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ADAR1 and ZBP1 in Breast Cancer: Pathological Mechanism and Therapeutics

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Abstract: Breast cancer is a heterogeneous disease in which a variety of genetic and environmental factors are involved. Among them, adenosine deaminase acting on RNA 1 (ADAR1) and Z-DNA binding protein 1 (ZBP1) are the factors that have opposite functions in the process of regulating cell viability as well as inflammatory and immunity. Recently, the two factors have been proved to act as a key player in caspase-8-dependent PANotosis and IFN-γ-dependent immunoregulation in the development of most types of cancers. In this review, we discuss the basic functions of ADAR1 and ZBP1 as well as the interactions between them in regulating innate immune responses in breast cancer therapeutics.

Keywords: ADAR1; ZBP1; Breast Cancer; Cell Death.

1. Introduction

Breast cancer is the disease with the highest incidence among women worldwide, which could be characterized by both molecular and histological evidences, and mainly categorized into three groups: hormone receptor (estrogen receptor (ER+) or progesterone receptor (PR+)) positive breast cancer, human epidermal receptor 2 (HER2+) positive breast cancer and triple-negative breast cancer (TNBC). Although a variety of approaches that targets ER, PR and HER2 has been carried out for the treatment of breast cancer, in this review, we focus on the potential therapeutics of controlling the immunoregulation of cell death in Breast Cancer.

ADAR1 and ZBP1 are the only two mammalian proteins that contain a Zα domain, which is thought to bind to nucleic acids in the Z-conformation. These two molecules are crucial in regulating diverse biological processes. While ADAR1-mediated RNA editing supports host survival and development, ZBP1-mediated immune responses provide host defense against infection and disease. Recent studies have expanded our understanding of the functions of ADAR1 and ZBP1 beyond their classical roles and established their fundamental regulation of carcinogenesis in breast cancer, including regulation of cell death, establishment of tumor microenviroment and cancer immunity. It has been well documented that overexpression of ZBP1 could trigger cellular necrosis in breast cancers whereas loss of ADAR1 might lead to ferroptosis in MCF-7 and SKBR3 cells by modulating miR-335-5p and METTL3 activities. Furthermore, beyond ZBP1 and ADAR1's individual functions, a recent discovery showed that there is a regulatory connection between them. Specifically, in murine macrophages, ADAR1 immunoprecipitates with ZBP1 upon stimulation with IFN-β and/or nuclear export inhibitors (NEIs), indicating that ADAR1 interacts with ZBP1; additionally, loss of ADAR1 leads to accelerated ZBP1-dependent cell death in murine macrophages under the same stimulating conditions, suggesting that ADAR1 suppresses ZBP1-mediated cell death as well as the immune response and then promote cell homeostasis. Thus, the role of ADAR1 and ZBP1 is important in breast cancer treatment, which has not well concluded yet.

In this review, we aimed to investigate currently how breast cancers are treated and how immunity and immunotherapy work in Breast cancer especially the ADAR1 and ZBP1 which are related to the cell death like PANoptosis. ADAR1 mainly functions as a inflammation inhibitor while the ZBP1 is always served as an activator for cell death and inflammatory response related to IFNs. We also noticed and focused on their interaction as ADAR1 can mask the function of ZBP1. Besides, we also intend to accomplish what challenges have we faced such as the difficulties associated with ADAR1 and ZBP1 and their related pathway.

2. Introduction of ADAR1 and ZBP1

ADAR1 stands for adenosine deaminase acting on RNA 1, which is an enzyme functioning in editing RNA. To be more specific, ADAR1 catalyzes the conversion of adenosine (A) to inosine (I) in double-stranded RNA (dsRNA). During the viral infection process with IFN response being triggered, ADAR1, working as a negative regulator of IFN production, can prevent the shutdown of translation and cell growth arrest, helping to relieve cell death and delayed cell development. As ADAR1 can convert adenosine to inosine in dsRNA regions and disrupt the formation of stable RNA duplexes, this avoids the accumulation of dsRNA that triggers the immune response.

ADAR1 plays a role in inhibiting IFN production and response as it can prevent endogenous RNA from activating innate immune sensors PKR and MDA5 to allow efficient translation during IFN response. Here, MDA5 and PKR are essential for the double-stranded segment RNA virus, reovirus, to induce IFN production while the absence of the MDA5 and RIG-I completely abrogates the IFN production, indicating that both sensors are involved in the recognition of reovirus[12]. In this case, with enough translation, the cell death pathway as well as the production of IFN is blocked. During the IFN response, ADAR1 blocked translational shutdown by repressing hyperactivation of the dsRNA sensor PKR. ADAR1-dsRNA binding and catalytic activities were required to fully prevent endogenous RNA from activating PKR. Thus, ADAR1 regulates the sensing of self-versus nonself RNA, allowing pathogen detection while avoiding autoinflammation. On the contrary, the loss of ADAR1 will cause excessive MDA5-mediated IFN production, PKR overactivation by dsRNA, and finally, apoptotic cell death

leading to tissue damage[10].

ADAR1 primarily edited pol II Alu elements embedded in mRNA, but not independently transcribed putative pol III Alus. As the ISGs are robustly induced during IFN response, while the overall frequency of A-to-i editing increases during IFN response, there is no obvious increase in ADAR1-editing sites or editing frequency in ISGs mirroring the non-ISGs.

By suppressing the immunogenic dsRNAs, the RNA-editing enzyme ADAR1 appears as a determinant of resistance to immune checkpoint blockade (ICB) therapy, which is a disappointingly small proportion of patients with cancer show lasting responses to ICB-based monotherapies. As these dsRNAs can drive IFN-dependent antitumor responses by activating A-form dsRNA-sensing proteins such as MDA-5 and PKR5, ADAR1 disrupts the therapeutic effect of ICB therapy whose antitumor effect is dependent on the IFN-response[5].

ZBP1 has emerged as a central innate immune sensor of double-stranded nucleic acids in the left-handed Z-conformation, which is a critical innate immune receptor for both nuclear Z-DNA and double-stranded Z-RNA as it has Z-DNA or Z-RNA binding domains. Z-DNA has a non-canonical structure that differs from canonical B-DNA (classic double-stranded DNA). Z-DNA binding protein 1, as the nucleic-acid-sensing pattern recognition receptor (PRR), can stabilize Z-form DNA[1]. Simultaneously, after binding with Z-form DNA, ZBP1 is activated, which triggers a series of immune responses. Its functions generally fall into the following categories: cell death regulation, inflammasome activation, and induction of proinflammatory responses[7].

ZBP1 plays a vital role in sensing the viral infection. As one of the key inflammasome sensors controlled by PAMP and DAMP, ZBP1 is usually activated after the virus was captured by those receptors when they enter the cells of the host. Afterwards, ZBP1 could trigger the formation of NLRP3 inflammasome complex which is composed of AIM2, Pyrin, ZBP1, ASC, caspase-1, caspase-8, RIPK3, RIPK1, and FADD. This special complex can activate caspase-1 leading to the cleavage of its downstream substrates, leading to inflammatory signaling and inflammatory cell death via the releasing of the inflammasome-dependent cytokines IL-1 beta, as the pro-inflammatory cytokine, and IL-18[2].

Unlike other well-known viral sensors that detect patterns associated with infecting virions, ZBP1-mediated sensing happens later during infection, after virus replication, and is dependent on IFN signaling[7]. Generally, ZBP1 senses the changes and synergies with RIPK3 or RIPK1 via the RHIM domain which activates parallel pathways of caspase-8-dependent apoptosis and MLKL-mediated necroptosis. Meanwhile, the ZBP1-RIPK1 axis transduces downstream signaling and mediates the secretion of proinflammatory cytokines which then leads to inflammation during the infection.

ZBP1 was also initially regarded as an IFN-inducible Z-DNA binding protein[6]. When Z-form DNA accumulation occurs due to the mitochondrial genome instability, ZBP1 can sense the changes and stabilize Z-form DNA. This nucleates the assembly of a cytosolic complex, containing cGAS, RIPK1, and RIPK3, to sustain STAT1 phosphorylation and IFN-I signaling. The cGAS-STING-dependent IFN-I signaling axis is essential for ZBP1-mediated inflammatory cell death. Here, the Z-alpha domains of ZBP1 sustain detection by cGAS to augment IFN-I signaling. Besides, the RHIM domains of ZBP1 are required for maximal cytosolic interactions with cGAS[1]. These suggest that, specifically, Z-alpha domains and receptor-interacting protein homotypic interaction motif (RHIM) domains are necessary requirements for signaling.

The expression of ZBP1, which can drive inflammatory cell death (PANoptosis), can be induced by IFN. As for the mechanism, IFN signaling can induce ISGs that have robust antiviral properties and upregulate ISGs that trigger cell death. As there is a positive feedback loop between excessive cell death and IFN signaling that leads to cytokine storms, overstimulated inflammatory responses contribute to mortality. The lethality was increased after using IFN-beta treatment during the infection (beta-coronavirus) while the genetic lack of the Zbp1 or its Z-alpha domain repressed cell death and then reduced the IFN-mediated lethality during viral infection[3].

ADAR1 and ZBP1 are the only two mammalian Z-alpha-containing proteins. The main role of ZBP1 is to regulate cell death (necroptosis) while ADAR1 is responsible for the survival and development of host cells. In this case, the regulatory relationship between ADAR1 and ZBP1 indicates that ADAR1 represses ZBP1-mediated inflammatory cell death, PANoptosis[6].

In another aspect, ADAR1 also prevents the accrual of endogenous Z-form dsRNA elements (Z-RNAs) that were abundant in the 3'UTRs of IFN-stimulated mRNAs. With this kind of prevention of Z-form dsRNA accumulation, the innate immune sensor ZBP1 cannot be activated to fulfill a role, leading to ZBP1-RIPK3-mediated cell death (necroptosis). In a nutshell, ADAR1 inhibits endogenous Z-RNAs and identifies ZBP1-mediated necroptosis as a new determinant of tumor immunogenicity masked by ADAR1 as it blocks the stimulating factor (Z-RNA) of the ZBP1[5].

ADAR1 has some isoforms such as ADAR1p150 and ADAR1p110, but only the interferon-inducible p150 isoform possesses a Z-alpha domain that can bind to Z-form nucleic acid. At the same time, ZBP1 has a related Z-alpha domain as well which is the target of Z-form nucleic acid. ZBP1, as the sensor, senses Z-form nucleic acid and drives a hyperinflammatory form of nucleus-initiated cell death during viral infection. In this case, ADAR1 can competitively bind Z-form nucleic acid to repress the accumulation of endogenous Z-RNAs which would function as necroptosis-activating ligands for ZBP1[5]. Both having the specific Z-alpha domain makes it possible for ADAR1 to inhibit the ZBP1-mediated inflammatory responses.

3. The Application of ADAR1 and ZBP1 in Cancer Treatment

Discovering and utilizing molecules that can modulate ADAR1-ZBP1 or RIPK3-ZBP1 interaction can be a potential therapeutic for treating ZBP1-mediated inflammatory and infectious diseases. While the interaction of ADAR1 with ZBP1 inhibits cell death as there is an antagonistic relationship between them, the RIPK3 synergizes with ZBP1 to drive innate immune inflammatory cell death[6]. ZBP1 is a well-appreciated driver of RIPK3 and mixed lineage kinase domain-like pseudokinase (MLKL)-dependent necroptosis where necroptosis is an inflammatory form of cell death that can be induced by interferon and can feed forward to potentiate IFN-I and pro-inflammatory responses[1].

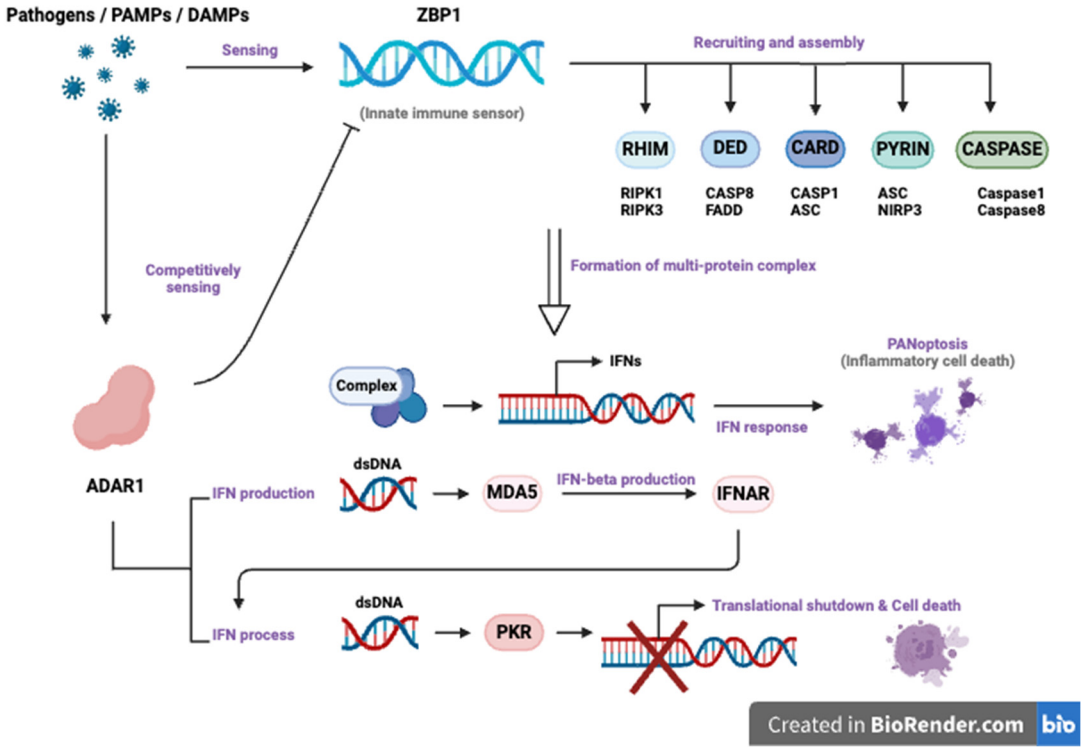

Figure 1. The signaling pathways of ADAR1 and ZBP1[2][21]

During the infection, knockdown of the Zbp1 seems a feasible way to regulate the excessive ZBP1-mediated cell death and inflammation, which may cause tissue damage, to protect the infected mice from death. However, the sensing happens during the viral replication, as the virus persists and replicates in the infected host cell, the recovery from infection is delayed[7].

Some recent studies have revealed that ADAR1 may be related to facilitating tumorigenesis as the IFN and ADARI expression augment are observed in many cancer types as well as the ADAR1 in breast cancer cells reduced cell proliferation. It is suggested that with potentiated editing in tumors, the tumorigenesis may be driven by the coding changes of the protein. As ADAR1 prevents IFN response which is an essential mechanism in IFN treatment, suppressing ADAR1 or its expression during IFN therapy could lead to PKR activation and subsequent cell growth arrest, thereby enhancing the anti-proliferative effects and efficacy of IFN therapy[10].

In such cases, when we focus on the presence or absence of ADAR1, the study found that the loss of ADAR1 in tumors helps to overcome the resistance to ICB. A large number of patients with cancer suffer either non-respond or resistance to the immune checkpoint blockade, which is often because of acquired mutations that impair antigen presentation. Without ADAR1, A-to-I editing of interferon-inducible RNA species is reduced, leading to the sensing of double-stranded RNA ligands by PKR and MDA5; this results in growth inhibition and tumor inflammation, respectively. At the same time, loss of ADAR1 overcomes resistance to PD-1 checkpoint blockade caused by the inactivation of antigen presentation by tumor cells. Thus, effective anti-tumor immunity is constrained by inhibitory checkpoints such as ADAR1 that limit the sensing of innate ligands[17].

Compared with the loss of ADAR1, on the aspect, the presence of ZBP1 can effectively enhance immunotherapy by triggering the death of inflammatory cancer-associated fibroblasts (CAFs). CAFs can promote tumor growth by fostering immune exclusion or creating a highly immunosuppressive environment. However, CAFs are competent to undergo necroptosis, a highly immunogenic form of cell death that is triggered when Z-DNA or Z-RNA (collectively called ZNA) is sensed by the IFN-induced ZBP1. Such ZBP1-dependent necroptosis can effectively control the tumors by limiting the CAFs' functions. In such cases, the drug which combines ZBP1 and ICB can improve cancer treatment as a potential immunotherapy method[18].

Recent studies suggest that a newly discovered small molecule, the CBL0137, can potently activate ZBP1 by triggering Z-DNA formation in cells, which then can effectively activate ZBP1 to drive the following IFN-responses and inflammatory cell death. This induction, by CBL0137, of ZBP1-dependent necroptosis in cancer-associated fibroblasts and strongly reversed ICB unresponsiveness in mouse models of melanoma reveal a potential strategy for antitumor therapy. More specifically, by inducing the formation of Z-form DNA which induces ZBP1-induced necroptosis in cells of the TME, CBL0137 triggers CD8+ T cell recruitment into tumors and strongly enhances ICB response in vivo. Such therapeutic activation of ZBP1-induced necroptosis indicates a readily translatable avenue for rekindling the immune responsiveness of ICB-resistant human cancers[5]. Additionally, CBL0137 also triggered ZBP1-dependent necroptosis in CAFs in vivo when tested in mouse models of melanoma and drove regression of tumors that are either completely (B16.F10) or partially (YUMMER 1.7) refractory to ICB (α-programmed cell death 1) monotherapy. It was also demonstrated that the CBL0137-induced T cell priming in draining lymph nodes promoted ICB-driven abscopal responses[18].

The combination of IFNs and nuclear export inhibitors (NEIs) activates ZBP1-dependent PANoptosis while this cell

death can be repressed by ADAR1's Z-alpha2 domain interacting with ZBP1 which indirectly disrupts the interaction of ZBP1-RIPK3. Relating to the control of ADAR1 and ZBP1, with IFNs treatment, which upregulates ADAR1 and ZBP1, and nuclear export inhibitors, which sequester ADAR1 in the nucleus, the tumorigenesis in vivo is repressed by the induction of strong cell death, revealing a potential therapeutic pathway[8]. Here, the modest or suitable PANoptosis mediated by ZBP1 can help with the tumor regression to serve as a cancer therapy.

With the research of caspase-6, which is required for innate immunity and ZBP1-NLRP3 inflammasome activation, we suggest that caspase-6 may have the potential to potentiate the ZBP1-mediated cell death cancer therapy by its binding with RIPK3 and enhancement of the interaction of ZBP1 and RIPK3. Besides, researches reveal that mice lacking caspase-6 were more vulnerable to viral infection[13].

Here is the table summarizing the effects of ADAR1 and ZBP1 on immunotherapy of some of the typical cancers with their treatments.

Table 1. The effects of ADAR1 and ZBP1 on immunotherapy of the typical cancers with their treatments

Types of Cancers	ADAR1/ZBP1 function	Potential Approach	References
Menaloma (B16 tumour)	The loss of ADAR1 can sensitize the tumor to immunotherapy which increases the tumor inflammation and overcomes the resistance to ICB.	ADAR1 functions as a checkpoint that limits anti-tumor immunity by preventing the sensing of endogenous dsRNA. Loss of ADAR1 improves responses to PD-1 blockade and overcomes common mechanisms of resistance to immunotherapy.	[17]Ishizuka, J. J., Manguso, R. T., Cheruiyot, C. K., Bi, K., Panda, A., Iracheta-Vellve, A., ... & Haining, W. N. (2019). Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade. Nature, 565 (7737), 43-48.
Menaloma (YUMMER 1.7)	Use of the ZBP1 to enhance the immunotherapy by triggering death of inflammatory CAFs.	CBL0137 triggered ZBP1-dependent necroptosis in CAFs to drive the regression of tumours.	[18]Herbert, A., & Balachandran, S. (2022). Z-DNA enhances immunotherapy by triggering death of inflammatory cancer-associated fibroblasts. Journal for Immunotherapy of Cancer, 10(11).
Menaloma (B16-VOA)	CBL0137 was able to reverse ICB unresponsiveness in a refractory model of cutaneous malignant melanoma, as well as in a clinically relevant model of this malignancy. CBL0137 manifested these effects by activating ZBP1 in fibroblasts of the Tumor Microenvironment (TME).	CBL0137 treatment to increase the normally low ZBP1 level in the cell. Thus, the increase of IFN-induced ZBP1 expression can represent a potential tumor vulnerability exploitable by CBL0137, ADAR1 inhibitor, and ZBP1 activator.	[5]Zhang, T., Yin, C., Fedorov, A., Qiao, L., Bao, H., Beknazarov, N., ... & Balachandran, S. (2022). ADAR1 masks the cancer immunotherapeutic promise of ZBP1-driven necroptosis. Nature, 606(7914), 594-602.
Triple-negative breast cancer (TNBC)	ZBP1 can induce IFN responses, further leading to the necrosis and prevention of metastasis.	Utilizing B cell marker genes (like ZBP1) to predict prognosis and immunotherapy response in TNBC patients, contributing novel insights into the understanding of the TNBC molecular landscape and its implications for further therapeutic interventions.	[19]Zhao, F., Zhao, C., Xu, T., Lan, Y., & Li, X. (2023). Single-cell and bulk RNA sequencing analysis of B cell marker genes in TNBC TME landscape and immunotherapy. Frontiers in Immunology, 14, 1245514.

4. Current Potential Therapeutic Approaches-Relating to Breast Cancer

Due to various unknown reasons like uncontrolled cell growth, and genetic mutation, cancer may occur and disrupt normal cellular functions with tumorigenesis. Among all types of cancers, breast cancer is one of the most typical and sophisticated. With its high heterogeneousness and various outcomes, it's a considerable challenge to treat breast cancer with precise medicine. The well-recognized feature of breast cancer cells is the chromosomal instability, the gains and losses of whole chromosomes or chromosome arms, which is

probably caused by the missegregation of chromosomes during cell division[11].

Some breast cancer genomes have distinctive mutation processes, which may lead to the instability of the nucleic acid. This instability may cause the formation and accumulation of Z-form nucleic acid that can be sensed by ZBP1 and ADAR1, suggesting a potential therapeutic pathway apart from conventional methods like chemotherapy or immunotherapy[11].

Despite the remarkable clinical efficacy of immune checkpoint blockade (ICB) in cancer treatment, ICB benefits for triple-negative breast cancer (TNBC) remain limited. Through pooled in vivo CRISPR knockout (KO) screens in syngeneic TNBC mouse models, we found that deletion of the E3 ubiquitin ligase Cop1 in cancer cells decreases secretion of macrophage-associated chemokines, reduces tumor macrophage infiltration, enhances anti-tumor immunity, and strengthens ICB response[20]. In this case, the use of ZBP1 can enhance the therapeutic effect of ICB drug by triggering the necroptosis of CAFs[18].

Patients with TNBC exhibit a significantly higher level of immune infiltration compared to other breast cancer subtypes, despite their overall poor prognosis. The higher immune infiltration is characterized by elevated tumor-infiltrating lymphocytes (TILs), increased levels of PD-L1 expression in tumor cells and immune cells, and a greater number of non-synonymous mutations, which produce tumor-specific neoantigens, activate neoantigen-specific T cells and trigger anti-tumor immune responses. This unique immune landscape suggests a greater potential for benefit from immunotherapy in TNBC in comparison to other subtypes[20].

The tumor suppressor BRCA1 and certain of its partners, NUMB and HES1, prevent the abnormal transdifferentiation of mammary epithelial cells to a mesenchymal state by engaging in crosslink DNA repair which is essential to avoid tumorigenesis (BRCA1 breast cancer or basal-like breast cancer (BLCL)) due to the DNA damage[15].

Under the premise that the heterogeneity of breast cancer (BRCA) biology deeply challenges the drive for individually personalized treatment, contemporary relative precision therapies target defects in DNA repair, activated protein kinases, the estrogen receptor (ER), and the immune tumor microenvironment, usually in combination. As for the defection of DNA repair leading to the instability of nucleic acid, the specific Z-form nucleic acid sensor (ADAR1 and ZBP1) with the Z-alpha domain can serve as a potential therapy with related protein kinases like RIPK3 and RIPK1, to name but a few. Effective application of these strategies depends on our ability to accurately profile tumors to identify individual therapeutic vulnerabilities, however, current approaches in early-stage BRCA are inadequate[16].

A potential therapy for triple-negative breast cancer (TNBC) is suggested by its robust dependence, like the addiction, on the transcriptional kinase CDK7, which regulates the specific cluster gene expression that is vital for the survival of TNBC cells. As TNBC cells are highly dependent on CDK7 for cluster gene expression and cancer cell formation, the covalent CDK7 inhibitor treatment may be a potential therapeutic method for TNBC tumor controlling as TNBC cells will suffer apoptosis in the condition of CDK7 inhibitor treatment[14].

As ADAR1 can impress the inflammatory response, the loss of ADAR1 will lead to an increase in tumour inflammation with its sensitizing the tumours to IFNs. The induction of sufficient inflammation in tumours that are sensitized to IFN can bypass the therapeutic requirement for CD8+ T cell recognition of cancer cells and may provide a general strategy to overcome immunotherapy resistance[17].

With analysis of the B cell marker genes, including ZBP1, SEL1L3, CCND2, TNFRSF13C, CXCR4, GZMB, and CCDC50, which exhibited protective characteristics; in contrast, HSPA6 and PLPP5 were identified as having negative implications, the discovery of these genes signatures adds to our understanding of TNBC and offers a promising avenue for improving patient outcomes and guiding therapeutic strategies in this challenging subtype of breast cancer. To be more specific, ZBP1, overexpressed in necrotic breast tumors, has a relation to the induction of interferon. In the absence of ZBP1, both the process of tumor necrosis and the suppression of metastasis are prevented, which suggests the therapeutic potential of ZBP1 in TNBC treatment[20].

5. Conclusion, and Future Perspectives

There are still a lot of undiscovered functions and mechanisms of the ADAR1 and ZBP1 waiting to be clarified. The specific response substances of some mechanistic reactions still need to be identified. Like although we find that mitochondrial genome instability upregulates ZBP1 and promotes ZBP1-cGAS interactions, both DNA sensors form basal complexes with RIPK1 and RIPK3[1]. What's more, as researched, RNA editing of ADAR1 is frequently detected in Alu element loops rather than stems. Thus, the destabilization of dsRNA structures by A-to-I editing may not be the major function of ADAR1. Simultaneously, inosine-binding proteins can modulate dsRNA detection by PKR, or dsRNA elements containing inosines might bind PKR and inhibit activation. These and other possible mechanisms merit further investigation when specific PKR-activating species are identified[10].

All in all, research focused on the roles of ZBP1 and ADAR1, as well as responses dependent on ZBP1 and ADAR1, has the potential to offer a deeper understanding of the molecular processes that mediate cell death and inflammation in different situations including various kinds of cancers, both normal and disease-related. These findings and research may contribute to the development of therapeutic approaches for addressing infectious and inflammatory diseases caused by cancer and its therapeutic process.

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