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Cytoplasmic PML: From Molecular Regulation to Biological Functions

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ABSTRACT

The tumor suppressor promyelocytic leukemia protein (PML) is predominantly localized in the nucleus, where it is essential for the formation and stabilization of the PML nuclear bodies (PML-NBs). PML-NBs are involved in the regulation of numerous cellular functions, such as tumorigenesis, DNA damage and antiviral responses. Despite its nuclear localization, a small portion of PML has been found in the cytoplasm. A number of studies recently demonstrated that the cytoplasmic PML (cPML) has diverse functions in many cellular processes including tumorigenesis, metabolism, antiviral responses, cell cycle regulation, and laminopothies. In this prospective, we will summarize the current viewpoints on the regulation and biological significance of cPML and discuss the important questions that still need to be further answered. J. Cell. Biochem. 115: 812–818, 2014.

KEY WORDS: CYTOPLASMIC PML; CANCER; TUMOR SUPPRESSOR

PML was originally identified in patients with acute promyelocytic leukemia (APL) in which the t (15, 17) chromosome translocation results in fusion proteins of PML and retinoic acid receptor alpha (RARα) [Goddard et al., 1991; Kakizuka et al., 1991; Pandolfi et al., 1991; de The et al., 1991]. In normal cells, PML can form a nuclear multiprotein complex, which is known as PML nuclear bodies (NBs), ND10 or PODs. PML-NBs has been revealed to mediate cellular apoptosis [Guo et al., 2000; Lin et al., 2006] and senescence [Pearson et al., 2000; Vernier et al., 2011; Martin et al., 2012]. In addition, PML-NBs is also involved in neoangiogenesis [Bernardi et al., 2006], hematopoietic stem cell (HSC) maintenance [Ito et al., 2012] and DNA damage response [Dellaire and Bazett-Jones, 2004; Dellaire et al., 2006]. In APL cells, the expression of fusion protein PML-RARα disrupts PML NBs, resulting in dispersed PML microspeckles [Dyck et al., 1994; Weis et al., 1994]. The treatment of As2O3 or all-*trans* retinoid acid (RA) promotes the degradation of PML-RARα and reforms PML NBs [Daniel et al., 1993; Zhu et al., 1997]. Strikingly, As2O3 treatment leads to complete remission of APL diseases in around 70% patients [Mathews et al., 2010].

The *PML* gene consists of nine exons and contains a nuclear localization signal (NLS) in exon 6 (Fig. 1), which leads the protein to localize in the nucleus. However, the nucleo-cytoplasmic fractionation studies have revealed that there is a small portion of PML present in the cytoplasm [Lin et al., 2004; Condemine et al., 2006; Giorgi et al., 2010; Carracedo et al., 2011]. Recently, studies demonstrated that cytoplasmic PML (cPML) plays an important role in cellular function regulations. Lin et al. showed that cPML is involved in the activation of transforming growth factor β (TGFβ) signaling and results in cell proliferation arrest, apoptosis and senescence [Lin et al., 2004]. Consistently, another study by Giorgi et al. demonstrated that cPML is enriched in the endoplasmic reticulum (ER) and the mitochondria-associated membranes (MAMs) to mediate apoptosis responses [Giorgi et al., 2010]. A recent review summarized that cPML is involved in many distinct cellular functions including tumorigenesis, antiviral responses, metabolism, laminopathy and cell cycle regulation [Jin et al., 2013]. This serial of findings has attracted lots of attentions on the regulation and biological significance of cPML. In this prospective, we will review current

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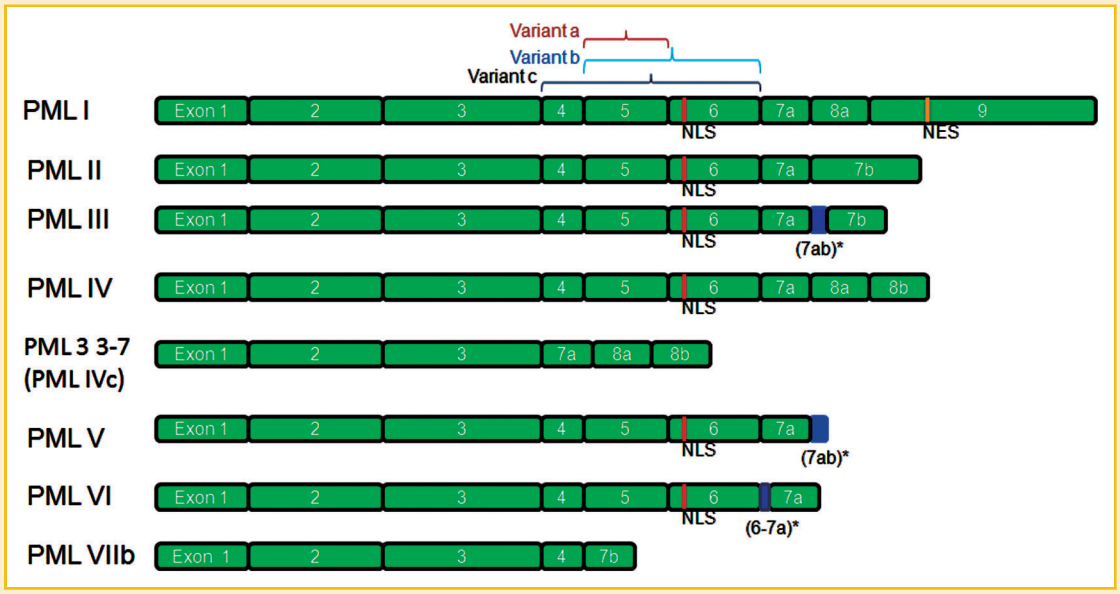

Fig. 1. PML isoforms. There are seven groups of PML isoforms due to mRNA alternative splicing. Intronic sequences (indicated by *) are retained in PML III, PML V, and PML VI. PML II to PML VI contains nuclear localization signal (NLS), likely localized in nucleus. PML VIIb is devoid of NLS and retains in cytoplasm. PML I contains both NLS and nuclear export sequence (NES) and may be present in both nucleus and cytoplasm. Three variant may exist for each group of PML isoforms. Variant a lacks exon 5, variant b is without exon 5 and 6, variant c loses exon 4, 5, and 6. Variant b and c are potential cPML isoforms due to the missing of NLS motif. The PML 3 3–7 involved in TGFβ signaling [Lin et al., 2004] is PML IVc.

viewpoints in the field and discuss some important questions that need to be further addressed.

PML CYTOPLASMIC DISTRIBUTION

As aforementioned, although PML is localized in the nucleus predominantly, PML actually displays both nuclear and cytoplasmic localization. Evidence has demonstrated that cPML is critical for comprehensive cellular function regulation (Fig. 2). Interestingly, from literatures published so far, the cPML isoforms are different unless not clearly defined in individual cellular function regulation. For instance, the cPML isoform PML3 3–7 is required for the activation of TGFβ signaling to orchestrate its downstream events [Lin et al., 2004]. Another example is PML Ib, which is an alternative splicing cPML isoform specifically identified in HSV-1 infected cells

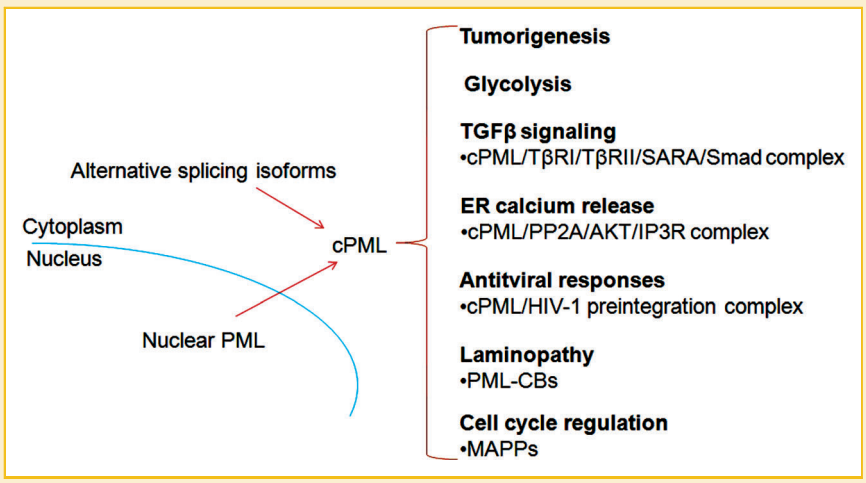

Fig. 2. cPML cellular functions. cPML is mainly derived from alternative splicing and the redistribution of nuclear PML from nucleus to cytoplasm. cPML regulates distinct cellular processes, including tumorigenesis, glycolysis, TGFβ signaling, ER calcium release, antiviral responses, laminopathy and cell cycle regulation. In many cases, cPML plays its role through forming a multiprotein complex, such as cPML/TβRI/TβRII/SARA/Smad complex in TGFβ signaling regulation, cPML/PP2A/AKT/IP3R complex for ER calcium release, cPML/HIV-1 preintegration complex under HIV-1 infection, PML-CBs in laminopathy disease and MAPPs complex during cell cycle regulation.

and is required to inhibit viral replication [McNally et al., 2008]. In some other studies, PML cytoplasmic localization may be derived from the redistribution of nuclear PML isoforms or simply identified through fractionation [Jin et al., 2013]. Clearly identification of the cPML isoforms in different cellular processes will further facilitate the understanding of cPML cellular functions.

PML alternative splicing is one of the major approaches to localize PML in cytoplasm. Although the exon 6 of PML gene contains the NLS motif, the alternative splicing may produce isoforms lacking exon 6, thus resulting in its cytoplasmic retention. These cPML isoforms include the previously mentioned PML3 3–7 involved in TGFβ signaling and PML Ib expressed in HSV-1 infected cells [Lin et al., 2004; McNally et al., 2008]. In general, there are seven groups of PML isoforms from PML I to PML VIIb [Jensen et al., 2001]. Due to the alternative splicing, PML II to PML VI contains the NLS sequence in exon 6, leading to their nuclear localization. PML VIIb is devoid of NLS and likely localizes in the cytoplasm. The longest isoform PMLI not only has NLS but also contains a nuclear export signal (NES) in exon 9 and has been shown to localize both in nucleus and cytoplasm [Jensen et al., 2001] (Fig. 1). Notably, PML VIIb is not the only isoform without NLS motif. Other cPML isoforms identified include PML 3 3–7, PML Ib and PML VIb [Reymond et al., 2001; Lin et al., 2004; McNally et al., 2008]. Essentially, all groups of PML isoforms may exist in a/b/c three variants. Variant a contains no exon 5; variants b lacks exon 5 and 6, and variants c is devoid of exon 4, 5, and 6. Among them, both variants b and c lack exon 6 and thus are devoid of the NLS motif [Fagioli et al., 1992; Jensen et al., 2001] (Fig. 1), suggesting that there may be many alternative splicing cPML isoforms to be further identified.

In addition to the alternative splicing cPML isoforms, cPML can also derive from the redistribution of nuclear PML. An interesting finding is the dynamic regulation of PML-NBs during cell cycle progression [Dellaire, 2006]. In the mitosis phase, PML is redistributed from PML-NBs to the cytoplasm where it forms a specific complex termed mitotic accumulation of PML proteins (MAPPs). MAPPs is currently recognized as the transient depot of PML-NBs dynamic regulation during cell cycle progression [Dellaire, 2006]. In the G1 phase, the MAPPs will be disrupted, and the dissociated PML proteins from MAPPs will be subjected to reform PML-NBs. Although it is unclear what role MAPPs may play, we speculate that they may have specific cytoplasmic functions during mitosis that have yet been determined. In addition, viral infection of the respiratory syncytial virus (RSV), the lymphocytic choriomeningitis virus (LCMV) or the human immunodeficiency virus type 1 (HIV-1) also redistribute nuclear PML to cytoplasm, where it may interact with the LCMV Z protein to inhibit eIF4E and consequently reduce viral protein translation [Borden et al., 1998; Kentsis et al., 2001] or it may colocalize with HIV-1 preintegration complex to impair HIV-mediated transduction [Turelli et al., 2001].

cPML MOLECULAR REGULATION

Although various evidence suggests that cPML is involved in regulating many cellular functions including apoptosis, metabolism, tumorigenesis, antiviral responses, laminopathy, and cell cycle regulation [Jin et al., 2013]. How cPML can regulate numerous processes remains largely unclear. It is well known that nuclear PML modulates its downstream events largely through the formation of the multiprotein complex termed PML-NBs. In line with this, cPML may also form a large protein complex to participate in these cellular processes. For instance, cPML forms a complex with TβRI/TβRII/SARA/Smads and is required for the assembly and early endosome localization of this large complex, thereby inducing TGFβ signaling activation [Lin et al., 2004]. Consistent with this notion, nuclear sequestration of cPML by TG-interacting factor (TGIF) and c-Jun negatively regulates TGF-β signaling through dissociating this complex [Seo et al., 2006]. Moreover, inhibition of TGIF by PCTA relocates cPML from nucleus to cytoplasm and promotes the complex formation as well as TGF-β signaling activation [Faresse et al., 2008].

In addition to its localization in early endosome, cPML is also found at the endoplasmic reticulum (ER) and the mitochondria-associated membranes (MAMs) where it forms a large complex that contains cPML, PP2A, Akt and IP3 receptor (IP3R) to regulate ER calcium release and apoptosis [Giorgi et al., 2010].

Furthermore, cPML complex has been identified in HIV-1 infected cells. As mentioned above, HIV-1 infection causes the redistribution of PML together with the integrase interactor 1 (INI-1) from nucleus to cytoplasm, where they form a complex with HIV-1 preintegration complex and inhibit HIV-mediated transduction [Turelli et al., 2001]. Similarly, PML relocates from nucleus to cytoplasm and forms the complex MAPPs during the mitosis phase [Dellaire, 2006]. In addition, cPML is also identified in laminopathy cells in which cPML is present as the PML cytoplasmic particles (PML-CPs), although what components other than PML within PML-CPs have not yet been identified. Laminopathies are a group of genetic disorders associated with the mutation of LMNA gene which causes the defects of nuclear envelope and eventually leads to various laminopathy syndromes such as muscle dystrophy, neuropathy, diabetes and premature aging. Interestingly, the number of PML-CPs is correlated with the severity of laminopathy disease [Houben et al., 2013], suggesting that the formation of PML-CPs may directly contribute to the development of laminopathy disease. Altogether, these studies suggest that cPML may function through forming multiprotein complexes similar to PML-NBs (Fig. 2), although this assumption needs further validation.

On the other hand, the mechanism by which cPML is regulated remains poorly understood, although numerous biological functions have been attributed to cPML. As nuclear PML localized in NBs is shown to be regulated by distinct posttranslational modifications including SUMOylation, phosphorylation and ubiquitination (reviewed in Carracedo et al. [2011], Cheng and Kao [2013]), it will be interesting to determine whether cPML also undergoes similar regulatory mechanisms to orchestrate its level and activity like nuclear PML.

IS cPML A TUMOR SUPPRESSOR OR ONCOGENE?

TGF-β signaling is generally recognized as a tumor suppressive factor. Its activation induces the transcription of two cyclin inhibitors p15 and p21, which leads to cell growth arrest. In addition, TGF-β

signaling mediates apoptosis and cellular senescence [Katakura et al., 1999; Derynck et al., 2001; Siegel and Massague, 2003]. As aforementioned, cPML facilitates TGF-β signaling and consequently inhibits cell growth, promotes apoptosis and cell senescence [Lin et al., 2004], suggesting that cPML may be a tumor suppressor. In further support of this notion, MAMs cPML also mediates a variety of apoptosis responses through promoting ER calcium release [Giorgi et al., 2010], implying additional molecular mechanisms for the tumor suppressive role of cPML. Another supporting evidence came from the observation that the PML-RARα, which is present in both nucleus and cytoplasm [Kastner et al., 1992], interacts with cPML and disrupts cPML-Smad2/3 interaction, thereby inactivating the tumor suppressive TGF-β signaling in APL cells, providing a novel mechanism of PML-RARα oncogenic function [Lin et al., 2004]. Based on these studies, cPML likely serves as a tumor suppressor.

However, we speculate that cPML may also play tumor promoting activity at certain stage of tumor development, as TGF-β signaling has been shown to play a dual role not only in tumor suppression but also tumor promotion dependent on the distinct stages of tumor development. In the early stage of tumor development, TGF-β suppresses tumor growth through cell cycle arrest and apoptosis. As tumor progresses, it may become resistant to TGF-β tumor suppressive activities but still respond to TGF-β to promote migration, invasion and metastasis (reviewed in Jakowlew [2006], Siegel and Massague [2003]). Importantly, this dual role of TGF-β signaling has been described in many tumor types [Cui et al., 1996; Siegel and Massague, 2003; Jakowlew, 2006]. Thus, it remains to be determined whether cPML may suppress tumor initiation, but promote tumor metastasis at late stage by activating TGF-β signaling.

Accumulating evidence implies that cPML may likely play oncogenic functions. Deregulation of PML in cytoplasm is found in both skin carcinomas and hepatocellular carcinomas [Terris et al., 1995; Chan et al., 1998; Condemine et al., 2006], suggesting that cPML may play a role in promoting tumor progression. A PML truncated mutant was found in the cytoplasm of recurrent plasmacytoma cell, where it performs an oncogenic role possibly due to the dominant negative effect on nuclear PML-NBs [Zheng et al., 1998]. Moreover, two PML mutations (1272delAG and IVS3–1G-A) were found in the aggressive APL patients. Such mutations lead to premature halt in transcription before the NLS motif, thereby generating cytoplasmic PML mutants [Gurrieri, 2004]. Interestingly, these cPML mutants interact with and stabilize PML-RARα cytoplasmic complex, thus promoting PML-RARα oncogenic function [Bellodi, 2006]. Furthermore, these two mutants can also induce the PML redistribution from nucleus to cytoplasm, resulting in the inhibition of p53 tumor suppressive ability [Bellodi et al., 2006].

Interestingly, several recent studies revealed that cPML may be involved in tumor progression though the regulation of cell metabolism, providing additional clues on the role of cPML in tumorigenesis. Deregulated metabolism is a hallmark of cancer progression. A high rate of aerobic glycolysis which known as Warburg effect is utilized in cancer cells and has been shown to be important for tumor development. The M2 isoform of pyruvate kinase

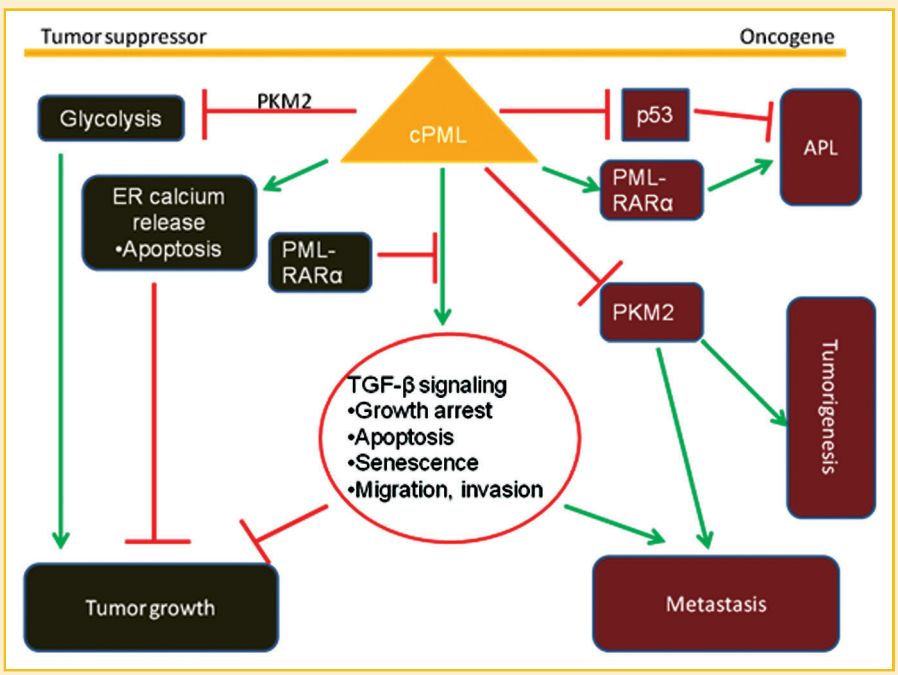

Fig. 3. The dual role of cPML in tumorigenesis. cPML displays both tumor suppressive and oncogenic abilities. On one side, cPML induces cell growth arrest, apoptosis and senescence through activating TGFβ signaling and ER calcium release to suppress tumor growth. In acute promyelocytic leukemia (APL) cells, PML-RARα inhibits cPML mediated TGFβ signaling activation and antagonizes its tumor suppressive effect. cPML may also prevent tumor growth through inhibiting glycolysis. On the other side, cPML might promote tumor metastasis, since TGFβ signaling activation eventually leads to aggressive tumor metastasis. cPML may also promote tumorigenesis and metastasis through inhibiting PKM2 activity. In addition, cPML can inhibit tumor suppressor p53 and enhance the oncogenic functions of PML–RARα in APL cells.

(PKM2) is a critical regulation enzyme in aerobic glycolysis and is normally expressed in proliferating cells during embryogenesis and tumorigenesis (reviewed in Chaneton and Gottlieb [2012], Mazurek [2011]). A study showed that cPML may be involved in aerobic glycolysis by interacting with PKM2 to reduce lactate production [Shimada et al., 2008]. Due to the critical role of glycolysis in cancer cell survival, the crosstalk between cPML and PKM2 likely provides another evidence for the role of cPML in tumor suppressive abilities. However, this notion should be carefully examined, since some recent reports revealed contrary effects of PKM2 on tumorigenesis. Goldberg and Sharp [2012] showed that in vivo injection of PKM2 specific siRNA reduces the xenograft growth of liver HepG2 and ovarian SKOV3 tumor cells, supporting the tumor promoting activity of PKM2. In contrast, specific knockdown of PKM2 does not affect the growth of HCT116 colon carcinoma xenograft in vivo, although it decreases glycolysis rate and impairs the cell growth in vitro [Cortes-Cros et al., 2013]. Surprisingly, *PKM2* isoform-specific deletion in the breast cancer mouse model of *Brca1fl/fl;MMTV-Cre;Trp53*$^{+/-}$ promotes tumor formation and metastasis [Israelsen et al., 2013], suggesting that PKM2 may also suppress tumorigenesis. Since PKM2 activity is inhibited by cPML, these observations suggest that cPML can also be both tumor suppressive or oncogenic though inhibiting PKM2 activity, possibly dependent on different tumor types or distinct microenvironment.

Besides the regulation of PKM2 activity and glycolysis, two other studies demonstrated that PML regulates fatty acid oxidation (FAO) and ATP generation [Carracedo et al., 2012; Ito et al., 2012], which is required for cancer cell survival under metabolic stress [Schafer et al., 2009; Zaugg et al., 2011]. These studies revealed an unexpected role of PML in FAO, ATP generation and cell survival. It would be interesting to characterize which PML isoform contributes to FAO, ATP mediated cell survival and whether cPML is involved in this process.

Altogether, these studies suggest that cPML may play a dual role in tumor suppression and tumor promotion, although more studies are needed to exactly define its functions (Fig. 3).

CONCLUSION AND PROSPECTIVE

Although a number of studies have demonstrated the role of cPML in regulating various signaling pathways and biological processes, several issues still remain elusive and further efforts are required in order to gain a better understanding of cPML action in cells. First, although cPML has numerous isoforms from either alternative splicing or cytoplasmic redistribution of nuclear PML, little is known about how individual cPML isoform is involved in distinct cellular processes. Second, it is unclear as to how cPML regulates distinct cellular functions at the molecular level. Current clues suggest cPML may play its role through forming specific cytoplasmic multiprotein complexes. However, such notion needs further confirmation. Third, although several studies have identified some cellular functions for cPML, we speculate that cPML may be also involved in other biological processes. To comprehensively understand what other functions cPML may play in cytoplasm, it is required to identify cPML interacting proteins by systematical approaches, such as affinity purification. Fourth, there is thus far no evidence to show whether cPML also undergoes the posttranslational modifications like nuclear PML does. If so, what are the functions of these modifications play for cPML? Perhaps, the most important question to be asked is what exact function of cPML plays in the process of tumor development. Is it a tumor suppressor or oncogene? Given TGF-β signaling plays a tumor suppressive role in tumor initiation, but promotes tumor progression and metastasis during the late stage of tumor development, it will be interesting to determine whether cPML also displays stage-dependent functions in regulating tumor phenotypes as TGF-β signaling does.

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