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Regulation of Tumor-induced Platelet Clearance Modulated by the ERCC Family Through Mitochondrial Pathway

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Abstract

Thrombocytopenia, a common complication among patients with solid tumors, can be life-threatening when it leads to thrombosis. Although routine and frequent transfusion of blood components to those patients effectively improves the outcome of treatment, it brings a huge cost and burden to the health care system. Apoptosis mediated by intrinsic mitochondrial pathways has been well described in platelet clearance in vivo. However, the biological mechanism of thrombocytopenia modulated by mitochondria in tumor patients is unclear. In this paper, the expressions of the excision repair cross-complementing (ERCC) family, a set of proteins in DNA damage repair, are investigated by a bioinformatics analysis. The results presented that the mRNA expression level of 5 genes in the ERCC family has been significantly decreased in platelets from six different tumor patients versus healthy donors. There were no patterns of the downregulation of the ERCC family correlating to specific tumor types among the six test samples. In nucleated cells, cell death mediated by the intrinsic apoptotic pathway occurs when ROS overproduction demolishes the mitochondrial integrity and damages the mitochondrial DNA (mtDNA). Given platelets are anucleate, the expression of the ERCC family to target mtDNA repair is hypothesized.

Keywords

Thrombocytopenia; intrinsic apoptosis; solid tumors; the ERCC family

Introduction

Thrombocytes, also known as anucleate platelets, are essential in hemostasis, thrombosis, and immunological modulation. However, thrombocytes' role extends beyond blood clotting, as they participate in the systemic and local responses to tumor growth and metastasis [1]. In patients, the most common disorder associated with platelets is thrombocytopenia, defined as having a platelet count that falls below the lower limit of 150000/microliter for adults. Thrombocytopenia can be life-threatening, especially when serious bleeding in a patient's brain occurs. Bruising, malaise, fatigue, and general weakness are some general symptoms of thrombocytopenia [2]. Thrombocytopenia is also associated with the risk of acquiring thrombosis in conditions like heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome (APS), disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA), and paroxysmal nocturnal hemoglobinuria (PNH) [3]. One of the major causes of thrombocytopenia is having a tumor [4]. Previous studies have shown that thrombocytopenia is a common complication among patients with solid tumors, which are heterogeneous groups of malignancies resulting from an out-of-control proliferation of cells, which limits chemotherapy dose and frequency [5, 6].

Apoptosis normally occurs during development and aging as a homeostatic mechanism to maintain tissue cell populations [7]. In nucleated cells, there are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. However, in platelets, the intrinsic mitochondria-dependent apoptosis

pathway has been well-documented [8]. It is defined by the loss of the mitochondrial transmembrane potential and the release of two main groups of normally sequestered pro-apoptotic proteins from the intermembrane space into the cytosol [9]. Beyond that, mitochondria are also complex regulators of cytosolic homeostasis, sensing and responding to perturbation of intracellular K+, ROS, or lysosomal stability that results in mitochondria dysfunction and apoptosis [10, 11]. Particularly, the rate of mitochondrial ROS production, the extent of mtDNA oxidative damage, and the degree of membrane fatty acid unsaturation (a determinant of vulnerability to lipid peroxidation) are all inversely correlated with the lifespan across different cells [12]. Previous research has shown that mice expressing mitochondrially targeted catalase (MCAT) show reduced total DNA oxidative damage (in skeletal muscle), fewer mtDNA deletions, and extended mean and maximal life spans by 17% to 21% [13]. This suggests that accumulation of oxidative damage in mitochondria can limit rodent lifespan [12].

Correspondingly, the excision repair cross-complementing (ERCC) superfamily (ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, and ERCC8) is a group of genes known for encoding many proteins that play essential roles in many DNA damage repair processes when exposed to stresses like reactive oxygen species (ROS) or ultraviolet (UV) radiation [14, 15]. Most notably, ERCC1 and XPF (encoded by ERCC1 and ERCC4 respectively) form an endonuclease, ERCC1-XPF, which performs excision in many DNA repair pathways [16, 17]. It is generally believed that ERCC1-XPF is responsible for repairing 8-oxoG in mitochondrial DNA (mtDNA) with oxidized or ring-saturated bases in human and mouse cells [18].

In the absence of nuclei, platelets acquire all the needed RNA for responding to stress and communicate it to other cells and organelles from megakaryocytes through strategic repackaging. Upon platelets' activation or apoptosis, platelets show the capability to synthesize new proteins corresponding to specific events induced by various agonists or apoptotic inducers. In tumor patients, platelets have been shown with different mRNA expression profiles compared to healthy donors, which has been verified by studies of tumor cells-educated platelets in vitro, suggesting that tumor cells can differentiate platelets by altering their mRNA expression profile [19]. Although the repairing mechanism of mtDNA damage in nucleated cells has been intensively investigated, the signaling pathway in platelets is still unknown. Employing Expression Atlas, a renowned online database that provides information on the differential gene expression of down or up-regulation of mRNA from RNA-Seq and Microarray studies, can give novel insights into the connection and changes of the ERCC family in the platelets of the donors with tumors versus healthy donors. In this study, a bioinformatic analysis was used to identify that the mRNA expression profiles of 5 genes of the ERCC family in platelets have been downregulated in patients with 6 different tumors compared to healthy donors. Thus, this paper was able to identify the specific interaction between the ERCC family and mtDNA damage, which might play a vital role in intrinsic apoptosis in the platelets of patients with tumors. A proposed method to check the protein expression level of the ERCC family using methods like qPCR, western blot, and mRNA-LNP is presented along with promising applications with this paper such as improving the outcome of solid tumor treatment while avoiding excessive damage to thrombocytes and extending platelet's lifespan to decrease the transfusion rate of tumor patients is highlighted.

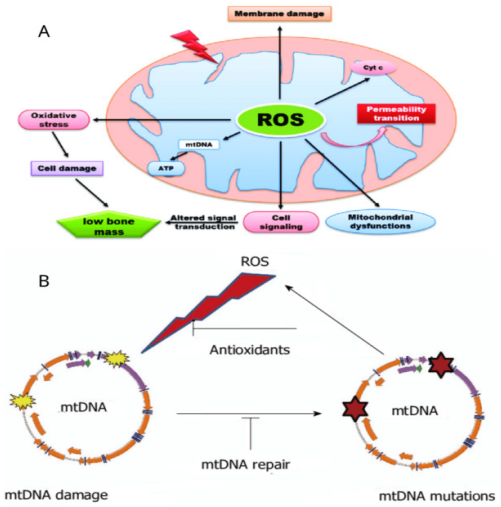

Figure 1. The intrinsic pathway of apoptosis after undergoing an oxidative stress.

Figure 1(A) describes some common pathways after mitochondria are exposed to ROS [20]. Figure 1(B) is specifically related to the pathway that mtDNA undergoes after exposure to ROS [21].

1. Methods

1.1 Resources used

The EMBL-EBI Expression Atlas (https://www.ebi.ac.uk/gxa/home) is an open public repository of gene expression pattern data across species, tissues, cells, and under different biological conditions from RNA-Seq and Microarray studies [22]. Established in 2009, Expression Atlas derives its database from curation, re-annotation, and statistical analysis with Experimental Factor Ontology terms and the database is processed using standardized microarray and RNA-sequencing analysis methods [23, 24]. This paper focused on acquiring data from the Differential Altas, one of the components of the Expression Atlas, where changes in expression between two different conditions are reported. According to PubMed, Expression Atlas has been used in more than 25,000 research papers and continues its original purpose as a value-added database for documenting gene expression across tissues [25].

1.2 Research process

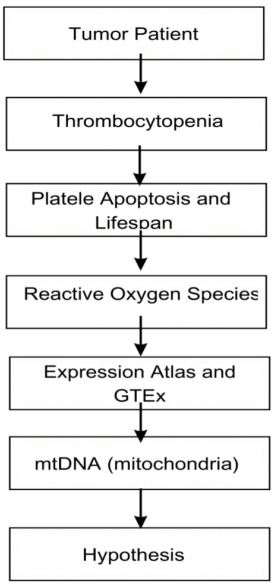

Figure 2. A flow chart with the research process.

Previous research has shown that thrombocytopenia is a common complication among patients with solid tumors that predispose them to bleeding disorders [26]. Solid tumors include sarcomas, carcinomas, and lymphomas [26]. However, the reason for clearance of platelets is pondered upon as platelets have a fast renewal rate with each of them only having a lifespan of 7-10 days [27]. Systemic chemotherapy and changes in cytokines are some of the frequent causes of thrombocytopenia [4]. Most importantly, cancer cells can have ROS-induced tumor-promoting events [28]. In cancer cells, high levels of ROS upon increased metabolic activity result in mitochondrial dysfunction, peroxisome activity, increased cellular receptor signaling, or through crosstalk with infiltrating immune cells [28].

As excessive amounts of ROS cause loss of mitochondrial integrity and lead to mtDNA damage which initiates cell apoptosis, ROS's effect on the DNA repair system is wondered upon. When searching on Expression Atlas, there is raw data comparing the ERCC family's expression level in platelets from patients with various tumors. The ERCC family (including ERCC4, ERCC5, ERCC6, ERCC6L2, and ERCC8) are all downregulated in the platelets of patients with 6 types of tumors. This is a significant finding as there is no nucleus and DNA in platelets except for mtDNA in mitochondria. Damage to either the mtDNA or the membrane of mitochondria is also the cause of intrinsic

apoptosis in platelets. Thus, the hypothesis that the ERCC family mediates tumor-induced platelet clearance through intrinsic apoptosis is proposed.

2. Results

This table presents the RNA-sequence of 5 members of the ERCC family (ERCC4, ERCC5, ERCC6, ERCC6L2, and ERCC8) in blood platelets from six tumor types and healthy donors. The first column from the left is the y-axis for the comparison between platelets from healthy donors and from patients with one type of tumor out of the 6 types of tumors. The top row is the x-axis for the name of the gene in bold; under the name is the log_2-fold change (the changes in the mRNA expression level) and the adjusted p-value in brackets to measure the significance of the log_2-fold change.

To find the data of mRNA expression profile in tumor patient's platelets, Expression Atlas was used. As shown in Table 1, the data from the research, RNA-seq of blood platelets from six tumor types and healthy donors (Experiment Accession: E-GEOD-68086), is collected from 228 adult patients with localized and metastasized tumors and 55 healthy individuals with 96% accuracy.

Table 1. RNA-seq of blood platelets from six tumor types and healthy donors

	ERCC4 Log_2-fold change (Adjusted p-value)	**ERCC5** Log_2-fold change (Adjusted p-value)	**ERCC6** Log_2-fold change (Adjusted p-value)	**ERCC6L2** Log_2-fold change (Adjusted p-value)	**ERCC8** Log_2-fold change (Adjusted p-value)
'pancreatic adenocarcinoma' vs 'normal'	-3 (1.95e-12)	-1.7 (4.72e-9)	-2.2 (3.78e-8)	-1.6 (6.02e-10)	-1.8 (5.53e-5)
'breast carcinoma' vs 'normal'	-2.7 (3.26e-16)	-2 (3.34e-17)	-1.8 (5.76e-8)	-1.7 (3.16e-9)	-2.4 (6.70e-10)
'non-small cell lung carcinoma' vs 'normal'	-2.5 (8.72e-12)	-2.3 (5.89e-18)	-1.8 (7.85e-8)	-1.7 (5.31e-9)	-2.2 (8.83e-8)
'colorectal carcinoma' vs 'normal'	-1.8 (1.34e-5)	-1.6 (1.44e-10)	-2 (7.43e-8)		-1.1 (2.48e-2)
'hepatobiliary carcinoma' vs 'normal'	-1.6 (3.14e-4)	-1.8 (7.40e-8)	-1.6 (2.59e-4)		
'glioblastoma' vs 'normal'	-1.4 (5.53e-5)		-1.4 (9.10e-5)		-1.6 (4.70e-5)

The patient cohort included six tumor types, i.e., non-small cell lung carcinoma, colorectal cancer, glioblastoma, pancreatic cancer, hepatobiliary cancer, and breast cancer. All of the genes are downregulated by a Log_2-fold of negative 1 to 3. In ERCC4, which encodes for XPF, the most down-regulated is pancreatic adenocarcinoma with a Log_2-fold of -3 (p-value = 1.95209776786095e-12), and the least down-regulated is glioblastoma with a Log_2-fold of -1.4 (p-value = 0.0000552543938353251). In ERCC5, which encodes for XPG, the most down-regulated is non-small cell lung carcinoma with a log_2-fold of -2.3 (p-value = 5.88565164904593e-18), and the least down-regulated is colorectal carcinoma with a Log_2-fold of -1.6 (p-value = 1.43730230748673e-10). In ERCC6, which encodes for CSB, the most down-regulated is pancreatic adenocarcinoma with a Log_2-fold of -2.2 (p-value = 3.78430374091483e-8), and the least down-regulated is glioblastoma with a Log_2-fold of -1.4 (p-value = 0.0000909816659356547). In ERCC6L2, which encodes for XPG, the most down-regulated is breast carcinoma with a Log_2-fold of -1.7 (p-value = 3.16083211977814e-9), and the least down-regulated is pancreatic adenocarcinoma with a Log_2-fold of -1.6 (p-value = 6.01913228379823e-10). In ERCC8, which encodes for XPG, the most down-regulated is breast carcinoma with a Log_2-fold of -2.4 (p-value = 6.7005849973842e-10), and the least down-regulated is colorectal carcinoma with a Log_2-fold of -1.1 (p-value = 0.0247680854924728).

3. Discussion

Besides serving as a powerhouse for healthy platelets, mitochondria have also been demonstrated to serve key functions in a variety of activities, including platelet activation, regulation of immune responses, and control over platelets'

life spans through apoptosis [29]. mtDNA copy number, a measure of mtDNA levels per cell, is considered an indirect measure of not only mitochondrial function but also the life span of platelets [30, 31]. Compared to nuclear DNA, mtDNA is more susceptible to damage under exogenous and endogenous stresses due to its proximity to the sites of oxidative phosphorylation and the deficiency of protection from abundant histones in mitochondria [33]. The repair mechanisms including base excision repair (BER), and mismatch repair (MMR) have been reported to fix mtDNA damage in nucleated cells [33]. However, the repair mechanism in platelets still needs further investigation.

It is generally believed that the heterodimer, ERCC1-XPF, is responsible for a role in the repair of mitochondrial DNA (mtDNA) with oxidized or ring-saturated bases in human cells [18]. In nucleated cells, ERCC1's and ERCC4's functions are interdependent as their gene products, ERCC1 and XPF, must be joined together to have their proper function [31]. This complex cuts DNA specifically near junctions between single-stranded and double-stranded DNA, where the single strand departs 5′ to 3′ from the junction [31]. In platelets, their mtDNA is still repaired through base excision repair and single-strand crosslink. ERCC1-XPF is involved in single-strand crosslink, by cleaving the 3' end of the damaged DNA. Although there is no data on ERCC1, neither ERCC1 nor ERCC4's gene product can function alone in the DNA repair pathway [31]. Previous research has shown that the platelet RNA profiles are down-regulated in nearly all cancer patients, regardless of the type of tumor, although the abundance of tumor-associated RNAs is predominantly influenced by tumor type and, to a lesser extent, by tumor progression and metastases [29]. This may lead to further investigation into the effect of different cancer types on platelet apoptosis. With the downregulation of ERCC1 and ERCC4, it poses a greater risk for mtDNA as damaged DNA cannot be fixed regularly.

ERCC5 and ERCC6L2 share similar functions with ERCC4; ERCC5 encodes a single-strand specific DNA endonuclease, XPG, that makes the 3' incision in DNA excision repair following UV-induced damage [34]. It is known to interact with ERCC1-XPF during nucleotide base excision repair. ERCC6L2 encodes a member of the Snf2 family of helicase-like proteins which have shown to play a role in DNA repair and mitochondrial function [35]. They are also significantly downregulated in all the platelets from patients with 5 different types of carcinomas and 1 type of blastoma. This suggests that multiple steps of the DNA repair pathway may be altered in tumor patients to prevent the fixing of damaged mtDNA.

ERCC6 and ERCC8, on the other hand, have functions that are less relevant to mtDNA repair. ERCC6 encodes a DNA-binding protein, CSB, that is important in transcription-coupled excision repair [36]. ERCC8 encodes a tryptophan-aspartic acid (WD) repeat protein, CSA; mutations in this gene have been identified in patients with the hereditary disease Cockayne syndrome (CS), which is abnormally sensitive to ultraviolet radiation [37]. The significance that they are also all downregulated in the platelets from patients with 6 different types of tumors highlights that they may participate in different functions other than DNA repair. They may be interacting with cytokines, inducing immune responses, or helping with cancer metastasis; Previous research has shown that platelets possess the capacity to transfer functional cytosolic RNAs to recipient cells, like stromal and immune cells, in the tumor microenvironment to exert biological effects [19]. This should be further investigated in future research.

The fact that most genes of the ERCC superfamily are present in the platelets highlights their need for repair to damaged mitochondria DNA. It is also essential to determine the ERCC family's expression level in healthy people. In the Supplementary Figure, the GTEx portal provides the bulk tissue gene expression for ERCC1 and ERCC4. Although ERCC1 and ERCC4's expression levels, measured by TPM, are the lowest in whole blood compared to the other tissues, it should be considered that whole blood includes not only platelets but also erythrocytes, leukocytes, and many other cells. Since the whole blood is only composed of a small portion (1%) of platelets, the mRNA expression level analyzed by the whole blood sample might not be well reflected in platelets. In addition, the erythrocytes, comprising most of the portion of whole blood, are also anucleate. Therefore, the whole blood's mRNA expression level is low compared to other nucleated cells that can generate more RNA through transcription.

There are limitations to this paper. First, the raw data measures the expression level of ERCC's mRNA sequences. Although previous research has shown that differentially expressed mRNAs correlate significantly better with their protein product than non-differentially expressed mRNAs, sometimes mRNA expression level does not correlate with protein expression levels [38]. However, most analysis is done on the DNA or the mRNA expression level as the analysis of the protein expression level is often complicated by epigenetic factors like regulatory proteins playing a role in controlling protein expression level. Similarly, since platelets do not have nuclei, proteins with commonly known functions in nucleated cells may not perform the same function in platelets. Thus, it is crucial to conduct lab research using the methods proposed above.

This paper also yields promising potential aimed at alleviating the effect of thrombocytopenia, a common complication with cancer, and decreasing the rate of transfusion of platelets for cancer patients. This research gives insight

into a new pathway that causes thrombocytopenia in cancer patients and highlights the novel connection between the ERCC family in platelets with intrinsic apoptosis and cancer.

4. Conclusion

The Expression Atlas analysis showed that the mRNA expression level of 5 members of the ERCC family was significantly decreased in several tumors, like small cell lung carcinoma, colorectal cancer, glioblastoma, pancreatic cancer, hepatobiliary cancer, and breast cancer. The downregulation of ERCC, especially ERCC1 and ERCC4, deters the pathway of mtDNA repair, leaving the mtDNA vulnerable to stresses like ROS. This research highlights a new pathway that leads to more frequent apoptosis in platelets in tumor patients.

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