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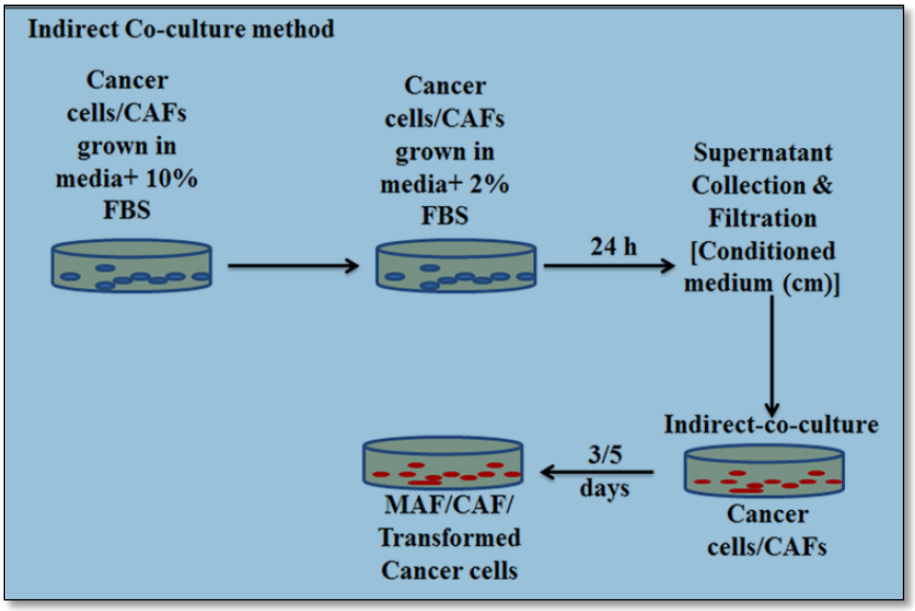
Model for Improving Existing Treatment Regime for BRCA1 Mutated Cancers



Hemalatha *et al.*, (2018), *Scientific Reports* (doi: 10.1038/s41598-018-32370-w)

A team of researchers from Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, Center for Cancer Research, National Cancer Institute, USA, Center for Cancer Research, National Cancer Institute, USA, and Regional Cancer Centre, Thiruvananthapuram, Kerala are the first to report that cancer associated fibroblasts (CAF's) isolated from primary breast cancer tissues when co-cultured with BRCA1 mutated HCC1937 cells transform CAFs to Metastasis Associated Fibroblasts (MAF's) *in vitro*[1].

Growth of the cancer cells is highly dependent on the growth signals from the surrounding cells. Among the surrounding cells, cancer stroma, fibroblasts are the most abundant ones. Cancer cells which arise from the normal epithelial cells in the body, transforms the normal fibroblasts into the CAF which enhances the cancer cell properties like proliferation, invasion and metastasis i.e., spread of cancer cells to new areas (secondary sites) of the body, often through lymph system or bloodstream, thereby, accelerates the cancer progression. The cancer progression is characterized

by increase in growth and invasion of cancer cells into new areas of host body and the cells become more aggressive and acquire greater malignancy potential.

During tumor progression, the cancer cells accumulate more and more mutations, and the metastasis is accompanied by initiation of secondary cancers. Such detached aggressive cancer cells have more deleterious mutations than others. However, it was not known if the cancer associated fibroblasts will respond differently to these more aggressive and less aggressive cancer cells within the same primary tumor.

The available research information reflects a tremendous increase in breast cancers, especially the cancers which occur at early ages and show poor treatment response. Of these, the triple negative breast cancers are one of the most aggressive ones, notably those which are defective for a tumor suppressor gene 'BRCA1', which constitutes a larger sub-group. Triple-negative breast cancer is cancer that tests negative for estrogen receptors, progesterone receptors, and excess human epidermal growth factor receptor 2 (HER2) proteins. The higher incidence as well as the augmented drug resistance exhibited by this sub-group, calls for an urgent need of a better targeted therapy.

It has been reported that the full length BRCA1 protein interacts with key proteins including Ezrin, Radixin and Moesin at the plasma membrane which controls cell motility. However, in cancers with truncated BRCA1 protein, this efficient control is lost and leads to migration of such cancer cells to secondary sites in host body.

Dr. Priya Srinivas and her research team at her laboratory in the RGCB, Faridabad proved that BRCA1 mutated cancer cells induce proliferative signals more efficiently in CAF's, which results in generation of their altered form, called MAF's, which can further induce invasion and migration of cancer cells more effectively.

The BRCA1 mutated cancer cells which interacted with cancer associated fibroblasts as well as metastasis associated fibroblasts over-expressed Ezrin and CCL5. The study carried out at Dr. Srinivas's laboratory proved that inhibitors to Ezrin could be used as potential anti-metastatic agents when used along with standard chemotherapeutics to target BRCA1 defective cancers. This study will also provide a useful model for clinical trials, improving the existing treatment regimen which would not be limited to BRCA1 mutated cancers.

The findings of the research have been published in reputed scientific journal '*Scientific Reports*' and the work has highlighted the intriguing possibilities of combination therapy of MAF inhibitors as anti-metastatic agents along with anticancer drugs, to control the metastatic spread of cancer cells from primary tumor site to the secondary sites.

References:

1. Hemalatha, S.K., Sengodan, S.K., Nadhan, R., Dev, J., Sushama, R.R., Somasundaram, V., Thankappan, R., Rajan, A., Latha, N.R., Varghese, G.R. and Mathew, A.P., (2018). Brcal defective breast cancer cells induce *in vitro* transformation of cancer associated fibroblasts (CAFs) to metastasis associated fibroblasts (MAF). *Scientific Reports*, 8(1), 1-14.

Dr. Bilqeesa Bhat
Project Scientist,
bhat.bilqeesa3000@gmail.com

Contact Person for further information:

Dr. Anish N. P
Scientist at RGCB, Thiruvananthapuram, Kerala
Phone +91 471 2529 693