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STRUCTURAL CHANGES IN MITOCHONDRIA OF BREAST CANCER CELLS AND ROLE OF VITAMIN –D – A REVIEW

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ABSTRACT

In the beginning period of Oncological research cancer is the challengeable one among the people particularly breast cancer has been form due to poor self hygienic and social hygienic status. But this review to explain the structural changes in mitochondria in breast cancer cells and role of vitamin-D. The characterisation of the cyto morphological features in the malignant stages may infer the molecular level changes that have taken place inside the cancer cells which in turn have a bearing on better patient management. The clear understanding of breast cancer and identification of some cardinal changes in the ultra structure of organelles like mitochondria will provide more insights and possibilities about the oxidative status and oxidative stress. The histological findings beforehand will enable various precautionary measures to be taken to avoid the risk factors in general by all women and very particularly by the familial group individuals who inherit the pedigree relationships. The study reported the structural abnormalities in the mitochondria of breast cancer tissue cells and collates the above changes with other causation agent's viz., vitamin –D.

KEYWORDS: Breast cancer cell, Vitamin-D, Mitochondria, Patients, Abnormalities.

INTRODUCTION

As malignant cell transformation in cancer necessitates the accumulation of a very large number of mutations both in the nuclear and mitochondrial genomes, it is very difficult to go for genomic analysis more frequently considering the long latent period of 15-20 years and the prohibitive cost in developing countries. On the contrary the ultra structural changes in cells by biopsy of a glandular tissue like the breast may be enumerated and the pre-malignant symptoms may also be established at a break up period of analysis, every five years after age 40. As most women attain menopause after 45-50 invariably, the resultant outcome of hormonal imbalance may trigger some ultra structural changes in breast, ovary, and uterus glandular epithelial cells, consequent to some environmental factors interaction. This may prove to be a prudent strategy in cancer prevention.

Unlike other body tissues and glands which were functional after menarche in a women throughout until menopause, the breast is unique in showing full physiological activity only periodically during the reproductive cycle / life. Moreover its function and morphological conditions are influenced by the endogenous hormones like prolactin, oxytocin, estrogen and progesterone etc. Its physiological functioning is also influenced by the blood and lymph circulation and the artifacts carried through them. The active state of breast during gestation period and during lactation, the repetition of its periodic growth before and after every child birth, the chances of exposure to blood borne and lymph borne toxic substances, the formation of cracks and fissures in the nipple and areolar regions, and blockage of lactiferous ducts and engorgement of the breast with milk or the blood / lymph fluids may become an inadvertent source of constant infection by bacterial organisms like *Staphylococcus pyogenes* and viruses like HSV (Herpes Simplex Viruses).

Physio-Biochemical Conditions

The cumulative effect of all these physio-biochemical conditions may cause breast as an all time tissue to develop an inflammation. Besides inflammation the hormones of the pituitary, ovary and even of the thyroid and parathyroid during the menstrual cycles may cause cyclic enlargement and retrogression of breast. The uneven and irregular cyclical growth and regression of the event in the bilateral breast tissues may cause histological alterations like glandular tissue hyperplasia (Adenosis) increase of interstitial fibrosis and formation of cysts. In addition, the development of a benign tumour in the terminal lactiferous ducts which cause discharges in the nipple is not uncommon. Over whelming these complications, the formation of a haematoma and a hard craggy mass due to fat necrosis may represent the prognostic conditions or factors for the future development of a malignant carcinoma (cancer).

Various Risk Factors are attributed to the Genesis of Breast Cancer

Since, various risk factors are attributed to the genesis of breast cancer, like short lactation duration, smoking habit, non vegetarian food intake, lack of exercise, stress factor, menopause, free radicals generation, loss of immunity, lack of supplementary vitamins anti-oxidant nutrients, ethnicity, old age, environmental pollution and its nexus, radiation injures, etc (Kanakavalli 2011; Ramalingam 2019) oral contraceptives etc, a more crucial approach in scanning clinics is paramount to avoid the changes of development of breast malignancy through systemic anomalies and / or through metabolic and physiological phase abnormalities through the diagnosis of the difference between a non-malignant lump and a malignant one.

Vitamin –D

Vitamin –D, is basically referred to as a sun source vitamin and is an essential supplement nutrient for women after 40 age. Circulating vitamin –D is metabolized to 25 [071] vitamin –D in the liver and its hydroxylated form viz the calcitrol [1,25-dihydroxy-vitamin –D] present in other tissues including the breast.The nutritional source of vitamin –D is in the form of D_2 and D_3 , the former is manufactured by the UV radiation of ergosterol in yeast and the latter D_3 is manufactured by the radiation of 7- dehydroxy cholesterol from the cholesterol derivative lanolin. Vitamin- D_3 is more effective and efficient in raising the levels of 25(OH) Vit-D in the body than its D_2 counterpart and its metabolites show superior affinity for D- binding proteins in plasma. Vitamin-D receptors in tissues play an active role in the transcription of several genes that regulate cell cycle phases, apoptosis and metastatic potential. Vitamin –D also regulates the phenotypes of human breast cancer cells. Randomized trials and prospective cohort/ ecological studies have revealed that vitamin- D and calcium supplementation reduced the cancer risks of breast and prostate glands. Several studies have elucidated the importance of vitamin D (D_3) in cancer, as a prognosis factor /risk factor. Women deficient of vitamin D/D_3 show worse disease free survival in cancer and worse overall survival. (Robsahm et al 2004; Moan et al 2005; Goodwin et al 2008).

MATERIAL AND METHODS

TEM- Structural Studies

The study reports the structural changes in the mitochondria of poor prognostic cancer cases and their breast tissue samples. The breast fibroadenoma tissue of the body were fixed for 24 hours at 4°C in glitaraldehyde buffered to pH 7.2 with 0.1m Soudium cocodylate-HCl containing 3% Sucrose and 0.55 Sodium Chloride (Ramasamy 1995). They were washed and stored at 4°C in 4% Sodium Chloride Cacodylate buffer until required further. The tissues were post fixed for one hour with 15% aquous Osmium tetroxide, dehydrated through ethanol to propylene oxide and embedded in Epon resin. Thin sections of 60-90 nm were cut using a Richert Ultra cut E Ultra-microtone with diamond / glass knives. Sections were collected on copper grids stained with Uranyl acetate and Lead citrate and examined using a Philips Transmission Electron Microscopy operating at 100KV.

DISCUSSION

In the study from 100 patients breast analysis of cancer revealed that the histological type of their cancer are of varied nature. They are infiltrating ductal carcinoma with schirrous and nonschirrous nature, infiltrating ductal carcinoma with fully differentiated, moderately differentiated and poorly differentiated nature, infiltrating ductal carcinoma with comedo type, infiltrating ductal carcinoma with colloidal and apocrine nature and mixed infiltrating types etc., Out of 100 cases infiltrating ductal carcinoma dominates in ninety cases compared to ductal carcinoma six cases, (mucin secreting) colloid carcinoma two cases and papillary carcinoma of duct single case were noted. There was no blood vessel invasion and perineural invasion.

Factors that can raise the risk of getting breast cancer include

- Not getting enough exercise, drinking more than one alcoholic drink per day, and being overweight.
- Breast cancer prevention also includes avoiding exposure to carcinogens, chemicals, and radiation from medical imaging.
- Some kinds of hormone therapy and birth control pills can also elevate risk, but the risk returns to normal after stopping these medications.
- Some studies have shown that regular physical activity may help lower the risk of recurrence in women who have survived breast cancer.

Common breast cancer symptoms include the following:

- Non-painful lumps or masses
- Lumps or swelling under the arms
- Nipple skin changes or discharge
- Noticeable flattening or indentation of the breast
- Change in the nipple
- Unusual discharge from the nipple
- Changes in the feel, size, or shape of the breast tissue

In the study the electron microscopic structural details of mitochondria of the breast cancer tissue are presented (Fig-1).

The results of the study on the structural changes in the malignant breast tissue of patients who were diagnosed with breast cancer give a cue that the differentiation of ultra structural variations in the mitochondria, is to be viewed as the manifestation of ultimate cellular bio-chemical and bio-molecular changes. Considering the long latent period the normal cells take to discern and

manifest the malignant changes, the diagnosis of the cellular profile of breast tissue even before the lump formation seems to be important in scanning clinics. Coupled with such structural analysis the analysis of such biochemical criteria as urine hydroxy proline, serum calcium levels, free fatty acids the liver function metabolic profile tests will help to confirm the healthy condition of the breast, either to prevent the disease origin or make the individual immuno competent. Such confirmations will go a long way in preventing the formation of cancer in breast, both after menarche and menopause.

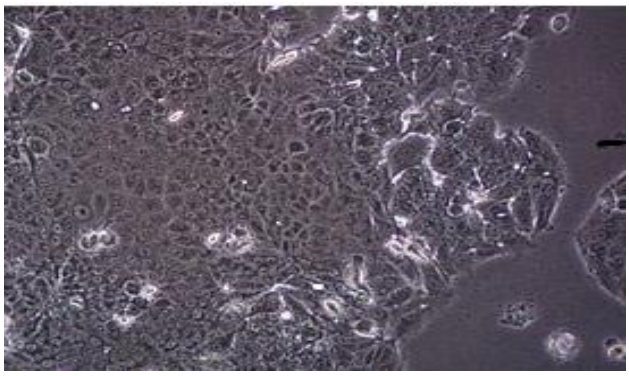

Fig. 1: L Breast Cancer Cell.

The structural studies in mammary carcinoma have been made previously with reference to different types. These studies have revealed that the ultra structure of all types of mammary carcinoma cells basically is characterized by prominent organelles. The frequent variations from cell to cell have been inferred to represent various functional statuses of the neoplastic cells. These studies have also revealed that hyperplastic mammary epithelium with prominent organelles also resemble the structural features of the malignant carcinoma cells. The various structural details noticed in the present study also supports the hypothesis that the malignant cells show the different functional phases. Various ultra- structural details noticed in the present study also support that mitochondrial morphological features and their variations, are evidences to the above assumption of different functional states. In the present study the electron microscopic structural details of the breast cancer tissue are presented.

In cancer cells generally an increase in the number of mitochondria as well as reduction of their numbers has been reported in earlier studies. Electron microscopic observations have shown that cancer cells often contain smaller mitochondria than normal cells. In some they may be normal in size but with a larger diameter due to luminal swelling. Very occasionally cancer cells contain elongated/giant mitochondria In the study the electron micrographs prepared from the breast cancer tissue revealed both the elongated and swollen mitochondria with electron dense granules and also the degenerating mitochondrial structures. The above observations reveal that the cells are under respiratory stress. It is an indication of development of malignancy.

Role of Vitamin-D

Mostly vitamin –D is contributed by the marine fishes like Herrings, Cod, Catfishes, Salmon, Mackerels, Tunas, and Sardines. Vitamin- D3 fortified cereals, egg yolk, liver and cheese are other miscellaneous sources. Studies have estimated that 75 to 150 n.mols /L(30-60mg/ml) is the optimum range of (25OH)-D in serum.

- High calcium intake, higher vit-D intake and higher 25(OH) D levels were associated with lower breast cancer risk.
- Supplementation of the above vitamin and minerals represents a breast cancer risk reduction strategy.
- Substantially higher level of vit-D intake viz., 1000-2000 IU/day would be needed to lower the breast cancer risk.
- Women who took 1000 mg of elemental calcium as calcium carbonate and 400 IU of Vit-D_3 daily were found to be free of breast cancer based on clinical finding and mammography.
- Breast cancer cell lines treated with vit-D, reverted the malignant myoepithelial features that are associated with a more aggressive phenotype and a poorer prognosis.
- Normal cell architecture in regard to actins filaments; microtubules, nuclear profile and cell-cell contact were reinstated by D_3 supplementation.

Direct evidence to the deficiency of vitamin –D and causation of breast cancer and other types came from the histopathological changes, found in breast tissue. In breast cancer cells the mitochondrial swellings were most conspicuously noticed. Studies on rats revealed that the above swellings in mitochondria were attributed to the action of thyroid and parathyroid hormones and irregularity in calcium metabolism and vitamin-D deficiency in mitochondria. The swollen mitochondria in cancer cells accumulate higher concentrations of calcium which prevent ATP formation through oxidative phosphorylation and stimulate synthesis of free fatty acids which become potent uncouplers. It is also of interest to mention the traditional concept that Ca^{2+} is an uncoupling agent.

CONCLUSION

The above point also supports the concept of innocuous fatty acids in the etiology of cancers. Previous studies as well as our studies and personal observations that the increased levels of n-6 E.F.As and the specific procarcinogenic fatty acids like linoleic, palmitic acid, myristic acid, excess cholesterol, absence of short chain butyric acid and deficiency of oleic acid constitute the cardinal principles and prognostic factors of carcinogenesis, (Ramalinam et al., 2019) remain justified by the fact that the above histopathological changes in mitochondria such as rectangular mitochondrial shape, loss of cristae, degeneration, swellings etc, might have

been induced by ca^{2+} enhancement free fatty acids and vit-D deficiency. The above facts also give a cue to revive the concept of warburg's hypothesis (Warburg (1956) (1956a) that deficiency or irregularity of aerobic respiration and switch over to anaerobic respiration or fermentation trigger transformation of normal cells to abnormal cancerous cells. It also infers that in normal cells vit-D and calcium absorption by cells go hand in hand; but in malignant cells such an import of Ca^{2+} + D Vit has not happened.

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