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CARCINOGENIC MEDIATORS FOR BREAST CANCER DIAGNOSIS REVEALING POTENT BIOMOLECULAR TARGETS FOR DRUGS

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Abstract
Cancer biomarker and mediators are driving tools of tumorigenic pathways. Breast carcinoma is the most frequently diagnosed cancer among women, it possesses the highest incidence approximately 26% of all cancers. The review aims to remove and confront logical fallacies improvised for breast cancer cell, additionally excavating the insights into the therapeutically targeted biomarkers for the breast cancer eradication. The signaling cascades induce down streaming of pro-apoptotic mediators such as Cytochrome C, FAS L, Bak/ Bax, Lamin B. The functional coordination of cellular apoptotic and proliferative pathway includes tumor agonists (FAIM1, 2, 3), PKcs, LCL161, Bcl2 & Bcl-xL, PKA, MAPK & PKB e.tc, playing legitimate role in oncogenesis. Granzyme B cytotoxically increased in malignant /proliferative breast tumor cases, indexing high CD8 and TIL activation. Next the cytotoxic granule arbitrated route is Fas R/ FasL, in prosurvival route is FAIM-L, FAIM2 may interfere CD95/ CD95L in the presence of XIAP (anti-apoptotic protein). The complications in cancer advancement can be trekked if the weapons in cancer treatment and strategies that take benefit of cancer cell's "Achille's heels", are identified. Conclusively the review will converge the gaps regarding exploitation and prediction of cancer markers. Documenting the forthright biomarkers will provide significant and novel milestones for breast cancer diagnosis and prognosis in clinical oncology.

INTRODUCTION
Breast carcinoma is the most frequently diagnosed major global health issue and the most common invasive type of carcinoma among women in both developing and industrialized countries (1). Breast cancer has become second in the lethal diseases of women in the America; nearly 12% of women, or one out of every eight, are diagnosed with the disease during their lifetime, with over 40,000 deaths occurring each year. Particularly 20 percent of women suffering with painful type of locally recurring breast

cancer, the median survival period is one or two years. Whereas, 5-year survival rate is recorded for cutaneous metastases (CM) (2). In Asian countries, the breast carcinoma prevalence was lower when compared with Western countries. However, during the modern era, the proportional involvement of the breast carcinoma global burden in Asia is increasing rapidly (3, 4).

Biomarkers and Breast cancer mediators; The landscape of cytosolic proteins and ligands associated to breast cancer is highlighted in this review to describe the tumor cell proliferation status as well as the distant metastasis. The hormone receptor expression levels, namely PR and ERα are the common examples regarding weak predictive but significant prognostic biomarkers (5). While a few more relatable biomarker proteins are focused her in the review.

Method of Review; We searched PubMed, Scopus, Clinicaltrials.gov, MEDLINE, Embase, and Cochrane library databases for literature review for the diagnostic and bioactive markers of breast cancer.

Apoptosis (programmed cell death) mediators: Cells become quiescent and their cycle check spots are often evaded by cancer cells, rendering them resistant to the cytotoxic signals for apoptosis (6). The anti-apoptotic B-cell lymphoma 2 (Bcl-2, Bcl-xL) proteins, that has about 20 different proteins till to date. Yet key regulators of cellular death are constantly growing (Figure 1). The ratio of pro- apoptotic (Bax, Bak, and Bad) and anti-apoptotic proteins determines a cell's sensitivity or resistance to apoptosis. Table I shows that Bad's phosphorylation state is a crucial apoptotic stage (7).

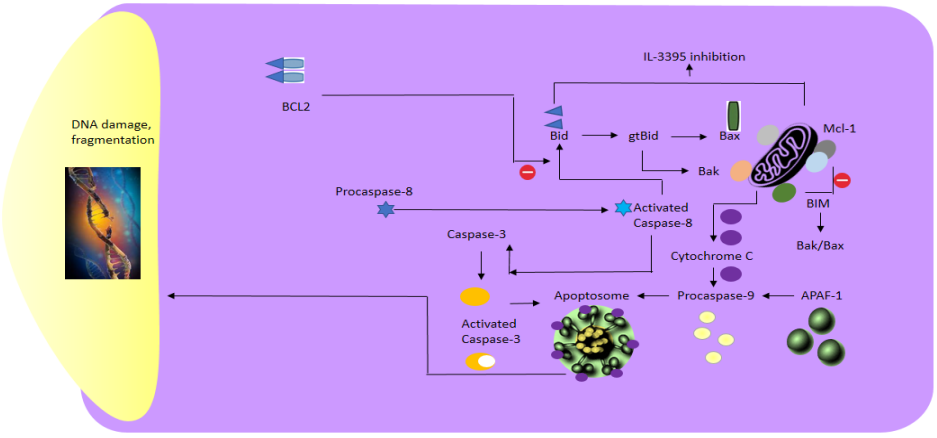

Figure 1. Apoptotic events under the influential role of pro-apoptotic cytosolic proteins

From up streaming of pro-apoptotic proteins tBid-Bak- Bax and down streaming of Bcl2, mitochondrial components cytochrome C, caspases-3,-8,-9 and apaf-1 involved in apoptosome formation (Apoptotic events). Apoptosome formation drags cellular components to cell death and DNA damage and fragmentation. (7).

Landing of LCL161 and TNFα: Increased IAP expression in a variety of malignancies, including TNBC, might reduce apoptosis. In TNBC xenograft models, a new class I small molecule antagonist of IAP proteins, (LCL161) was reported by Firestone to evoke anti-tumor necrosis factor (TNF) on sensitive cell lines (8). Further preclinical analysis in BC cell lines established a TNF-dependent GS related to LCL161 sensitivity and included three IAP-critical genes (Figure 2).

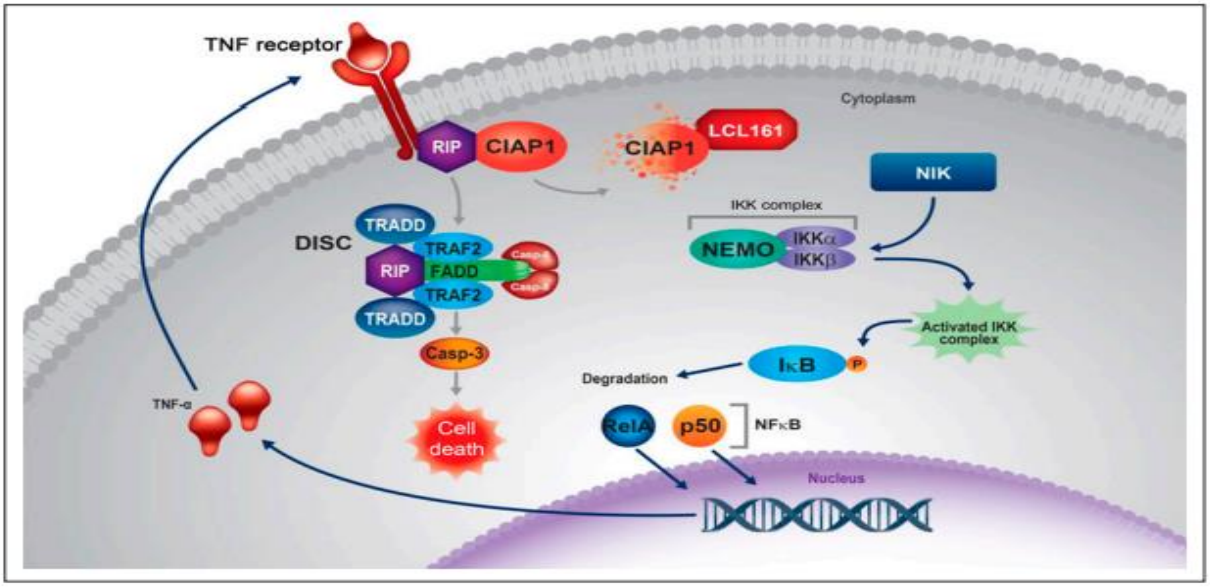

Figure 2. Tumor necrosis factor mediated the apoptosis pathway by action of LCL161's cytosolic protein.

TNFα released by the continuation of NEMO and IKB release and relative change in DNA sequence. TNFα ligand binds to THFr and signals RIP which can initiate the apoptotic pathway by sandwiching between TRADD discs transducing further caspase recruitments. The apoptosis inhibiting protein (AIP) subgroups LCL161 induce denaturation of CIAP delivering unstoppable growth, which was higher in TNBC xenograft models, derived from actual patients (9-11)

Twenty-six percent of TNBC samples were GS-positive, compared to seven percent of the other subtypes, and LCL161 response (Table I).

Table I. Tug of war between pro-apoptosis and anti-apoptosis pathways

Pro-Apoptosis			Anti-Apoptosis		
Action	**Reaction**	**Reference**	**Action on**	**Reaction**	**Reference**
Bax-Bak oligomerization	(OMM) permeabilization	(12)	Bcl2 & Bcl-xL	Inhibits Bax-Bak dimer	(13)
OMM permeability	Releasing cytC	(14)	Inhibit Bax-Bak oligomerization	Inhibits cytC release	(13)
CytC& apoptotic complex	Activates executioner caspases(-3,-7,-8,-9)	(14, 15)	PKA, MAPK & PKB	Phosphorylates Bad	(16, 17)
t-Bid	Induces Bax-Bak oligomerization and release of Cytochrome C	(12)	Phosphorylated Bad	Dissociates from mitochondria & binds to 14-3-3 protein	(7)
Bad (dephosphorylated)	Inhibits anti-apoptotic proteins (Bcl2 & Bcl-xL)	(18, 19)	Growth factor signaling i.e. EGFR	Phosphorylation of Bad	(7)

FasR/Fas L Suicide system and Tumor agonists: When the immune system and chemotherapeutic drugs attack cancer cells, the FasR/ FasL pathway (cytotoxic granule arbitrated route) and the mitochondrial pathway are activated, rendering malignant cells death. FasR/FasL active in several cell types is most significant signaling pathways in the control of cell death, Fas Ligand binding to Fas receptor may induce intrisically the procaspase 8 mitochondrial permeabilization and ER efluxing Ca $^{+2}$ ions for autophagal machineray accumulation. FasL (CD95), is a type I trans membrane receptor expressed in lymphocytes, tissues, and tumor cells (20). Its expression is limited and controlled, with activated T-cells, macrophages, and natural killer cells being the primary FasL producers (9).

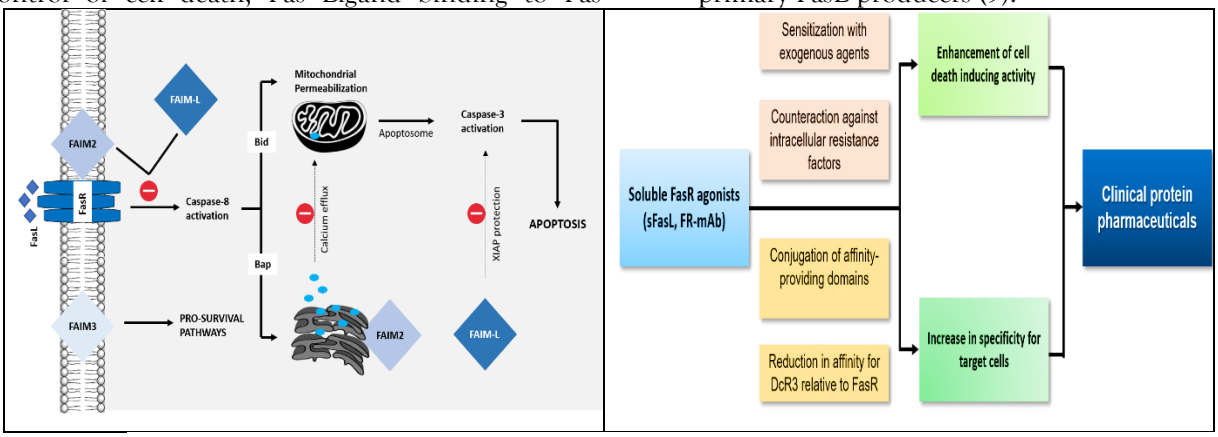

Figure 3. a) FasL/FasR provide targets for pharmaceutical proteins via progressive apoptosis or identifying target cells.b) The prosurvival signal FAIM-L and cytotoxic FasR/ FasL balance

The apoptotic death receptor (DR) signaling cascade is shown here. In order to avoid cell death, FAIM1 isoforms (FAIM-S and FAIM-L) connect to the Fas receptor and block caspase-8 breakdown. Besides, the neuron-specific isoform FAIM-L can inhibit FasL-triggered apoptosis by reducing the ubiquitinational degradation and consequent deprivation of the anti-apoptotic protein X-linked inhibitor of apoptosis protein (XIAP). FAIM2 binds to Fas, inhibiting caspase-8 cleavage and calcium efflux from the endoplasmic reticulum, preventing apoptosis delaying cytC release. FAIM2 and Bcl-xL interact in the ER. FAIM3 inhibits apoptosis by interfering with apoptosome formation and death signals, and can reverse cell death by stimulating MAP Kinase/ERK and NF-kappa B pathways. (21).

Role of Fas apoptotic Inhibitory Molecules (FAIM): Even though FAIM1, FAIM2, and FAIM3 constrain Fas prompted cell death via death receptors (DR), their existence with several signaling molecules is well established. Besides, they hinder apoptosis through entirely diverse mechanisms either sensitizing the foreign chemicals or reducing internal immune responsive elements (Figure 4). FAIM2 play cell death reversal by inhibiting activation of caspases -3, -8, while FAIM3 transduces MAP Kinase /ERK and NF-kappa B pathways. The Fas system and molecules provide targets for many pharmaceutical metabolites, either by enhancing cell suicide or by targeting drugs to specific cell sites (21).

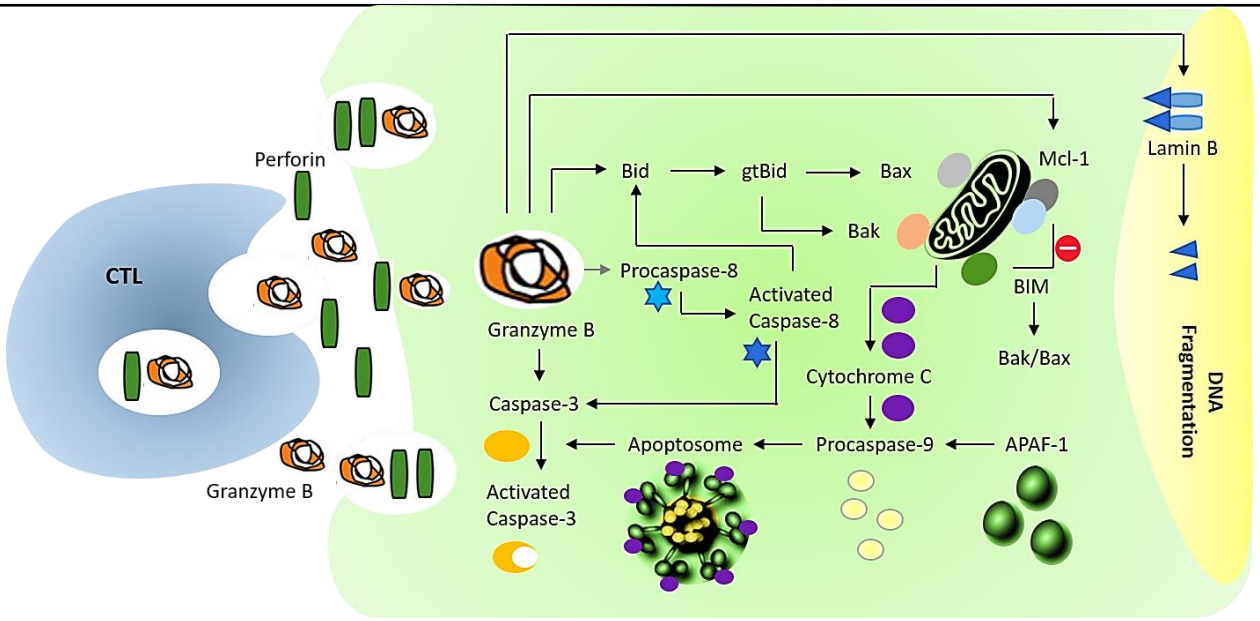

Figure 4. Granzyme B-Perforin complex induced cell suicidal pathways

Perforin is required for the entry of Granzyme B and into the target cell. Both BID-dependent mitochondrial permeability and uninterrupted caspase functioning and stimulation increase apoptosis upon granzyme B entrance into the target cell cytoplasm. Exposed myristoylation signals in BID lead to mitochondrial targeting of this protein, where it stimulates dimerization of BAX and/or BAK. The apoptosome is clump of cytochrome C (transported to cytosol), procaspase-9 and Apaf-1 which stimulated cascade of caspases. Antiapoptotic BCL-2 family may suppress release of cytC. Another mechanism by which Granzyme B may cause DNA hydrolysis inside nucleosomes is by its ability to cleave ICAD, a DNase inhibitor (CAD). Granzyme B breaks down Lamin B, MCL-1, DNA-PKcs, microtubules consisting proteins i.e. tubulin and (NuMa, Mi-2) a host of autoantigens (28).

Suicidal protease Granzyme B as mediator: Granzyme B (32-kDa), serine protease, is one of robust enzyme among the entire human granzymes generated through CTLs (22). Because of its cytotoxicity, it is regarded as inactive pre pro-enzyme, the active form is generated through the removal of two peptides by the action of lysosomal dipeptidyl peptidase I/cathepsin C (23).

During a CTL or natural killer cell-interceded resistant response, the following factors are required: (i) instantaneously releases with permeable carrier proteins known as perforin, which are concerned with the specific receptors at the intercellular gaps known as immunological synapses (24, 25); (ii) helpful to enter in cell cytosol; (iii) various pro-apoptotic pathways activation through proteolytically attacking numerous intracellular protein substrata (Figure 4) (22). (26) A study by Wang found that Granzyme B manifestation was high in 46.5% of patients with primary TNBC without neoadjuvant chemotherapy. This was linked to elevated levels of TIL, CD8, and PD-L1 tumor cells (tumor infiltrating lymphocytes (p¼ 0.004), the expression of CD8 by the T cell (p¼ 0.016) and tumor cells PD-L1 (P=<0.0001). The study suggests that anthracycline treatment improved prognosis in the high Granzyme-B group. Granzyme B's impact could be an interpreter for postoperative chemotherapy and could explain proinflammatory rundown, leading to future issues. Characterizing these substrates could provide new insights into chronic inflammation. (27). Also, a nuclear pro-apoptotic passageway is described for human Granzyme B and engages breakdown of the cell cycle regulating proteins and kinase CDC stimulation. The granzyme B capability to activate directly the post-

caspase cytoplasmic cell death way was asserted as well (23).

Granzyme B and death mechanism in Cancer Cells: When Granzyme B is transported in the cytosol, this proteolytically may dose various protein substrata and start programmed cell death (PCD) (apoptosis). Recently, over 300 extracellular and intracellular human proteins as possible Granzyme B substrata have been recognized (29). When ≤300 intracellular proteins were identified among humans, as possible Granzyme B substrates. Which can cleave Lamin B, MCL-1, DNA-PKcs, proteins i.e. tubulin and (NuMa, Mi-2) (22), just a few were confirmed to be associated with Granzyme B interceded cell death. For example, activation of several members of the caspase family (3,6,7,8,9 & 10) (Figure 5) and the breakdown of domain of BH3 only pro-cell death protein (Bid) are very well recognized in the recent reports (30).

Outer Membrane Permeability of Mitochondria (OMPM): Granzyme B is believed to activate cell death through modifications of the mitochondrial membrane (OMM) rather than direct caspase stimulation (31).. It can disturb OMM by cleaving and triggering the cytosolic BH3-only protein Bid (32), which encourages mitochondrial permeability to cytochrome C, leading to the secretion of pro-apoptotic proteins (t(c) Bid facilitated MOMP) and activation of caspase-dependent and caspase-independent death pathways. Additionally, granzyme B. compound at OMM, alleviating its OMM-permeabilizing activity (33).

Mitochondrial component (Cytochrome-C), the pro-apoptotic protein's constable; Cyt C protein, found in the mitochondrial inner membrane, is linked to the peptide series through thioether bonds(34). It contains iron, Met80, and His18 amino acid ligands, which contribute to its high-redox capability. The interaction between Met80 and heme is responsible for its low 695nm incorporation (35, 36). Cyt c is a significant protein involved in cellular life and mortality decisions. It plays a role in electron shift, energy production, apoptosome development, and apoptotic cell death progression. Cyt c also participates in cardiolipin peroxidation, ROS formation, cell signaling regulation, and redox-attached protein import. Its role is crucial in apoptosis, apoptosis, and cell signaling pathways regulation (37-40). The anti-apoptotic Bcl-2 protein confines towards membrane of mitochondria, it permeates mitochondrial membrane to release of cytochrome C (component of electron transport chain) (41) (42, 43), which inds to Apaf-1, initiating apoptosome formation, leading to cell death. Pro-apoptotic proteins induce cell death, while down-streaming of TNFα, IL6, IL1β favors cytochrome c release (44).

The Physiological role of Cytochrome C in the Production of Respiration and Energy: ATP, an elevated-energy atom, is crucial for biological procedures and all living organisms ties elevated of ΔGo'= -100 kJ/mol (45,46). . Around 90% of cellular ATP is synthesized by OXPHOS tools in the inner mitochondrial membrane, including ATP synthase and ETC. Cytochrome C, a key electron transporter, is essential for cellular energy generation in the form of ATP(35, 46). Knockout mice, which undergo a transition from glycolysis to respiration, expire around mid- gestation (39, 44).

Conclusion: Cytosolic proteins and ligands associated to breast cancer are highlighted in this review, not only to represent the breast cancer cell proliferation status, its metastatic provisions revealingt mediators and biomarkers such as LCL161, CytC, FAS L, FAIM1, 2, 3, The predictive biomarkers discovery and validation, leads to the detection of genetic aberrations at the genomic level. The study emphasizes the functional and regulatory pathways related to the peptide profiles of specific proteins in breast carcinoma. Novel cytosolic protein LCL161 (apoptotic inhibiting protein subgroup), antagonize with TNF xenografts models, surrendering the cascade of TNFα and autophagal events. Carcinogenesis in BC involves activation of pro-inflammatory caspases and Granzymes, specifically Granzyme B (breast cancer) breaking Lamin B, MCL-1, DNA-PKcs, proteins i.e. tubulin and (NuMa, Mi-2). In pro-survival route FAIM-L, FAIM2 may interfere CD95/ CD95L in the presence of XIAP protein. These cytosolic proteins and tumor necrotic cell populaces will be predictive cursor for proliferative breast cancer diagnosis.

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