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REVIEW

# Expression and function of FRA1 protein in tumors

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**Abstract**
AP-1 is a dimeric complex that is composed of JUN, FOS, ATF and MAF protein families. FOS-related antigen 1 (FRA1) which encoded by *FOSL1* gene, belongs to the FOS protein family, and mainly forms an AP-1 complex with the protein of the JUN family to exert an effect. Regulation of FRA1 occurs at levels of transcription and post-translational modification, and phosphorylation is the major post-translational modification. FRA1 is mainly regulated by the mitogen-activated protein kinases signaling pathway and is degraded by ubiquitin-independent proteasomes. FRA1 can affect biological functions, such as tumor proliferation, differentiation, invasion and apoptosis. Studies have demonstrated that FRA1 is abnormally expressed in many tumors and plays a relevant role, but the specific condition varies from the target organs. FRA1 is overexpressed in breast cancer, lung cancer, colorectal cancer, prostate cancer, nasopharyngeal cancer, thyroid cancer and other tumors. However, the expression of FRA1 is decreased in cervical cancer, and the expression of FRA1 in ovarian cancer and oral squamous cell carcinoma is still controversial. In this review, we present a detailed description of the regulatory factors and functions of FRA1, also, the expression of FRA1 in various tumors and its function in relative tumor.

**Keywords** FRA1 · Cancer · AP-1

## Introduction

In 1988, Cohen DR and Curran T isolated a new cDNA by screening rat c-DNA libraries with *FOS* DNA probe. This gene is very similar to *FOS* and is named *FOSL1*. *FOSL1* encodes a protein (FOS-related antigen 1, FRA1) of 275 amino acids. With the ability to induced rapidly by serum in the presence of protein synthesis inhibitors, *FOSL1* is considered as cellular immediate-early gene [1]. Subsequently, they went further and found that the FRA1 protein is localized in the nucleus and cytoplasm, and is mainly modified by post-translational phosphorylation. Like c-FOS, FRA1 can bind to JUN to recognize the AP-1 site [2]. By the same method, Matsui et al. confirmed the existence of *FOSL1* in human cells in 1990, which is 90% similar with rat *FOSL1* gene [3]. Since then, a large number of researches on FRA1 have been published.

In this review, we summarize the regulatory factors and functions of FRA1, especially its expression and corresponding functions in tumors.

## AP-1 and FRA1

The *FOSL1* gene is located at the 11q13 locus, which encodes the FRA1 protein consisting of 271 amino acids. FRA1 belongs to the FOS protein family, and other members of the family include c-FOS, FOSB, and FRA2. FOS is an important member of the transcription factor AP-1. AP-1 is a dimeric complex that is composed of the JUN (c-JUN, JUNB, JUND), FOS, ATF (ATF1–4, ATF-6, b-ATF, ATFx) and MAF (c-MAF, MAFA, MAFB, MAFG/F/K, and NRL) protein families [4, 5]. In mammals, AP-1 is mainly composed of JUN and FOS. Among them, FOS can only form JUN-FOS heterodimer with JUN, but JUN itself can also form JUN–JUN homodimer. The formation of AP-1 dimer is dependent on the basic leucine zipper (bZIP) domain on JUN and FOS, which also binds to DNA, while AP-1 can regulate target genes through this bZIP domain by binding to the TRE (TGAC/GTCA), a specific DNA sequence on the promoter or enhancer of target genes, thereby affecting

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the proliferation, differentiation, invasion and apoptosis of tumor cells [6, 7]. In addition, the bZIP domain of FRA1 is located at 115–168 region.

The FOS family has the highly homologous bZIP domain, but compared to c-FOS and FOSB, FRA1 and FRA2 lack a C-terminal transactivation domain and are therefore considered to be poor activators of transcription [8]. Even, since FRA1 can inhibit the expression of c-FOS from the promoter level and inhibit c-FOS-mediated transcriptional activation, it is considered to be a repressor of AP-1 transcriptional activity [9, 10]. In turn, other members of AP-1 can upregulate *FOSL1* transcriptional activity by binding to its promoter [11].

## Regulation of FRA1

### Regulation of FRA1 by post-translational modification

The regulation of FRA1 expression is multifaceted. In addition to the transcriptional regulation of other members of AP-1 and some upstream genes (i.e. *PI3K*, *WNT3a*, *STAT3*, *SIRT1*) [12–15], FRA1 is also regulated by itself. Early studies have used 12-*O*-tetradecanoylphorbol-13-acetate (TPA) to stimulate bronchial epithelial cells and found that the transcriptional activation of *FOSL1* is associated with multiple cis-elements of itself (EBS, a GC box, and TRE) [11], While the transcript elongation of *FOSL1* is the result of a series of reactions triggered by the phosphorylation of the serine 10 at histone H3 on *FOSL1* enhancer [16].

In all regulation of FRA1, post-translational phosphorylation is crucial.

The common phosphorylation sites of FRA1 are at serine and threonine residues, of which S265 and S252 are the most important. Phosphorylation of FRA1 in the C-terminal tail at S265 and S252 can neutralize its degradation while favouring its stabilization [12, 17]. And also, PKCθ-induced phosphorylation of FRA1 at T217 and T227 can enhance its transcriptional activity [18]. In addition, T223, T230 and T240 are also phosphorylation sites of FRA1, but their influence on FRA1 is not as critical as S265 and S252 [17].

FRA1 can be phosphorylated by some kinases, such as mitogen-activated protein kinase (MAPK), protein kinase C (PKC), cAMP-dependent kinase (PKA), and cyclin-dependent kinase 1-cdc2 (CDC2) [19]. FRA1 is directly phosphorylated by MAPKs, and occasionally MAPKs also indirectly regulate FRA1 phosphorylation by RSK1/2 [17]. ERK1/2 and Ste20-related proline-alanine-rich kinase (SPAK) are two mechanisms of PKCθ-induced phosphorylation of FRA1 [20]. PKCα can significantly up-regulate the phosphorylation level of FRA1 without affecting the total FRA1 level [21].

In addition to phosphorylation, FRA1 has other post-translational modifications. With the help of the HDAC6 deacetylase, IL6/STAT3 axis can deacetylate the lys-116 residue of FRA1, and ending with the acquisition of stemness in colon cancer cell [22].

## Degradation of FRA1

As a transcription factor protein, FRA1 itself is an unstable protein with a short half-life, and its instability is caused by a single destabilizer located within 30–40 amino acid residues at the C-terminus [17, 23]. The degradation of FRA1 mainly relies on ubiquitin-independent proteasome action. First, the ubiquitin-independent proteasome recognition is initiated by the 19S proteasome subunit-TBP1, and the subsequent proteolytic process is performed by the C-terminal degron [24].

In addition to reducing the degradation of FRA1 by down-regulating the expression level of TBP1, its stability is enhanced mainly by its phosphorylation, as we mentioned above.

### Regulation of FRA1 by MARKs pathway

Among the upstream regulatory pathways of FRA1, MAPKs pathway topped the list. As mentioned above, phosphorylation and transcriptional activity of FRA1 are mainly dependent on MAPKs. In mammals, there are at least four different MAPK signaling pathways: extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 MAPK and ERK5 [25].

The MAPK pathway is a tertiary cascade reaction consisting of MAPKKK–MAPKK–MAPK. When the external stimulus such as growth factors stimulate cells, it can trigger the activation of the proto-oncogene *RAS*, thereby affecting the downstream *RAF* gene and activating the MEK1/2-ERK1/2 pathway. Low level of ERK-MAPK activity mainly regulates the transcription of the *FOSL1* gene, while a higher level of ERK activity increase FRA1 accumulation by phosphorylating it and preventing its proteasome-dependent degradation [26]. Moreover, recent studies have further revealed that the production rate of FRA1 protein has a linear relationship with the total activity of ERK, and there is also a linear relationship between the total expression levels of FRA1 with the duration of ERK activity [27]. To remove the effects of exogenous stimuli, mutations in the proto-oncogenes *RAS* and *RAF* are themselves very common in the development of tumors. However, this is not the only way, *RAS* can also activate FRA1 by triggering the PI3K/AKT pathway [12]. The regulation of FRA1 by PKC is divided into RAS/ERK-dependent pathway and non-RAS/ERK-dependent pathway [20]. However, when external stimuli are stress signals, inflammatory factors, etc., the activated MAPK pathway is

not RAS/ERK, but MLKs, MEKKs, TAK1 and ASK1, some of them activate p38 through MKK3/6, and the other activates JNK1/2/3 through MKK4/7, the expression of FRA1 is then regulated [28] (Fig. 1).

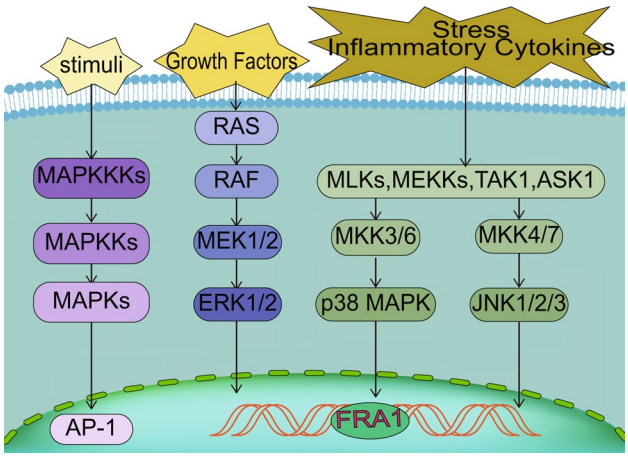


**Fig. 1** Regulation of FRA1 by MARKs pathway. FRA1 is mainly regulated by MAPKKK/MAPKK/MAPKs signal pathways, and different exogenous stimuli activates different MAPK pathways. Growth factors activate ERK1/2 pathway, whereas stress signals and inflammatory factors activate JNK/p38 MAPK signaling pathway

## Regulation of FRA1 by microRNAs

MicroRNAs (miRNAs) are a class of endogenous small RNAs with approximately 22 nucleotides that have a variety of important regulatory roles in cells. Recently, many miRNAs have been shown to inhibit tumorigenesis by down-regulating FRA1 expression. These include but not limited to the miR-19a/b in breast cancer and cervical cancer [29, 30], miR-138 in squamous cell carcinoma [31], miR-497 in colorectal cancer [32], miR-130a in breast cancer [33], miR-195 in prostate cancer [34], miR-34 in breast cancer and colon cancer [35, 36] (Fig. 2). Based on the role of miR-34 in breast cancer, researchers have found a nanohybrids targeted miR-34a could inhibit tumor growth in vivo [37]. These miRNAs modulate FRA1 expression through directly bind the seed sequence of itself to its partially complementary seed match sequence in the 3′ untranslated region (UTR) of *FOSL1*. However, miR-138 was found to bind not only to the 3′UTR of *FOSL1* but also to its 5′UTR and coding sequences (CDS). Canonical and non-canonical targeting sites work together to inhibit FRA1 expression [38]. In contrast, certain miRNAs are also FRA1-targeting genes. FRA1 can indirectly affect the expression of ZEB by regulating the transcription of miR-221/222 [39]. In ovarian cancer, up-regulation of FRA1 can increase the expression

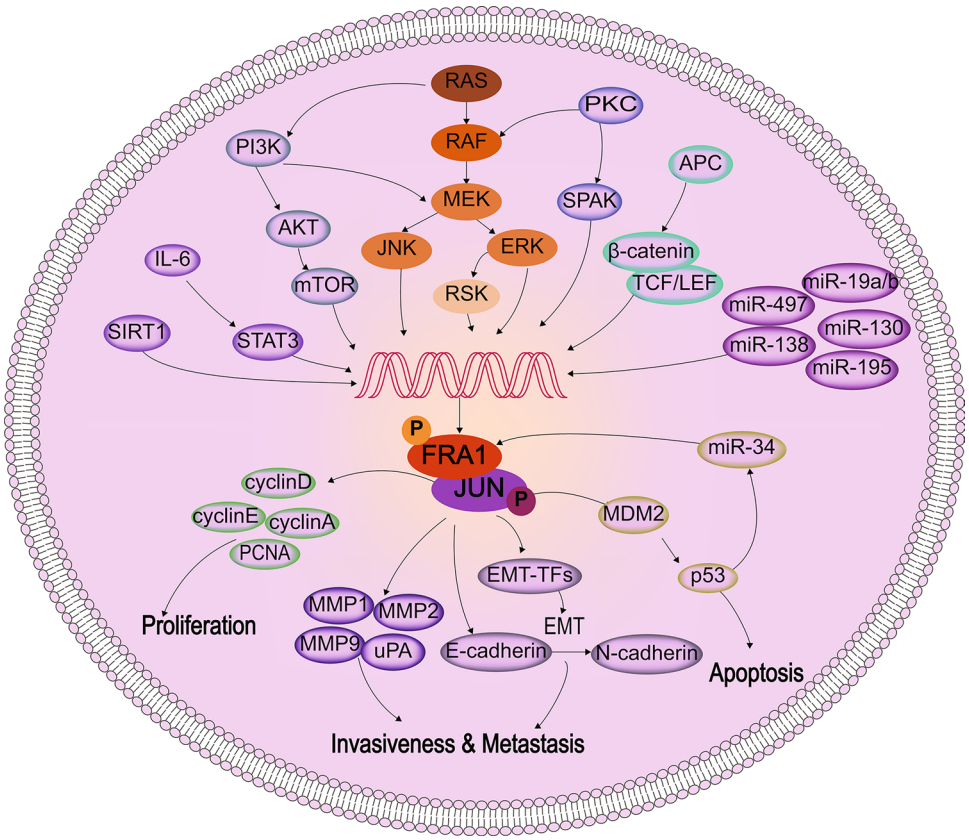


**Fig. 2** Regulation and functions of FRA1 in tumor. Fra-1 is primarily regulated by transcriptional levels and post-translational phosphorylation and plays a crucial role in tumor progression. The RAS/RAF pathway, PKC, PI3K, WNT/APC, IL-6/STAT3, SIRT1 and miRNAs can all regulate the transcription and post-translational phosphorylation of FRA1. p-FRA1 and p-JUN form heterodimers, which then affect tumor proliferation by regulating cycle-associated proteins, affect tumor invasion and metastasis through MMPs and EMT-TFs, and affect tumor apoptosis through p53 pathway

level of miR-134 and enhance the chemotherapy resistance of ovarian cancer [40].

## The expression of FRA1 in tumors

At first, the researchers thought that FRA1 is involved in embryonic development and bone formation. Later, more and more studies have confirmed that FRA1 is abnormally expressed in many tumors, which plays an important role in tumorigenesis and progression. So far, studies on FRA1 have covered tumors of almost all parts of the body, such as breast cancer, colorectal cancer, lung cancer, cervical cancer, ovarian cancer, skin cancer, melanoma, and esophageal cancer. Interestingly, the abnormal expression of FRA1 in various tumors and its effect on tumors vary depending on the type of tumor [14, 34, 40–71] (Table 1).

## Breast cancer

Breast cancer is the most common malignant tumor among Chinese women and the leading cause of death among women under 45 years of age in all tumors [72]. Among the cancer in female worldwide, the diagnosis rate and mortality rate of breast cancer have exceeded lung cancer and ranked No. 1 [73], which seriously threatens women's health and life. Among all the tumors that have been studied for FRA1, breast cancer was the most studied.

**Table 1** The expression of FRA1 in different types of tumor

| Tumor types | The expression level | | Biological functions | Pathways | References |
|---|---|---|---|---|---|
| | Cancerous tissues and Paracancerous tissues | Cancerous tissues and benign/normal tissues | | | |
| Breast cancer | – | Up | Diagnose | – | [41, 42] |
| Breast cancer | Up | – | – | – | [43] |
| Lung cancer | – | Down | – | – | [44] |
| Lung cancer | Up | – | Apoptosis | MDM2/p53 | [45] |
| Colorectal cancer | – | Up | – | β-catenin | [46] |
| Colorectal cancer | Up | – | Aggressiveness | IL-6/STAT3 | [14] |
| Cervical cancer | Down | – | – | – | [47] |
| Cervical cancer | Down | – | Apoptosis | p53 | [48] |
| Ovarian cancer | – | No difference | – | – | [49] |
| Ovarian cancer | – | up | Proliferation, migration, invasion | miR-134 | [40] |
| Prostate cancer | – | Up | Invasion | miR-195-5p | [34] |
| Prostate cancer | Up | – | Proliferation, metastasis | – | [50] |
| Head and neck squamous cell carcinomas | Up | – | – | – | [51] |
| Oral squamous cell carcinoma | – | Down | – | – | [52] |
| Tongue cancer | – | Down | Proliferation | – | [53] |
| Thyroid carcinoma | – | Up | – | – | [54–56] |
| Skin cancer | – | Up | – | – | [57] |
| Bladder cancer | – | Up | Motility | AXL | [58] |
| Endometrial cancer | – | Up | Proliferation | p21 | [59] |
| Pancreatic ductal adenocarcinoma | – | Up | Migration, invasion, metastasis | MUC1 | [60] |
| Pancreatic ductal adenocarcinoma | – | Up | Proliferation | AURKA | [61] |
| Hepatocellular carcinoma | Up | – | Vascular invasion | – | [62] |
| Hepatocellular carcinoma | Up | – | Proliferation | – | [63] |
| Gastric cancer | Up | – | Proliferation, invasion | PI3K, p53 | [64] |
| Gastric cancer | Up | – | – | – | [65] |
| Melanoma | – | Up | Proliferation, invasion | HMGA1 | [66] |
| Esophageal squamous cell carcinoma | Up | – | – | – | [67, 68] |
| Malignant mesothelioma | – | Up | Invasion | CD44 | [69] |
| Glioblastoma multiforme | – | Up | – | – | [70] |
| Osteosarcoma | Up | – | Proliferation, migration, invasion | ERK/p38 | [71] |

Very early studies have found that FRA1 is highly expressed in breast cancer and plays an important role in the malignant progression of breast cancer. However, due to the differences in hormone receptor levels, there are still some differences in the expression levels and functions of FRA1 in different subtypes of breast cancer. In vitro, compared to less aggressive, estrogen receptor-positive (ER+) breast cancer cell line MCF7, highly invasive breast cancer cell lines MDA-MB231, BT549 and HS578T that are estrogen receptor-negative (ER−) have a higher expression level of FRA1 [74]. In vivo, the researchers confirmed that the expression of FRA1 was enhanced with the severity of the lesions through a large number of clinical specimens [42], and was negatively correlated with the patient's distant metastasis survival and overall survival [75]. At the meantime, compared with the normal tissues adjacent to the cancer, the expression of FRA1 in cancer tissues was found to be higher than that in the adjacent tissues.

According to the further analysis of the subtypes, it was found that FRA1 expression is only slightly increased in the HER-2 type, while the expression in the basal like type is increased significantly compared with the luminal type [43, 76]. Similar results were also obtained in Oliveira-Ferrer. L's study: ER- patients had higher FRA1 expression level than ER+ patients, and their survival was generally shorter than ER+ patients. Moreover, it was reported that the prognosis was significantly correlated with the level of FRA1 expression between ER+ patients, but there is no correlation between ER− patients [77]. However, unlike above studies, a recent study found that FRA1 can be used as a clinical outcome indicator for ER− breast cancer patients: the ER− patients with a higher expression level of FRA1 showed a shorter overall survival, but which was not found in ER+ breast cancer. In addition, the study also found that triple-negative breast cancer (NTBC) cells have a higher expression level of FRA1 than ER+ cells due to the presence of more enhancers on *FOSL1* sequence [78]. By copy number analysis of the DNA extracted from tissues, it was found that the copy number alterations of *FOSL1* in NTBC was significantly higher than that in luminal and HER2+ [79]. Moreover, as an oncogenic coactivator of FRA1, DDT5 can enhance the transcriptional activity of *FOSL1* and the proliferative effect of it. Like FRA1, DD5 is expressed more highly in TNBC than other subtypes [80]. Similarly, the architectural chromatin protein HMGA1 is also highly expressed in TNBC, and FRA1 can recruit RNA Polymerase II to its promoter by binding to its enhancer, promoting its transcription and malignant effects on TNBC [81]. To some extent, this explains why FRA1 has different effects in different breast cancer cells, but how this variation which depends on hormone receptor level produced has not been further studied.

## Lung cancer

As the cancer with highest morbidity and mortality in the world, lung cancer accounts for 11.6% of all cancer patients, and accounts for 18.4% of total cancer deaths. It is the leading cause of cancer death in men and ranks third among women [73].

*KRAS* is one of the most common mutations in non-small cell lung cancer (NSCLC). *KRAS* can regulate FRA1 through ERK1/2, ERK5 and JNK [61]. *KRAS* can also activate the PI3K-mTOR pathway. In general, the combination of inhibitors for two pathways is used as a treatment for this mutation [82]. In vivo, FRA1 participates in *KRAS*-induced lung cancer, by regulating the anti-oxidation and anti-apoptosis-related genes. The FRA1 deficiency mice reduce the mutant *KRAS*-induced lung tumorigenesis and show a longer survival time [83].

It is well realized that many environmental factors such as smoking, silica, asbestos, and DEP are high risk factors for causing lung cancer. The effect of these risk factors on lung cancer is closely related to FRA1 [84, 85]. For example, smoking can promote the expression of FRA1 by stimulating the MMPs-EGFR-ERK/JNK/p38 pathway of lung epithelial cells, thereby promoting the development of lung cancer [86]. EGFR-associated FRA1 expression which stimulated by smoking can also be regulated by the PI3K-PAK1-MEK1/2-ERK1 pathway, without the involvement of AKT [87]. Smoking can induce c-JUN/FRA1 to bind to the promoter of *SPRR3* and promote its upregulation, while *SPRR3* is an indicator of pathogenic keratinization [88]. Besides, smoking can also synergize with Nanoceria on FRA1 to enhance the growth and migration of lung cancer cells [89]. Asbestos can change the redox state of cells by regulating the glutathione, promoting the phosphorylation of ERGF, and then induce the expression of FRA1 [90].

## Colorectal cancer

So far, the mortality of colorectal cancer ranks second in the world. It has been estimated that more than 860,000 patients worldwide will die from colorectal cancer in 2018 [73].

Although the expression level of FRA1 in tumor tissues is higher than that in normal tissues, it is not essential for growth and proliferation of proto-oncological lesions. The regulation of FRA1 on colorectal cancer is mainly manifested in the invasion and metastasis ability of cancer [91].

The effect of FRA1 on the invasiveness of colorectal cancer can be reflected by the results of IHC: FRA1 is

not stained in normal epithelial cells and strongly stained in the nucleus of cancer cells, and its staining in marginal cancer cells with invasiveness and inflammation is stronger than the center of lesion. Moreover, it has been found that FRA1 staining in liver metastases is stronger than the primary lesion [14, 92].

## Cervical cancer

Cervical cancer has the highest incidence and death in female genital malignant tumors [73]. Unlike the tumors mentioned above, FRA1 has been shown to be lowly expressed in cervical cancer, inhibiting the malignant phenotype of cervical cancer cells.

Cervical cancer is one of the few cancers with a clear cause to date, and human papillomavirus (HPV) (especially HPV16/18) infection is the leading cause of cervical cancer. The oncoproteins E6 and E7 play a key role in the malignant progression of HPV-induced cervical cancer. In the process of HPV-induced cervical cancer formation, reorganization of AP-1 dimer (FRA1 down-regulation and c-FOS up-regulation) plays an important role [93]. Similarly, in HPV infection-associated tongue cancer, by FRA2 knockdown, the researchers found that FRA1 and p53 were up-regulated, while MMP9, cyclinD and HPV E6/E7 were down-regulated, suggesting that FRA1 has anti-tumor effects [53]. In HPV-positive (higher AP-1 activity) esophageal cancer, FRA1 expression is also very low, while FRA1 is highly expressed in HPV-negative esophageal cancer. Unlike in cervical cancer, FRA1 promotes the progression of esophageal cancer [68], which maybe the interaction of HPV and FRA1 in esophageal cancer is not dominant. Therefore, the effect of FRA1 on HPV-associated tumors is associated with host cell types. How HPV infection affects the biological behavior of related tumor cells through FRA1 still needs further exploration.

## Ovarian cancer

Although the incidence of ovarian cancer is not high compared to other gynecological malignancies, the degree of malignancy is the first in gynecological malignancies. Late diagnosis and treatment resistance are the two major causes of high mortality in ovarian cancer. The common chemotherapy regimen for ovarian cancer is the addition of paclitaxel to platinum, but patients eventually die due to chemotherapy resistance and cancer recurrence [94].

At present, there are few studies on FRA1 and ovarian cancer, and there is no unified recognition of the expression and specific effects of AP-1 and FRA1 in ovarian cancer. Oleg I Tchernitsa et al. found that the expression level of FRA1 in ovarian epithelial cells of rat with *KRAS* mutation was significantly increased. It has been demonstrated that silencing of FRA1 reverses some of the growth-promoting effects caused by *KRAS* mutations [95]. However, S Mahner et al. found that c-FOS is an independent factor for ovarian cancer, but not FRA1. Decrease of c-FOS expression can promote ovarian cancer progression and reduce progression-free survival and overall survival in patients [96], which was consistent with subsequent findings that c-FOS is beneficial for the prognosis of ovarian cancer, and overexpression of c-FOS can promote tumor cell apoptosis [97]. However, a recent study indicated that TGF-β induced the development of ovarian cancer by stimulating the c-FOS/c-JUN via the MAPKs pathway [98]. S Mahner et al. compared the expression levels of AP-1 in benign ovarian tumors, borderline ovarian cancer and malignant ovarian cancer. It was found that the JUN family was generally more highly expressed in malignant tumors than benign tumors. Whereas there was no significant difference in the expression level of FRA1 in ovarian specimens with different malignant degrees (including benign tumors). Although the number of specimens used in the study was small, the results of in vitro experiments also showed that there was no significant relationship between the expression level of FRA1 and the proliferation, invasion and metastasis of ovarian cancer cells [49].

## Other tumors

In liver cancer, the expression of FRA1 is positively correlated with the level of alpha fetoprotein (AFP) and the degree of vascular invasion [62]. The high expression of FRA1 corresponds to the poor prognosis of liver cancer, suggesting that FRA1 can be used as a prognostic biomarker for liver cancer [63]. As the fifth most common cancer worldwide, the incidence of gastric cancer has a clear regional difference. China is a region with high incidence of gastric cancer. Studies have shown that this is related to a functional single nucleotide polymorphisms (SNPs) rs1892901 in *FOSL1*, which can enhance the expression of FRA1 and promote the development of gastric cancer [99]. Recent study has found that the expression of FRA1 is regulated by *Helicobacter pylori* and plays an important role in the development of *Helicobacter pylori*-mediated gastric cancer [100]. The oncoprotein TAX encoded by *HTLV-1* is critical for the development of adult T cell leukemia (ATL), and previous studies have found that TAX can affect the transcription of *FOSL1* [101]. Recent studies have revealed that this is associated with TAX-induced activation of the PI3K/AKT-AP-1 pathway [5]. Cigarette smoke can activate the expression of FRA1 via CHRNA7 signaling, allowing it to bind to the promoter of the RNA polymerase II-associated factor, thereby inducing stem cell features in pancreatic cancer cells [102].

Similar to ovarian cancer, the expression of FRA1 in oral squamous cell carcinoma is also controversial. The positive rate of FRA1 in oral squamous cell carcinoma specimens was initially found to be lower than that in normal tissues [52], which was consistent with the results obtained by Gupta et al. in tongue cancer specimens [53]. However, through in vitro experiments, it was found that Yes-associated protein can promote the proliferation and invasion of oral squamous cell carcinoma cells by activating FRA1. And the results of IHC also showed that the expression of FRA1 in the edge of the invasive tumor was higher than that within the tumor [103]. Similarly, recent studies have also indicated that the expression of c-FOS is higher in normal tissues than in cancer, and the overexpression rate of FRA1 is elevated with the increased degree of malignancy and variation of clinical classification, along with the loss of c-FOS. The high expression of FRA1 is negatively correlated with the 5-year survival of patients [104, 105].

## Role of FRA1 in tumor

### Proliferation

FRA1 can directly regulate the expression of cell cycle-related protein, including cyclin-dependent kinases (CDKs) and cyclins to promote mitotic progression, thereby promoting cell proliferation (Fig. 2). Early studies analyzed the relationship between the seven members of the AP-1 family and cell cycle-associated proteins, and found that the predominance expression of FRA1, similar to FRA2, c-FOS and JUND, can lead to G1-S transition. Moreover, FRA1 expression level is closely related to the expression of cyclinE and p16 [106]. i.e. Silica can increase the expression of FRA1 and the accumulation of lung epithelial cells in S phase [107]. Similarly, in gastric cancer, FRA1 overexpression can increase DNA synthesis and promote cell proliferation by accumulate cancer cells in S phase [64]. In osteosarcoma, the knockdown of FRA1 can significantly down-regulate the expression of cyclinD1 and cyclinD3, and decrease the G1-S phase conversion rate [71]. In thyroid cancer, FRA1 can bind to the promoter of *ACCNA2* (encodes cyclinA) and convert cell from G2 to M phase. When the expression of FRA1 is decreased, most of the cells are retained in G2 phase, while parts of them continuation of mitosis, but ended in failure [108]. In oral squamous cell carcinoma and esophageal squamous cell carcinoma, proliferation is associated with overexpression of FRA1 and its downstream cyclinD [103, 109]. In malignant mesothelioma, HGF-induced cell proliferation is mainly due to increased expression of proliferating cell nuclear antigen (PCNA) caused by FRA1 [110]. The growth-promoting effect of UBE2N, a K63-specific ubiquitin conjugase, on melanoma is also closely related to the activation of MEK/FRA1 pathway [111]. As for breast cancer, in addition to directly affecting the expression of CDKs, cyclinD, and cyclinE, by using ChIP-qPCR, the researchers also found that FRA1/c-JUN can bind to the third intron of *CLCA2*, a gene negatively-associated with proliferation, and decrease its expression, promote cell proliferation [112]. The anti-proliferation effect of psoralen on breast cancer cells is due to the up-regulation of Axin2 and the down-regulation of FRA1 expression, resulting in G0/G1 phase and G2/M phase arrest in MCF-7 cells and MDA-MB-231 cells, respectively [113]. In neuroblastoma and nasopharyngeal carcinoma, cell proliferation is also performed by the c-JUN/FRA1 complex [114, 115]. However, in gliomas and cervical cancers, overexpressed FRA1 inhibits the proliferation of related cells [48, 116]. In prostate cancer, dihydrotestosterone can increase the proliferation of androgen receptor (AR)-positive LNCaP cell line by up-regulating the expression of FRA1, but has no effect on AR-negative PC-3 cell line, thus inferring the hormonal sensitivity of target organs maybe join in the relationship between FRA1 and cell proliferation [117].

### Invasiveness and metastasis

The metastasis of cancer cells is an important feature of malignant tumors, and is also the main cause of inability to perform surgery, as well as death in cancer patients. The occurrence of epithelial-mesenchymal transition (EMT) is a key step in cancer invasiveness and metastasis [118]. The effect of FRA1 on tumor invasion and metastasis is mainly achieved by regulating the expression of EMT- inducing transcription factors (EMT-TFs) and matrix metalloproteinases (MMPs) (Fig. 2).

For breast cancer, its strong invasiveness is closely related to FRA1. FRA1 can directly bind to the promoters of *PLAU* (encoding uPA) [74], *MMP1* [119] and *MMP9* [120], promoting the aggressiveness and non-adherent growth of cancer cells. Through the MLK3-KO human cell lines tested by murine xenografts, the researchers also found that the MLK3-ERK/JNK-FRA1-MMP1/9 signal cascade existed not only in the primary tumor but also in the circulating tumor cells, which was of great significance for the distant metastasis of cancer cells [121]. Radix Glycyrrhiza is used for the treatment of breast cancer because its main component Glycyrrhetinic acid (GA) can inhibit the FRA1/MMPs signal axis, but the main pathway of action is the p38MAPK/FRA1 pathway [122]. Studies have confirmed that FRA1 is involved in the EMT process of ER- breast cancer by direct binding to the promoters of *ZEB1* and *ZEB2* [75, 112]. FRA1 can also affect the expression of SLUG by targeting TGFβ [75], and inhibit E-cadherin, promoting EMT process. MiR-130a inhibits the EMT process of MDA-MB-231 cells by up-regulating the expression of ZO-1 through inhibition of *FOSL1* transcription [33]. In addition, recent studies have found that FRA1 is involved in the process of

CD137-induced monocyte/macrophages migration to the tumor microenvironment and differentiation into osteoclasts, of which favors bone metastasis [123].

The effect of FRA1 on invasiveness of lung cancer is correlated to the enhanced phosphorylation of EGFR mediated by stimulation of MMP2 and MMP9 by FRA1, and MMPs can also form a positive feedback loop with ERK to further promote the expression of FRA1 [124]. In *KRAS*-mutant lung cancer, even newly discovered molecular targets, such as differentiation-1, promote lung cancer progression and liver metastasis by regulating the level of FRA1 [125].

By using bioinformatics analysis, it has been found that six easily mutated genes (*APC*, *KRAS*, *BRAF*, *PIK3CA*, *SMAD4* and *p53*) in colorectal cancer are associated with invasiveness and metastasis [126]. FRA1 is involved in the regulation of colorectal cancer cell invasion by these genes. Moreover, FRA1 can form a complex with c-JUN and galectin3, and further bind to the promoter of *MUC2* to regulate its transcription, thereby enhancing the invasiveness of colorectal cancer [127]. FRA1 is involved in the effects of IL-6/STAT3 and SIRT1 on EMT processes in colorectal cancer cells [14, 15]. Studies have found that FRA1 can bind to the promoter of *vimentin*, directly promoting the expression of vimentin with interstitial cell characteristics [128].

In prostate cancer, FRA1 enhance cell metastasis by upregulating N-cadherin and SNAIL and downregulating E-cadherin [50]. In pancreatic cancer, FRA1 promotes EMT and metastasis of tumor upon the stimulation of MUC1 [60]. Moreover, the carcinogen benzidine can promote EMT of bladder cancer cells via ERK5-AP-1 (c-FOS, c-JUN, FRA1) [129]. It has been shown that the formation of complex between αB-Crystallin and 14-3-3ζ protein can promote EMT of liver cancer cells via KRAS-RAF-MEK1/2-ERK1/2-FRA1-SLUG pathway, as well as the resistance production of cancer cells to Sorafenib [130]. *CTHRC1* is one of the most highly expressed genes in esophageal squamous cell carcinoma. It can activate FRA1 through RAF-MEK1/2-ERK1/2, and then up-regulate SNAIL, MMP14 and HMGA1 to promote invasion of cancer cells [109, 131]. The EB virus-encoded latent membrane protein (LMP) is an important cause of nasopharyngeal carcinoma. LMP2A and LMP1 can promote the phosphorylation of FRA1/c-JUN through ERK, thereby activating MMP9 and promoting the invasion of nasopharyngeal carcinoma cells [132]. In addition, LMP1 can also activate the upstream pathway of FRA1, PI3K pathway [115].

The most common mutated gene in melanoma is *BRAF*. If the tumor suppressor gene *PTEN* is also silenced, HMGA1 expression can be induced by BRAF-ERK1/2-FRA1 and PI3K-AKT-mTOR-FRA1 pathways, resulting in down-regulation of MITF/AXL ratio, which finally lead to the melanocyte reprogramming and transformation [66, 133]. NRAS/BRAF pathway can induce the conversion of melanocytes into malignant melanoma cells by reorganization of EMT-TFs, that is the conversion of SNAIL2, ZEB2 to TWIST1 and ZEB1. The dedifferentiation and malignant switch are FRA1-dependent [134].

## Apoptosis

Although the relationship between FRA1 and tumor cell apoptosis varies greatly from tissue to tissue, it is closely related to the p53 pathway (Fig. 2). In lung cancer cells, elevated FRA1 can inhibit p53 and up-regulate the level of its negative regulator MDM2, ultimately inhibiting the apoptosis of lung cancer cells by enhancing apoptosis-related mitochondrial membrane potential ($\Delta\Psi m$) and down-regulating intracellular ROS and aggregation of $Ca^{2+}$ [45]. On the contrary, the expression of p53 in cervical cancer is consistent with FRA1, and overexpression of FRA1 can promote apoptosis of cancer cells through p53 [48]. So far, what caused this difference between organizations has not yet been elucidated.

## Treatment resistance

According to different treatment methods, tumor resistance can be divided into radiotherapy resistance and chemotherapy resistance.

As mentioned above, *BRAF* is one of the common mutation genes in colorectal cancer, and patients with $BRAF^{V600E}$ mutations often resist to the MEK1 inhibitor, Selumetinib. The reason is that a key protein CEMIP links the WNT pathway to the MEK1-ERK1/2 pathway, whereas CEMIP expression is induced by β-catenin- and FRA1-dependent pathways [135]. In addition, high expression of FRA1 is also associated with the formation of radiotherapy resistance in colorectal cancer [136].

The radiotherapy resistance of prostate cancer is related to the activation of EGFR and PI3K. Both pathways can increase the expression of AP-1 and enhance prostate cancer cells resistance to radiation [137].

In the treatment of cervical cancer, curcumin is considered a good anticancer agent. The use of curcumin before radiotherapy can increase the activity of ERK1/2 and ROS production, and enhance the radiosensitivity of cervical cancer [138]. Recent studies have confirmed that the radiosensitizer behavior of turmeric is related to its inhibition for AP-1 DNA binding activity and stimulation of AP-1 reorganization, i.e. down-regulation of c-FOS and up-regulation of FRA1 [139]. In other words, FRA1 has a radiosensitizing effect on cervical cancer.

In liver cancer cells, the formation of complex between αB-Crystallin and 14-3-3ζ protein can promote EMT of

cells via KRAS-RAF-MEK1/2-ERK1/2-FRA1-SLUG pathway, as well as the resistance production of cancer cells to Sorafenib [130]. In melanoma cells, PI3K/FRA1 is involved in the regulation of FGF1 secretion associated with BRAF inhibitor resistance, providing a basis for the combined application of FGF1 inhibitor and BRAF inhibitor [140].

For ovarian cancer, a study about miR-134 showed that the mRNA level of *FOSL1* was higher in cancer than in normal ovaries and positively correlated with the expression of miR-134. In the case of *HRAS* mutation, the JNK/ERK-FRA1-miR-134-SDS22-JNK/ERK-FRA1 positive feedback loop promotes the proliferation of tumor cells, enhances the chemotherapy resistance of ovarian cancer cells to doxorubicin, and reduces the median survival time of patients [40]. Similarly, cellular studies have shown that occurrence of JQ1 resistance during the treatment of BRD4-associated ovarian cancer cell is due to the activation of RTK-PI3K-AKT and RTK-PI3K-ERK-c-Myc/FRA1 pathways, suggesting that c-MYC/FRA1 can promote the growth of ovarian cancer cells in vitro [141]. Later, the team further studied that the FRA1-related RTK-RAF and RTK-PI3K pathways were also involved in the chemoresistance of MEKi [142]. Furthermore, as the most commonly used chemotherapy drug for ovarian cancer, studies have confirmed that cisplatin resistance is associated with abnormal expression of FRA1. FRA1 participates in ROS-IL-11-JAK2-STAT5-mediated cisplatin resistance by directly binding to the promoter of IL-11 [143].

Similar to ovarian cancer, c-MYC/FRA1 is associated with chemotherapy resistance of mesothelioma. A combination of JQ1 and cisplatin can promote tumor cell apoptosis by affecting FRA1/c-MYC in vitro [144], while trametinib can down-regulate FRA1 and CD44 by inhibiting ERK phosphorylation and elicit anti-tumor effect [145].

In summary, FRA1 has an effect on tumor radioresistance and chemoresistance, which may provide some ideas for future combination therapy. However, we also noticed that although FRA1 serves as a hub for many classical pathways and plays an important role in tumors, there are currently no inhibitors directly targeting FRA1. While, recently, Wei Yang et al. developed a multi-kinase inhibitor, LY-1816, which not only inhibits the phosphorylation level of SRC kinase, but also directly inhibits the expression level of FRA1. The inhibitor has confirmed its tumor suppressing effect in a variety of vitro cells and pancreatic ductal adenocarcinoma xenografts. Although the antitumor effect of the inhibitor was found to be stronger than that of gemcitabine and dasatinib, many difficulties still need to be overcome before its clinical trial [146]. In general, the development of small molecule targeted drugs for FRA1 still has a long way to go.

## Discussion and perspectives

In this review, we discussed the regulatory factors of FRA1. FRA1 can be regulated by transcription and post-translational modification, mainly by post-translational phosphorylation. The classic regulatory pathway is RAS/ERK signaling pathway. FRA is degraded by proteasome. FRA1 is also regulated by miRNAs. We also discussed the expression and function of FRA1 in various tumors. Whether *FOSL1* plays as a proto-oncogene or a tumor suppressor gene is closely related to the type of target organs. In general, FRA1 is highly expressed in most of tumors and promotes the malignant progression of tumors, except cervical cancer and some controversial tumors.

Heterogeneity is an important feature of malignant tumors, including clonal evolution and cell plasticity, and FRA1 plays a crucial role in this process. Readers can refer to the excellent review by AS Dhillon and E Tulchinsky [147]. The cell plasticity is manifested by the cell reprogramming. In melanoma, FRA1 can affect the chromatin remodeling factor HMGA and MITF, which is closely related to melanoma phenotype [66]. In hepatocellular carcinoma, hepatocyte growth factor (HGF), which derived from cancer-associated fibroblasts could regulate tumor-initiating cell plasticity through c-Met/FRA1/HEY1 Signaling [148]. However, in other tumors, the effect of FRA1 on cell reprogramming is mostly focused on altering cell polarity by EMT-TFs. There is no profound study on how FRA1 changes chromatin status, organelle structure, and cytoskeletal rearrangement. In addition, abnormal energy metabolism is one of the top ten characteristics of malignant tumors. As an important factor affecting the development of tumors, the role of FRA1 in energy metabolism is also worth exploring. At present, researchers have found that FRA1 and c-FOS can increase the rate of phospholipid synthesis and promote breast cancer cell proliferation by associating and activating the rate limiting enzyme CDP-DAG synthase, which is a phospholipid synthesis factor. The N-terminal domain plays a key role in this process [149].

The occurrence of tumors is a very complicated process, and the tumor microenvironment (TME) plays a very important role in the occurrence of tumors. Earlier studies have used co-culture techniques to find that breast cancer cells can promote the overexpression of FRA1 in tumor-associated macrophages (TAMs), activate the IL-6/STAT3 pathway, and induce the differentiation of tumor-associated macrophages from M1 to M2, which facilitate the immune evasion of tumor cells, and in turn promotes the aggressiveness of breast cancer cells [150, 151]. miR-19a-3p inhibits the polarization of TAM and the aggressiveness of breast cancer by inhibiting the level of FRA1

in TAMs [29]. Similar phenomenon exists in lung cancer. M2 macrophages can promote the invasion and metastasis of lung cancer by regulating CRYAB expression and activating the ERK1/2-FRA1-SLUG signaling pathway [152]. Based on the correlation between FRA1 and the TME, it is possible that target of FRA1 will be a breakthrough in cancer immunotherapy. But the current progress in this area is still relatively limited (only initial trials in breast cancer) and requires further efforts.

Targeted therapy as an important treatment for malignant tumors, many small molecule targeted drugs targeting specific targets have been developed. However, studies have shown that sustained targeted therapy can induce secretome, leading to drug resistance, and accelerate the spread of tumors, severely limiting the effectiveness of targeted therapy. The BRAF inhibitor vemurafenib reactive secretome is closely related to the down regulation of FRA1 [153]. In addition to simple drug resistance, some tumor cells even have an addictive reaction to drugs, and a sudden withdrawal of drugs will lead to the death of a large number of addicted cells. Using CRISPR technology, Professor Peeper's team found that the death of melanoma cells induced by drug withdrawal is closely related to the activation of the ERK2-JUNB/FRA 1 pathway [154]. Professor Roger's group also advocates that DNA damage and cell death caused by drug withdrawal are associated with robust p-ERK-induced up-regulation of the p38-JUNB/FRA1-CDKN1A pathway [155]. Rational use of the drug resistance and addiction of tumor cells can improve the lethality of cancer drugs on addictive cells, which provide new ideas for the treatment of drug-insensitive tumors.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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