may be attributed to increased cancer risks. However n-3 PUFA excerts anticancer effects contrary to n-6 fatty acids. In this line, oleic acid kills breast cancer cells [8]

It has also been reported that olive oil represses the gene viz., HER2/neu/erb-B2 involved in the development of breast cancer. By cutting the HER2/neu by 46%, it significantly down regulates its expression. Our personal observation on the fatty acid com position of breast cancer tissue also revealed higher percentage of n-6 linoleic acid (24.534%) as compared to the linolenicn-3 (0.1566%) acid [4,9]. Similar to linoleic (n-6) palmitic acid (n-6) boosts the cancer cells survival. Our personal observation revealed higher percentage of palmitic (n-6) similar to linoleic (n-6) It has also been revealed that palmitic acid silences the fatty acid synthetase-Fas genes in cancer cells and induce BRCA I expression.

Next in the line of cancer promotors is the myristic acid. All these findings correlate that structural composition of normal cells and the membrane components in regard to PUFA are altered to promote carcinogenesis supporting the concept of Warburg mentioned per-se. Recently researchers have revealed that n-3 PUFA alters cancer cell membrane's signaling assemblies or the lipid rafts and it represents a crucial event in down regulating to pro-carcinogenic cell signaling and to revoke the immunocompetence. In cancer cells several signal transducing pathway are operated by the gain of gene signatures and the hormone responsive cancer cells operate these pathways and well survive through their hormone specific receptors. Thus targeting cancer cell membranes and their lipid profile with more n-3 PUFAS seems to be a novel therapeutic approach towards cancer cure. Such novel approach viz., membrane lipid therapy and/or Lipidomic therapy was propounded very recently by several researchers [6,7]. These investigators have focused such membrane based anticancer lipidomic therapy. In making this realization pharmacopeia/pharmacognancy should involve in drug designs by adding the anti-carcinogenic n-3 essential Fatty acids sand deleting the innocuous n-6 FAs, Moreover the target focus towards cancer cells by such lipid modulation, with receptor orientation is all the more beneficial and efficacious.

n-6 VERSUS n-3 FATTY ACIDS

Considering the fact that more n-6 Fatty acids as compared to n-3 Fatty acids and the tilt of balance towards n-6 may be attributed to breast cancer induction, the ratio of two n-6 Fatty acids palmitic and linoleic combined percentage with one n-3linolenicrevealed ratio of 1:50, respectively in the present study. Though another n-3 oleic acid was in high proportion its ratio with n-6 palmitic and linoleic was 1:1.5, respectively.

To confirm whether this higher percentage n-6 linoleic-palmitic as compared to linolenic is specific to breast cancer alone or is a generalized and common factor to other types of cancers, the percentage difference of them in the colorectal and uterine- cervical cancerous tissues were observed [10,11]. In the uterine cervical tissues the palmitic and linoleic percentage was found to be 8.36 and 60.80, respectively. The linolenic was found in the range 0.29 to 0.55%. In the same tissue the methylated palmitate showed a range of 4.2 to 14.0%. While the methyl linoleate showed a range of 1.19 to 1.93% and the cholesterol showed a range between 47.5% to 85%. The linolenic was negligibly in low percentage of 0.29. In our study on free fatty acid analysis of three different cancerous tissues (breast, gastro-intestine, uterine-cervical) the short chain fatty acid namely the butyric acid which is the end product of microbial digestion of carbohydrates is conspicuously absent. Considering the multifarious functions of butyric acid viz., induction of apoptosis; cell cycle arrest; inhibition of histone deacetylases; regulation of aromatase promoters; alter the mitochondrial membrane potential, enhances apoptosis in cancers by a Ca^{++} dependent mitochondrial-intrinsic pathway, promotes FAS mediated cancer cell apoptosis; activates caspace-8, the conspicuous absence of butyric acid alongside n-6 fatty acids increase may be taken as evidence that these changes in Fatty acids profile are strong prognostic indicators for cancer development.

LONG CHAIN FATTY ACIDS AND CANCER

In recent years malignancy of cancer has been correlated to fatty acid metabolism. Since all cancers and especially the breast, uterus, ovary, cervical and all sub site cancers of gastro intestinal tract express hormone receptors viz., estrogen, progesterone, etc., it is postulated that fat content of these tissues particularly cholesterol may act as a precursor for the synthesis of above hormones.

CHOLESTEROL AND CANCER

In our study on uterine-cervical cancer tissue, the content of cholesterol was found predominantly in higher percentage. Harn et al. [12] have revealed that endometrial hyperplasia and endometrial in situ carcinoma have been ascribed to the cholesterol derived hormone estrogen. Recently investigator at Simon Frasher University have revealed that cholesterol binding puts the brakes on oxosterol related proteins ability to couple phosphatidyl inositol 4-phosphate and accelerates cell growth crazy. These cholesterol may function as an enhancer of cellular metaplasia.

OLEIC ACID - THERAPEUTIC SIGNIFICANCE

Oleic acid is a fatty acid that occurs naturally in various animal and vegetable fats and oils. Chemically it is $CH_3(CH_2)7CH=CH(CH_2)7COOH$. In the present study the significance of a markedly high percentage of oleic acid could not be explained, in view of the report that it kills cancer cells [8]. However the above result is of significance and therapeutic value in view of another observation that oleic acid boosts the effectiveness of the anti-cancer drug herceptin and helped to prolong the lives of many cancer patients.

THERAPEUTIC SIGNIFICANCE AND SELECTION

In the present study the fatty acid composition of normal breast tissue could not be reported due to difficulty in procuring the control samples from female subjects. However the present results are compared, taking in to account the reports of previous investigations. The serious draw back in such comparison may not also be unexpected. Inside the breast tissues of normal subjects the level of fatty acids belonging to both n-3 and n-6 categories could be in a state of flux, depending upon the various physiological and gynecological conditions of the female subjects. Holmes [13] in their paper revealed that there was no association of breast cancer incidence in both the pre-menopausal and post-menopausal groups (cohort study) with intake of animal fat, vegetables fat, polyunsaturated fat, saturated fat or cholesterol. In their paper they have reported that certain fatty acids like (n6-linoleic, Palmitic or PUFA) have modulated mammary tumors growth and metastasis in animals, while omega-3 from marine origin is endowed with an inhibitory effect. These authors also cited that human ecological studies supported the above observation [14-18]. However in an established and differentiated cancer tissue of breast the above flux may not be expected but only the tilt of balance between n-3 and n-6 FAs towards n-6 FAs, as the latter has been obviously attributed to promote the carcinogenesis. Hence what is presented in our present observation and the uniform pattern of the EFAs, (i) higher percentage of linoleic acid and palmitic acid; (ii) the complete absence of butyric acid, the short chain fatty acid; (iii) Higher percentage of cholesterol and iv. the negligible percentage (<1%) of linolenic acid in the different cancer tissues (stomach, colon, rectum, uterine-cervix, mammary, breast) may be considered as important bio markers to decide upon the mode of treatment procedures and also the phytonutritional requirements as adjuvants to prolong the survival period as well as to build up immunity which has been deprived by the cancer growth and proliferation.

In our investigation (epidemiological) out of 300 patients, 238 were (80%) were non-vegetarians. In view of the predominant incidence of breast cancers found among non-vegetarians it may not rule out the contribution of certain essential F.As such as linoleic, palmitic, myristic, etc., towards mammary carcinogenesis. More over the higher ratio of n-6 may not also be unexpected since internal metabolic changes like the post dietary lipid composition where some n3 F.A can be converted n-6 F.A and some n-6 can also be transformed into another n-6 counterpart. Hence the sum of n-6 F.As pool in breast tissues may promote carcinogenesis is quite tenable **(Figure 1 and Table 1)**.

Table 1. Fatly acids composition in cancerous breast tissue (relative percentage).

Name of the Fatty Acid	Mean and Standard Deviation
1. Palmitic Acid	24.099 ± 6.63
2. Stearic Acid	5.03 ± 1.8
3. Oleic Acid	39.56 ± 4.7
4. Linoleic Acid	25.534 ± 10.0
5. Linolenic Acid	0.157 ± 01
6. Arachidil Acid	0.74 ± 0.49
7. Behanic Acid	1.35 ± 1.2
8. Lignoceric Acid	0.49 ± 0.02
9. Myristic Acid	2.134 ± 1.53
10. Lauric Acid	0.332 ± 0.41
11. Richinoleic Acid	0.525

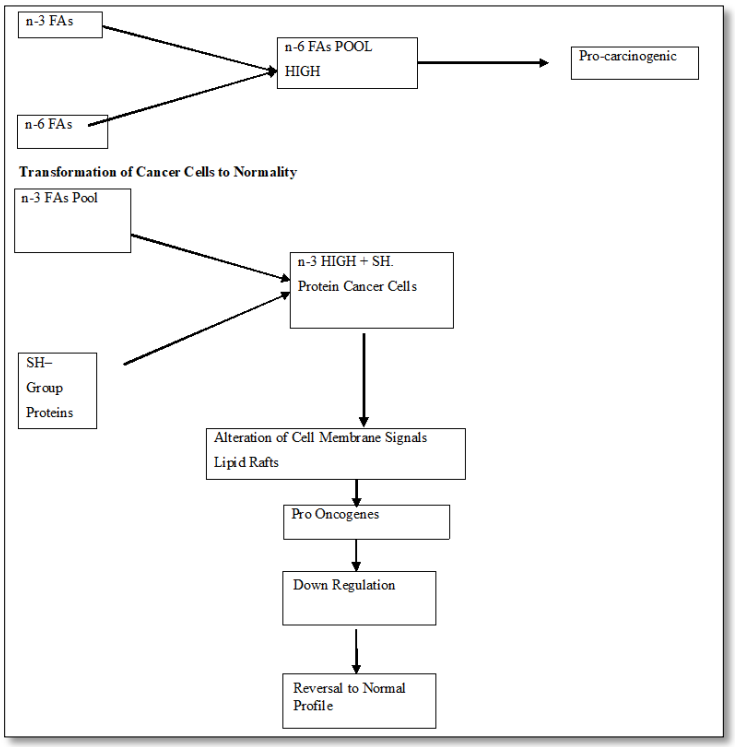

Figure 1. Transformation of normal cells to cancer cells (role of lipid profile probable pathway).

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