1. Introduction

1.1. Breast cancer: Leading cause of death Worldwide

Breast cancer is one of the most frequently diagnosed cancers in women, with a worldwide incidence of 16% cancer death. The rate of incidence varies among different countries. According to American cancer society, it was estimated that 231,840 new cases of invasive breast cancer will be diagnosed among women, as well as an estimated 60,290 additional cases of in situ breast cancer will be diagnosed leading to 40, 290 death in US [1]. The incidence of breast cancer in India is rising due to the lack of awareness and the absence of a proper breast cancer screening program. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India [2]. It is expected that in the coming decades, India would account for majority of new breast cancer patients diagnosed globally. In spite of extensive efforts, there is significant morbidity and mortality associated; therefore, understanding the pathogenesis of breast cancer is of immense importance.

1.2. Inflammation: Bridging innate immunity to breast cancer

Extensive efforts are being made to understand the mechanisms causing cancer that may help to prevent the extensive mortality. Now the efforts are made to understand physiological conditions that may be dysregulated during early stages to tumorigenesis. It has been observed that several inflammatory diseases increase the risk of developing cancer. For example, patients with ulcerative colitis and Crohn's disease are at increased risk for developing colorectal cancer [3]. Similarly, patients with schistosomiasis, stones, or long-term indwelling catheterization are prone to develop urinary bladder cancer and the patients with atrophic gastritis develop gastric cancer [4].

The experimental evidences demonstrating association of inflammation and breast cancer is emerging. Chronic inflammation plays a critical role in breast cancer occurrence/recurrence [5]. Though clinical manifestations of inflammation in form of "Inflammatory Breast Cancer (IBC)" are seen in a small proportion of patients, humoral and histological evidence of inflammatory response to carcinogenesis are evident in nearly all [6]. These observations suggest that there is a strong linkage between inflammation and breast cancer. The biochemical mechanisms regulating inflammation in breast tissue and their association with breast cancer are not understood.

1.3. Autophagy, inflammation and cancer: Emerging trio

Autophagy is a sequential process of engulfment and degradation of cellular components, infectious agents, damaged organelle etc [7]. Autophagy is a stress adaptive mechanism that protects against neurodegenerative and inflammatory conditions and aging [8, 9]. Autophagy is essential for cellular differentiation and development [10, 11]. It has also important function to play in innate immunity by removing invaded pathogens [7, 12]. Interestingly, mutation in any of the genes involved in mentioned autophagy regulated process such as inflammation, innate immunity, cellular differentiation leads to cancer.

Autophagy, inflammation and cancer are interlinked to each other. As discussed Inflammatory bowel diseases (IBD) greatly increase the risk of colorectal cancer due to elevated expression of inflammatory cytokines, such as IL-18, TNF, and IL-1β [13, 14]. The elevated level of cytokines is because of the defect in the autophagy related 16-like 1 (*ATG16L1*) protein[13]. This defect potentiates NF-κB signaling leading to elevated levels of tumor promoting cytokines. Another important risk of developing cancer is aging. Aging leads to defective autophagy that leads to accumulation of damaged mitochondria. This further leads to elevated inflammation and accumulation of ROS and protein aggregates that causes ER stress. The elevated inflammation and subsequent release of cytokines favors the process of tumorigenesis. It will be hence interesting to understand the detailed mechanism that interlinks autophagy, inflammation and cancer.

1.4. Mitochondria: Central regulator of Inflammation and autophagy

Mitochondria is known to be central regulator of energy metabolism however the emerging evidences have clearly demonstrated its role in several nontraditional pathways like cell death, autophagy and inflammation. The mitochondrial proteins have been identified that are central regulator of NF-κB and IFN pathway, suggesting the critical role in regulation of inflammatory pathways. MAVS (also known as Cardif, VISA, and IPS-1), localized to the outer mitochondrial membrane contains an N-terminal CARD-like domain and a C-terminal transmembrane domain. MAVS acts as scaffolding protein on mitochondria and assemble IKK complex and TBK-1-IKKε, which leads to activation of NF-κB and IRF3, respectively [15]. Coordinated activation of these transcription factors results in the induction of several key molecules such as TNF-α (tumor necrosis factor), IL-6 (interleukin 6) or vascular growth factor (VEGF).

Another signaling adaptor protein, MITA has been identified that plays an important role in innate immunity pathway. MITA (also known as STING; stimulator of interferon genes, MPYS; plasma membrane tetraspanner) is also localized to the ER-mitochondrial interface [16]. Studies showed that MITA forms a complex with MAVS, RIG-I, and TBK1, suggesting that MITA functions as an adaptor that links MAVS to TBK1 [17]. MITA is also an important part of dsDNA sensing machinery regulates by cGAS (cGMP-AMP synthase) [18, 19]. MITA is postulated to regulate both NF-κB and IRF3 transcription factors to regulate inflammatory pathways [16].

Mitochondria provide a signaling platform for the assembly of signaling complexes regulating inflammatory pathways like NF-κB and IFNs [17]. The transcription factors lead to the expression of various cytokines that mounts inflammation at the site of tumor. The cytokines attracts immune cells to the site favoring further release of cytokines. The immune cells and the cytokines are essential part of tumor microenvironment [20, 21]. This inflammatory response favors the process of angiogenesis and tumor progression. NF-κB and IFNs are also essential regulator of autophagy. NF-κB regulates the expression of p62, essential for the regulation of mitophagy [22]. The regulation of autophagy plays key role in tumor cells metabolism [23]. The selective elimination of defective organelles via autophagy is important for cellular homeostasis and plays essential role in development and pathogenesis of diseases. The selective degradation of defective mitochondria is essential for cell survival as well as innate immunity. The degradation of mitochondria may down regulate the level of several mitochondrial and mitochondrial associated membrane resident proteins like MAVS, MITA regulating inflammation hence regulating inflammation in physiological limits.

Hence we hypothesized that MAVS and MITA might prove to be an essential link between autophagy, inflammation and cancer. We intend to study the role of mitochondrial proteins MAVS and MITA in breast cancer in detail. The study will help us understand the linkage between mitochondria, inflammation and cancer. The study will also help understanding how autophagy, inflammation and cancer are connected to each other. The study will also help identifying new therapeutics for breast cancer. Modulating the pathway as to produce IFN can act as an essential therapeutic to breast cancer. The

alternative can be stimulating the tumor cells itself to produce IFNs which can have paracrine effect on the nearby tumor cells. MAVS and MITA are involved in IFN production during viral infection. The stimulation of this pathway in tumor cells in tumor cells can produce type-I IFNs locally. This is possible only after the detailed analysis of these proteins in breast cancer cells and tissue and their role in breast cancer tumorigenesis.