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The role of HSP40 in cancer: Recent advances

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Summary. Heat shock proteins (HSPs) are a family of proteins involved in protein folding and maturation that are expressed by cells in response to stressors including heat shock. Recent studies have demonstrated that HSPs play major roles in carcinogenesis by regulating angiogenesis, cell proliferation, migration, invasion, metastasis, apoptosis, as well as therapy resistance to certain anticancer drugs. Despite being the largest and most diverse subgroup of the HSP family, HSP40 (DNAJ) is an understudied family of co-chaperones. HSP40 family members are also known to be involved in various types of cancers. In this article, we review the involvement of human HSP40 family members in various aspects of cancer biology. In addition, we highlight the possible potential of HSP40 as a tumor biomarker or drug target for improving the prognosis and treatment of cancer patients in the future.

Key words: HSP40, Cancer, Diagnostic biomarker, Molecular chaperone protein, Prognosis, Target therapy

Introduction

Heat shock proteins (HSPs) are expressed by cells in response to stressful conditions such as high temperature and hypoxia (Rylander et al., 2005). They serve as "chaperones" to ensure that the target cellular proteins (client proteins) are in the correct conformation and location at the right time. HSPs are induced during short intervals of heat stress and their expression continues to increase for several hours, which might be due to the lack of introns in most HSP genes (Lindquist, 1986). Some HSPs, however, are expressed even under non-stress conditions and contribute to the regulation of normal cellular processes such as immune response, cell cycle regulation, transcriptional activation, and signal transduction (Hauet-Broere et al., 2006; Brundel et al., 2008; Wick et al., 2014).

HSPs are classified into five major families based on their relative molecular weight: HSP90, HSP70, HSP60, HSP40, and small HSPs (Bohen et al., 1995; Li and Srivastava, 2004). Many HSPs are conserved throughout evolution, suggesting their crucial role in cell physiology. Various diseases present challenges to the normal function of cells and can induce a variety of stress responses. Thus, it is par for the course that various diseases or clinical conditions induce the expression of different classes of HSPs (Jindal, 1996; Falkowska-Podstawka and Wernicki, 2003; Sun and Macrae, 2005). Protein conformation diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Kampinga and Bergink, 2016), acute and chronic kidney diseases (Razzaque and Taguchi, 2005), cardiovascular diseases (Wick et al., 2014), and various cancers (Calderwood and Gong, 2016; Wu et al., 2017) involve different types of HSPs. HSPs are overexpressed in many human cancers, and high expression levels are associated with poor prognosis and treatment resistance in many cancers (Jäättelä, 1999; Azad et al., 2015). Several reviews have detailed the important roles of HSP70 and HSP90 in cancer (Wu et al., 2017; Elmallah et al., 2020; Aswad and Liu, 2021). Recently, some HSP40s have been found to play important roles in cancer development and progression, metastasis, and chemo-resistance, and they have become a topic of increasing interest in the field of anticancer therapy. Therefore, we review the role of HSP40 in cancer development and progression, metastasis, and resistance to treatment, aiming to illustrate the role and regulatory mechanisms of the HSP40 family in human malignancies more intuitively and provide new avenues for anticancer research.

The HSP40 family

The HSP40 (DNAJ) co-chaperones are the largest and most diverse subgroup of the HSP family and are composed of over 40 members and 49 genes (Sterrenberg et al., 2011; Cyran and Zhitkovich, 2022). HSP40 family members contain a conserved J structural domain through which they can interact with HSP70; thus, HSP40 is considered a functional regulator of

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HSP70. It can induce the ATPase activity of HSP70 and thereby regulate protein folding, unfolding, translation, translocation, and degradation (Sterrenberg et al., 2011; Wu et al., 2017). It also acts as an indirect regulator of the HSP90 multi-chaperone complex. The HSP40 family is subdivided into three DNAJ subclasses: DNAJA, DNAJB, and DNAJC. The DNAJ subclasses contribute to cancer progression and proliferation by acting as co-chaperones of multiple oncogenes and tumor suppressors.

Numerous studies have demonstrated the overexpression of the HSP40 family in various human cancers, including colorectal, breast, prostate, ovarian, liver, and head and neck squamous cell carcinomas, suggesting a close relationship between the HSP40 family and carcinogenesis. Currently, HSP90 and HSP70 have been recognized as bona fide anticancer drug targets (Wu et al., 2017; Elmallah et al., 2020; Aswad and Liu, 2021). HSP40 acts as a co-chaperone of HSP70 and an indirect regulator of the HSP90 multi-chaperone complex, with dual roles in both pro- and anti-cancer processes (Wu et al., 2017). This implies that HSP40 may also be a potential target for overcoming chemoresistance.

HSP40 and breast cancer

Breast cancer is the most common cancer in women and the fifth leading cause of cancer deaths worldwide (Bray et al., 2018). Triple-negative breast cancer (TNBC) accounts for 10-20% of all cases of breast cancer. Recent studies have identified an important role for DNAJB9 in the development and metastasis of breast cancer. DNAJB9 is a metastasis suppressor in TNBC, and its low expression is associated with poor clinical prognosis owing to increased tumor aggressiveness and shorter overall survival in patients. It stabilizes the FBXO45 protein by inhibiting autoubiquitination and enhances Lys48-linked polyubiquitination of the ZEB1 protein, thereby suppressing epithelial-mesenchymal transition (EMT) and metastasis. Further, it has been used as a biomarker of breast cancer and a novel target for breast cancer treatment (Kim et al., 2021).

Studies have identified a novel chemoresistance mechanism directly driven by doxorubicin. Specifically, doxorubicin itself induces upregulation of ETV7, a repressor of the ETS transcription factor family. ETV7 expression, which transcriptionally regulates the expression of DNAJC15, is inhibited by DNA methylation in breast cancer cells, thereby causing doxorubicin resistance (Alessandrini et al., 2018).

DNAJC10 mRNA expression has good prognostic value in breast cancer. DNAJC10 expression was reduced in breast cancer cell lines (BT-20, MDA-MB-2311, ZR-75-1) and clinical samples; breast cancer patients with high DNAJC10 mRNA expression had better overall survival and recurrence-free survival. This suggests that DNAJC10 is a potential diagnostic/prognostic biomarker and tumor suppressor gene candidate in breast cancer (Acun and Senses, 2020).

HSP40 and ovarian cancer

Among the glycoproteins differentially expressed between the paclitaxel-sensitive ovarian cancer cell line (A2780) and the paclitaxel-resistant cell line

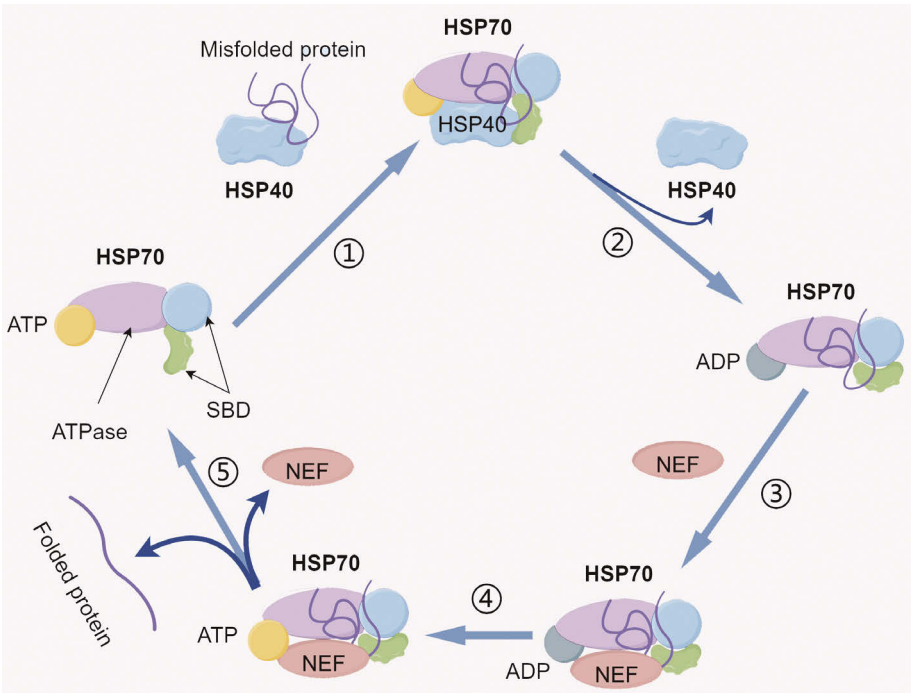

Fig. 1. Function of HSP40. **1.** HSP40 holds misfolded substrates, serving as a chaperone protein of HSP70, and interacts with HSP70. **2.** HSP40 regulates HSP70 ATPase activity, forming a more stable interaction between the ADP-bound form of HSP70 and the polypeptide. **3.** A nucleotide exchange factor (NEF) interacts with HSP70. **4.** ADP transforms to ATP. **5.** Both the polypeptide and NEF are released from HSP70.

(A2780TC1), four proteins are more strongly regulated with chemoresistance, namely tumor rejection antigen (gp96) 1, triose phosphate isomerase (TPI), palmitoyl-protein thioesterase 1 (PPT1) precursor, and endoplasmic reticulum-associated DNAJ (ERdj3). ERdj3 exhibited the greatest variation in expression between the two cell lines. These proteins may constitute potential biomarkers of paclitaxel resistance in ovarian cancer (Di Michele et al., 2010). The expression of ERDJ3 (also known as DNAJB11) was found to be associated with paclitaxel resistance in ovarian cancer (Sterrenberg et al., 2011), suggesting that changes in ERDJ3 protein expression may play an important role in conferring a drug-resistant phenotype to ovarian cancer cells (Shridhar et al., 2001). MCJ is another member of the HSP40 family whose deletion is common in human ovarian cancer due to loss of heterozygosity (LOH) and silencing of the other allele by hypermethylation. Its deletion results in *de novo* resistance to three therapeutic agents for ovarian cancer, namely, paclitaxel, topotecan, and cisplatin.

HSP40 and colorectal cancer

Colorectal cancer (CRC) is the third highest in mortality among cancer-related deaths worldwide (Xia et al., 2022). There is growing evidence that HSP40 plays two roles, enhancing and reducing the growth of CRC cells (Asgharzadeh et al., 2022).

The HSP inhibitor KNK437 has been reported to exert anticancer effects in several cancers. It enhances the cytotoxic effects of gemcitabine on pancreatic cancer cells (Taba et al., 2011) and sensitizes prostate cancer cells to the apoptotic effects of hyperthermia treatment (Sahin et al., 2011). Recently, a novel mechanism of action of KNK437 in the treatment of CRC has been identified. KNK437 inhibits CRC proliferation and metastasis through the DANJA1/CDC45 axis, which is regulated by the upstream transcription factor E2F1. DNAJA1 is significantly upregulated in CRC tissues and is closely associated with plasma membrane infiltration, increased lymph node metastasis, and poor survival in CRC patients. KNK437 effectively suppresses DNAJA1 levels in CRC cells (RKO, SW620, SW480, and LOVO) and attenuates its enhancing effects on CRC cell proliferation, infiltration, and metastasis. In addition, KNK437 in conjunction with 5-FU/L-OHP chemotherapy can inhibit liver metastasis of colorectal cancer (Yang et al., 2020).

DNAJB8 is expressed only in normal testicular tissue and in all human cancer cell lines (ACHN, Caki-1, SMKTR2, and SMKTR3), and is a novel cancer and testis antigen (Nishizawa et al., 2012). Cancer stem cells (CSCs) and Cancer-initiating cells (CICs) are characterized based on their tumor initiation, self-renewal, and differentiation abilities, and are resistant to stressors including chemotherapy and radiotherapy (Maccalli et al., 2018). DNAJB8 is preferentially expressed in the CSCs/CISs of human renal cell carcinoma (Nishizawa et al., 2012) and colorectal cancer (Morita et al., 2014), and DNAJB8 overexpression enhances the expression of stem cell markers (SOX2, LGR5, and POU5F1) and tumorigenicity, suggesting that DNAJB8 plays an important role in the maintenance of CSCs/CICs. DNAJB8 has been found to play a role in tumor formation, side population (SP) cell ratio, and tumor initiation, and knockdown of DNAJB8 reversed docetaxel resistance in human renal cell carcinoma (Yamashita et al., 2016). The introduction of DNAJB8 via small extracellular vesicles (SEV) from oxaliplatin-resistant colon cancer conferred a drug-resistant phenotype to colon cancer cells. Further studies revealed that DNAJB8 can interact with TP53 and inhibit ubiquitin-mediated degradation of TP53, leading to upregulation of MDR1, which promotes resistance to oxaliplatin in colon cancer. This demonstrates that DNAJB8 can promote oxaliplatin resistance through the TP53/MDR1 pathway (Wang et al., 2022).

DNAJB6 overexpression has also been shown to be a poor prognostic marker in CRC patients. Inhibition of DNAJB6 has been found to reduce IQGAP1 expression and ERK phosphorylation in CRC cells *in vitro* and inhibit CRC lung metastasis *in vivo* (Zhang et al., 2015).

DNAJB4 (HLJ1) is a member of the HSP40 family and plays important roles in proliferation, anchorage-independent growth, motility, invasion, tumorigenesis, and progression of the cell cycle (Tsai et al., 2006). Liu et al. (Liu et al., 2014) compared the expression of HLJ1 in seven CRC cell lines (SW480, LS174T, HT29, HCT116, Caco-2, SW620, and LOVO) and 120 cases of clinical paraffin-embedded CRC tissue. They showed that HLJ1 expression in strongly metastatic CRC cell lines was lower than in lowly metastatic ones. In addition, there was a positive correlation between HLJ1 levels and the survival rate in CRC patients. Therefore, HLJ1 could be used as a biomarker to predict the clinical outcome of patients.

Briefly, based on accumulating evidence in this part, HLJ1 is probably involved in CRC suppression, but DNAJB8, DNAJA1, and DNAJB6 are likely involved in CRC progression.

HSP40 and prostate cancer

Both enzalutamide and abiraterone have been approved by the United States Food and Drug Administration (FDA) for the treatment of metastatic castration-resistant prostate cancer (CRPC). Enzalutamide is a potent competitive antagonist that exerts antitumor activity by interacting with the androgen receptor (AR) ligand-binding domain (LBD) inhibiting AR nuclear translocation and transcriptional activation of androgen-responsive genes (Tran et al., 2009). In contrast, androgen receptor splice variants (ARv), such as AR-v7 and Arv567es, lack the ligand-binding domain at their C-terminus and are, therefore, insensitive to Enzalutamide. It has been reported that the androgen receptor variant AR-V7 is associated with

resistance to enzalutamide and abiraterone in CRPC patients (Antonarakis et al., 2014).

Therapeutic resistance of CRPC results from upregulation of AR and CYP17, induction of AR splice variants, point mutations in AR, upregulation of the glucocorticoid receptor (GR), activation of other oncogenic signaling pathways, neuroendocrine transformation, and immune escape through upregulation of PD-L1 (Boudadi and Antonarakis, 2016). A study (Moses et al., 2018) showed that both C86 (an inhibitor of HSP40) and JG98 (a potent metabotropic inhibitor of HSP70) can destabilize and disrupt the transcriptional activity of the FL-AR, AR-V7, and GR proteins and that HSP40/HSP70 inhibition can overcome multiple mechanisms of CRPC resistance. Both HSP40 and HSP70 are potential therapeutic targets for abiraterone- and enzalutamide-resistant CRPC.

HSP40 and pancreatic cancer

Pancreatic cancer is a highly fatal disease, as most patients remain asymptomatic until the disease has already progressed to an advanced stage (Kamisawa et al., 2016). Deaths related to pancreatic cancer are increasing globally, and it is expected to become the second leading cause of cancer-related deaths in the United States by 2030.

Pancreatic cancer cells have a four-fold downregulation of DNAJA1 compared with normal cells; thus, DNAJA1 is a potential biomarker and therapeutic target for pancreatic cancer. Pancreatic cancer has four major driver genes: *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*. Loss of SMAD4 in pancreatic ductal adenocarcinoma (PDAC) increases the aggressiveness and metastasis of PDAC, whereas a *KRAS* mutation is the initiating event of PDAC and is required for tumorigenesis (Liu, 2001; Waters and Der, 2018). Mutations in *KRAS* and *SMAD4* contribute to differences in metabolism and aggressiveness, and DNAJA1 overexpression appears to enhance these differences (Roth et al., 2021). Overexpression of DNAJA1 in the two PDAC cell lines BxPC-3 and MIA-PaCa-2 led to increased glucose consumption and intracellular accumulation of lactate and alanine. This suggests that DNAJA1 may regulate the activity of glycolytic enzymes such as lactate dehydrogenase (LDH) and alanine aminotransferase (ALT). In addition, overexpression of DNAJA1 results in weaker cytosolic lysosomal membranes, reduced actin formation, and increased cell invasiveness, emphasizing an oncogenic role of DNAJA1 in PDAC.

Studies have confirmed the importance of DNAJA1 in pancreatic cancer, where it regulates hyper-phosphorylation of c-jun and cell survival under stress; conversely, overexpression of DNAJA1 reduces the ability of pancreatic cancer cells to survive under stress. c-jun, a component of the JNK signaling pathway, is frequently overexpressed and hyperphosphorylated in cancer cells (Agarwal et al., 1995) and also plays an important role in pancreatic cancer. Under environmental stress, DNAJA1 activates the HSP70 protein by forming a complex with it. HSP70 has been shown to inhibit the JNK pathway, thereby inhibiting the hyperphosphorylated, anti-apoptotic state found in pancreatic cancer cells (Stark et al., 2014).

HSP40 and lung cancer

Lung cancer is a heterogeneous disease with a wide spectrum of clinical and pathological features. It is one of the most common cancers worldwide and is the leading cause of cancer-related deaths. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases; small cell lung cancer accounts for 15% (Thai et al., 2021).

HLJ1 (DNAJB4), a member of the HSP40 family, is associated with tumor growth, development, and regulation of local invasion and distant metastasis. HLJ1 inhibits the proliferation and invasiveness of lung cancer cells (A549), and high levels of HLJ1 are associated with reduced NSCLC-specific survival. Curcumin, the active component of turmeric, was found to upregulate HLJ1 expression through activation of the JNK/c-JUND pathway, ultimately inhibiting tumor cell invasion and metastasis by regulating E-cadherin expression (Chen et al., 2008; Forouzanfar et al., 2019).

HSP40 and tumors of the nervous system

Heat shock proteins are highly expressed in malignant brain tumors, but HSP40 and its role in brain tumors is still comparatively under-investigated. DNAJC10 is a member of the HSP40 protein family, and its protein expression increased with the increase in WHO glioma tumor grade. Furthermore, overexpression of DNAJC10 was associated with a poor survival prognosis for both lower-grade gliomas and glioblastomas (Liu et al., 2022).

MCJ (DNAJD1) is a member of the HSP40 family. Hypermethylation of MCJ was observed in medullo-blastoma, supratentorial primitive neuroectodermal tumors (stPNET), and ventricular meningioma, suggesting a role for MCJ epigenetic inactivation in the development of neurological tumors as well as in disease pathogenesis and chemoresistance (Lindsey et al., 2006).

HSP40 and Kaposi sarcoma

Kaposi sarcoma-associated herpes virus (KSHV) has been implicated as the etiological agent of Kaposi sarcoma. K1, a transmembrane glycoprotein encoded by KSHV, can transform rodent fibroblasts and block apoptosis. Wen and Damania (2010) performed genetic knockdown of HSP90β and ERDJ3/ ER-associated HSP40 using siRNAs in 293-K1 cells and found that knockdown of HSP90β and ERDJ3 could inhibit the

expression of K1 protein, accompanied by a slight decrease in the levels of AKt and p-AKt, which suggests that HSP90 and ERDJ3 are necessary for the stability of K1.

DNAJ is a viral oncoprotein chaperone that indirectly promotes tumorigenicity. ERDJ3 (also known as DNAJB11) is a cell-binding chaperone of the K1 protein of KSHV, which is essential for KSHV K1 protein expression and apoptosis inhibition. KSHV infection is associated with malignancy, and ERDJ3 expression of oncogenic viral proteins promotes cancer progression.

Conclusion and future perspectives

HSPs are promising targets for anti-cancer therapy, and several efforts have been made to develop inhibitors targeting the main HSPs. However, few studies have focused on HSP40. Based on the accumulating evidence, the HSP40 family plays a major role in the development, progression, metastasis, and chemoresistance of a variety of malignancies (Table 1). Furthermore, the following aspects and questions demand further investigation: (1) Whether HSP40 is dependent on HSP70 during tumor development and progression, or whether the conserved J structural domain region of the HSP40 family is involved in conjunction with HSP70; (2) The HSP40 family is diverse and serves different roles in different tumors. HSP40 is currently classified based on molecular weight, however, an improved classification of the HSP40 family may provide important clues to reveal its molecular functions; (3) HSP40 is secreted into the blood; can HSP40 can be used as a novel diagnostic marker for cancer diagnosis. In conclusion, a full understanding of the functional properties and mechanisms of action of the HSP40 family is essential for improving the accuracy of cancer diagnosis and developing more effective chemotherapeutic agents.

Table 1. Summary of human HSP40/DNAJ family members that play a role in cancer biology.

Name	HUGO nomenclature	Functionally tested	Cancer type	Role	Reference
MDG1	DNAJB9	Studied in breast cancer patients	Breast	Metastasis suppressor in TNBC□Increases tumor invasiveness and shortens overall survival by downregulating DNAJB9	Kim et al., 2021
MCJ	DNAJC15	Studied in breast cancer cells	Breast	Caused drug resistance to doxorubicin in breast cancer	Alessandrini et al., 2018
ERDJ5	DNAJC10	Studied in breast cancer cell lines and clinical samples	Breast	A potential diagnostic and prognostic biomarker and tumor suppressor candidate gene	Acun and Senses, 2020
ERDJ3	DNAJB11	Tested in ovarian cancer cells	Ovary	Conferred a drug-resistant phenotype to ovarian cancer	Sterrenberg et al., 2011
MCJ	DNAJC15	Tested in ovarian tumor cell lines	Ovary	Its absence results in de novo chemoresistance to three ovarian cancer therapy agents: paclitaxel, topotecan, and cisplatin	Shridhar et al., 2001
HDJ2	DNAJA1	In vitro human colorectal cancer cells; CRC patient study	Colorectal cancer	Upregulated in CRC tissues; enhanced proliferation, infiltration, and metastasis of CRC cells	Yang and Ren et al., 2020
DJ6	DNAJB8	In CSCs/CISs of colorectal cancer; Oxaliplatin-resistant CRC cells	Colorectal cancer	Preferentially expressed in CSCs/CISs of CRC; involved in tumor formation, SP cell proportion, and tumor initiation; Promotes Oxaliplatin resistance through the TP53/mdr1 pathway	Morita et al., 2014; Wang et al., 2022
MRJ	DNAJB6	In vitro human colorectal cancer cells; CRC patient study	Colorectal cancer	Poor prognostic factor in CRC patients and is overexpressed in CRC patients	Zhang et al., 2015
HDJ1	DNAJB1	In vitro human prostate cancer cells	Prostate cancer	DNAJB1 inhibition destabilizes the glucocorticoid receptor in Castration-resistant prostate cancer	Moses et al., 2018
HDJ2	DNAJA1	Tested in the two PDAC cell lines BxPC-3 and MIA-PaCa-2	Pancreatic cancer	Results in weaker cytosolic lysosomal membranes, reduced actin formation, and increased cell invasiveness	Agarwal et al., 1995; Stark et al., 2014; Roth et al., 2021
HLJ1	DNAJB4	In vitro human lung adenocarcinoma cell: NSCLC patient study	Lung	Tumor suppressor in NSCLC; Suppressed invasion by upregulating E-cadherin in lung cancer cells	Chen et al., 2008; Liu et al., 2014, Forouzanfar et al., 2019
MCJ	DNAJD1	Studied in childhood brain tumors of humans	Brain	Hypermethylation in medulloblastomas, stPNETs, and ependymomas	Lindsey et al., 2006
ERDJ3	DNAJB11	Tested in 293-K1 and 293-Vec stable cells	Kaposi sarcoma	Viral oncoprotein chaperone, promotes tumorigenicity	Wen and Damania, 2010
ERDJ5	DNAJC10	Studied in glioma cell lines and clinical samples	Glioma	Poor prognostic factor in glioma patients and is overexpressed in glioma patients	Liu et al., 2022

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