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Review Article

15d-PGJ2 is a new hope for controlling tumor growth

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Abstract: 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), a natural PPARγ agonist, has been investigated for over a decade. Studies have revealed that it has proapoptotic, anti-inflammatory, antiangiogenic, and anti-metastatic abilities, as well as a significant anticancer effect. However, the mechanisms underlying the actions of 15d-PGJ2 on various tumors are only partially known. In this review, we discuss the recent progress in elucidating these mechanisms. Understanding the various functions and mechanisms of 15d-PGJ2 are crucial for the development of new therapies for controlling tumor growth and providing the basis for further research.

Keywords: Prostaglandins, 15d-PGJ2, apoptosis, anti-inflammatory, angiogenesis, metastasis

Introduction

Prostaglandins (PGs) are a family of biologically active lipid compounds derived from arachidonic acid (AA), and they have important functions in animals, such as vascular contraction, platelet agglutination, and inflammatory mediation [1]. PGs have a diverse range of actions depending on the PG type and cell target. Moreover, PGs of the A and J series contain a cyclopentenone ring structure, which is characterized by a chemically reactive α,β-unsaturated carbonyl [2]. PGs are divided into conventional PGs, such as PGD2, and cyclopentenone PGs (cyPGs), such as 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) [3]. 15d-PGJ2 is one of the most-well defined cyPGs, and its functions are mainly dependent on or independent of a proliferator-activated receptor (chiefly gamma subtype, PPARγ). Numerous studies have shown that 15d-PGJ2, a natural product, exerts significant anticancer effects [4]. 15d-PGJ2 inhibited uterine sarcoma cell growth and increased apoptosis *in vitro* [5], and it functioned as an endoplasmic reticulum stress regulator in multiple myeloma both *in vitro* and *in vivo* [6]. These results indicate the potential of 15d-PGJ2 as an anticancer treatment. However, the molecular mechanisms underlying the cytotoxicity of 15d-PGJ2 in cancer cells remain unclear. 15d-PGJ2 has not only anti-inflammatory and anti-angiogenic but also pro-apoptotic and anti-metastatic properties [2, 7]. This review summarizes the recent results regarding actions and mechanisms of 15d-PGJ2 with respect to controlling tumor growth.

Biosynthesis of 15d-PGJ2

The general pathway for the biosynthesis of 15d-PGJ2 is illustrated in **Figure 1**. First, AA is released from membrane phospholipids induced by phospholipase A2 and is converted by cyclooxygenase (COX, also called PGH synthase) to PGH2. PGH2, an unstable intermediate, is enzymatically converted into a series of prostaglandins including PGD2, PGE2, PGF2α, PGI2, and thromboxane A2, and these prostaglandins all have their own specific receptors [8]. The rate-limiting enzyme of synthetic PGD2 is a prostaglandin D synthase (PTGDS, including H-PTGDS and L-PTGDS). PGD2 spontaneously gives off a water molecule to form PGJ2. 15d-PGJ2 and Δ12-PGJ2 are generated from PGJ2 via albumin-independent and albumin-dependent reactions, respectively (**Figure 1**). No specific 15d-PGJ2 synthase has yet been identified. 15d-PGJ2 is a derivative of PGD2, and its synthesis initially depends upon the enzymatic machinery for PGD2 generation [9].

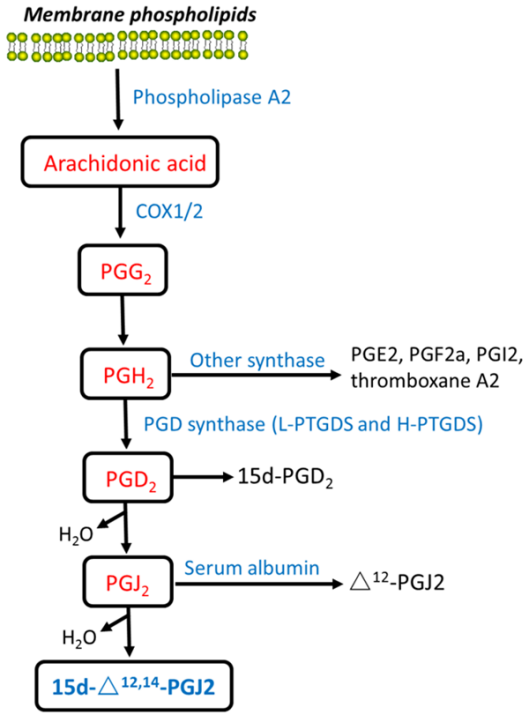

Figure 1. Process of 15d-PGJ2 biosynthesis. Membrane phospholipids are catalyzed by various enzymes (Phospholipase A2, COX1/2, and PGD synthase) to produce PGD2. PGD2 is dehydrated twice to produce 15d-PGJ2.

Effects and mechanisms of 15d-PGJ2-induced apoptosis and death of cancer cells

Although numerous agents inhibiting tumor development have been identified, little is known about how they work. Apoptosis is considered to be an important mechanism in this regard; apoptosis is a highly conserved, specific, and selective means of controlling tissue mass and shape, which can be exploited for the prevention or control of cancer [10]. Indeed, several studies have confirmed the role of 15d-PGJ2 in the induction of tumor cell apoptosis and have attempted to explore the underlying mechanisms (**Figure 2**).

PPARs are the primary targets of many natural and synthetic compounds including phthalate plasticizers, long-chain fatty acids, and pharmacologic drugs. Among them, PPARγ has been implicated in many human diseases including type 2 diabetes, atherosclerosis, hypertension, inflammation, and cancer [11]. PPARγ is expressed in human colon cancer, prostate cancer, and breast cancer cells, and its activation induces growth inhibition in these cells. PPAR-α agonists (bezafibrate) and other prostanoids (PGE2, PGF2α) were reported to not induce apoptosis [12]. However, PPARγ ligands induce terminal differentiation and growth inhibition of human breast cancer cells and prostate cancer cells [13]. PPARγ ligands, 15d-PGJ2 and troglitazone (TGZ), suppressed DNA synthesis to restrict colon cancer growth, whereas PPARα and PPARδ ligands had no significant effects [14]. The findings of the aforementioned studies suggest that PPARγ activation may be a key link in inducing apoptosis and death of cancer cells. Thus, 15d-PGJ2 may promote tumor cell apoptosis through a PPARγ-dependent manner, and PPARγ ligands may offer a new antitumor therapy.

15-PGJ2, the most potent endogenous ligand for PPARγ identified to date [15], induced a significant reduction of oral squamous cell carcinoma cell growth, mainly due to the upregulation of apoptosis [16]. Reactive oxygen species (ROS) can also promote anti-tumorigenic signaling by initiating oxidative stress-induced tumor cell death and apoptosis [17]. 15d-PGJ2 also triggers cell death through a caspase-independent mechanism, and ROS production and disruption of mitochondrial membrane potential play an important role in the 15d-PGJ2-induced cell death in A172 human glioma cells and non-small-cell lung carcinoma [11, 18]. Chen et al. discovered that 15d-PGJ2 induced the generation of ROS by enhancing intracellular iron accumulation and that the increased oxidative stress caused apoptosis of thyroid papillary cancer cell cells [19]. Shin and colleagues found that 15d-PGJ2 induced apoptosis in leukemia and colorectal cancer cells and led to ROS generation through mitochondria and NADPH oxidase activation, JNK activation, and AKT inactivation in leukemia and colorectal cancer cells [20].

Telomerase activity inhibition leads to cell senescence or death [21]. In addition to the regulation of oxidative stress, 15d-PGJ2 and PPARγ inhibited telomerase reverse transcriptase (hTERT) expression and telomerase activity and strongly reduced hTERT core promoter activity through the modulation of the Myc/Mad/Max network in colon cancer cells [22]. The oncogene signal transducer and activator of transcription 3 (Stat3) is critical in head and neck carcinogenesis [23]. Treating oral squamous cell carcinoma cells with 15-PGJ2 induced an

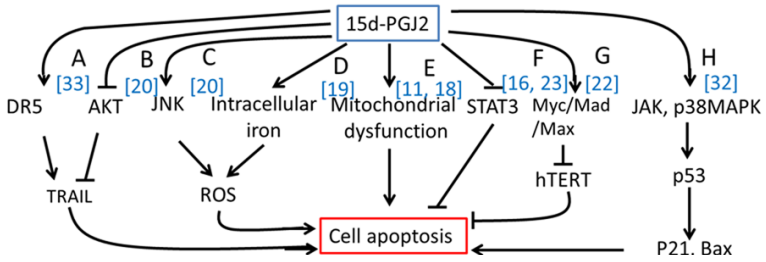

Figure 2. Mechanism of 15d-PGJ2-induced apoptosis. A and B: 15d-PGJ2 enhances TRAIL proapoptotic activity by inducing DR5 expression and inhibiting AKT activity; C and D: 15d-PGJ2 promotes ROS production by activating JNK signaling and inducing intracellular iron accumulation; E: 5d-PGJ2 increases apoptosis by inducing mitochondrial dysfunction of target cells; F: 15d-PGJ2 inhibits the expression of hTERT through the Myc/Mad/Max network; G: 15d-PGJ2 directly inhibits phosphorylated and unphosphorylated Stat3 protein levels to induce apoptosis; H: 15d-PGJ2 stabilizes p53 by activating the JAK and p38MAPK pathways and then induces the expression of P21 and Bax.

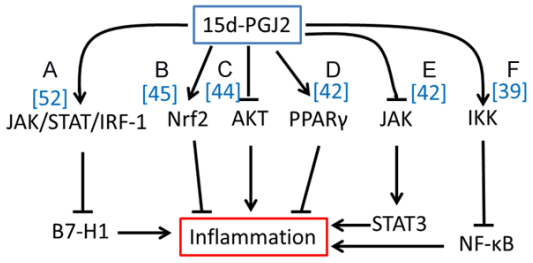

Figure 3. Mechanism of 15d-PGJ2-induced anti-inflammatory effect. A: 15d-PGJ2 inhibits the expression of B7-H1 through the JAK/STAT/IRF-1 pathway; B-D: 15d-PGJ2 inhibits inflammatory response through Nrf2, AKT, and PPARγ; E and F: 15d-PGJ2 suppresses STAT3 by inhibiting JAK signal and suppresses NF-κB by enhancing IKK activity.

initial reduction and eventual elimination of both phosphorylated and unphosphorylated Stat3 protein levels [16].

Although 15d-PGJ2 is the endogenous ligand of PPARγ, it promotes tumor cell apoptosis and is not entirely dependent on it. A study found that 15d-PGJ2 enhanced the antitumor action of docetaxel in lung cancer by PPARγ-dependent and PPARγ-independent mechanisms mediated by the induction of apoptosis [24]. Clay et al. found that 15d-PGJ2 activates PPAR-response element (PPRE)-mediated transcription and that PPARγ is not required for 15d-PGJ2-induced apoptosis in breast cancer cells [25]. 15d-PGJ2 was also reported to exert cytotoxic effects accompanying caspase-dependent apoptosis, and this effect was elicited through the activation of JNK and AKT instead of PPARγ in renal cell carcinoma-derived cell lines [26]. 15d-PGJ2 was revealed to induce caspase-dependent apoptosis associated with an influx of intracellular Ca^{2+} with no involvement of ER signaling [27]. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of the TNF cytokine family, has been reported to induce cell death in a wide variety of tumor cell lines, but it is not cytotoxic to many normal cell types in vitro or in vivo [28, 29]. 15d-PGJ2 sensitized cancer cells to a TNF-like weak inducer of apoptosis through an ROS-dependent cell death pathway and may have chemotherapeutic utility as an apoptosis-enhancing agent [30]. Han et al. found that 15d-PGJ2 augmented TRAIL-induced apoptosis in human leukemia cells by downregulating the expression and phosphorylation of AKT and that the sensitization to TRAIL-induced apoptosis by 15d-PGJ2 was not blocked by a PPARγ inhibitor (GW9662), suggesting a PPARγ-independent mechanism [31]. Another report revealed that 15d-PGJ2 induced ROS generation, activated JNK and p38 MAPK, induced p53 accumulation/phosphorylation, and then induced vascular endothelial cell (EC) apoptosis to inhibit angiogenesis [32]. The report also showed that both 15d-PGJ2-induced apoptosis and the induction of p21 and Bax could be abolished by p53 small interfering RNA but not by PPARγ inhibitor [32]. Sensitization of TRAIL-induced cytotoxicity by 15d-PGJ2 resulted from the upregulation of death receptor 5 (DR5) through gene transcription but was not associated with PPARγ activation [33].

Anti-inflammatory effects of 15d-PGJ2

Inflammation is a response that an organism uses to resolve infection, tissue injury, or other cellular stress and to restore tissue function through repair mechanisms [34]. However, long-term chronic inflammation can lead to tumor progression. Testing the efficacy of anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs or inflammation resolution

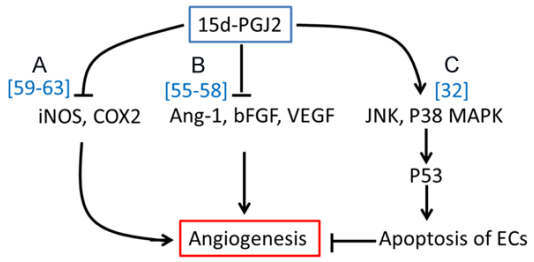

Figure 4. Mechanism of 15d-PGJ2-induced antiangiogenesis effect. A and B: 15d-PGJ2 inhibits the secretion of angiogenic factors (iNOS, COX2, Ang-1, bFGF, VEGF, etc.); C: 15d-PGJ2 stabilizes p53 by activating the JAK and p38MAPK pathways and then induces EC apoptosis.

mediators, as an alternative means to increase tumor drug delivery might prove promising [35]. In a previous study, treatment with dexamethasone significantly suppressed cancer dissemination through the suppression of epithelial-mesenchymal transition, a process used by epithelial cells for migration and invasion [36]. This part of the review focuses on the anti-inflammatory effects of 15d-PGJ2 (**Figure 3**).

Both PGD2 and 15d-PGJ2 seem to play major roles in regulating inflammation through both receptor-dependent (DP1 and DP2 receptors) and receptor-independent mechanisms [37]. Many inflammatory signaling molecules such as NF-κB and JAK-STAT can be inhibited by 15d-PGJ2 [38, 39]. NF-κB is a cluster of major transcription factor proteins that play a key role in the activation of inflammatory response genes [38, 40]. 15d-PGJ2 inhibits IKK and DNA binding of NF-κB [41]. It modifies and inhibits components of the proteasome pathway and consequently inhibits the activation of the NF-κB pathway in response to TNF-α [40]. 15d-PGJ2 protects against ConA-induced autoimmune hepatitis by reducing proinflammatory cytokines; this was correlated with the activation of PPARγ and the reduction in NF-κB activity in a model of acute hepatic inflammation [42]. Moreover, 15d-PGJ2 inhibited chemokine expression and attenuated IκBα phosphorylation and nucleus translocation of NF-κB through a PPARγ-independent mechanism in renal tubular epithelial cells [43]. Jung et al. also found that 15d-PGJ2 has a potent suppressive effect on inflammatory responses of osteoblast-like cells via the Akt and NF-κB pathways, independent of PPARγ activation [44]. 15d-PGJ2 and rosiglitazone, both PPARγ agonists, suppress the initiation of JAK-STAT inflammatory signaling independent of PPARγ to attenuate brain inflammation [39]. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates antioxidant and anti-inflammatory genes. 15d-PGJ2 exhibits anti-inflammatory properties in the pathogenesis of chronic obstructive pulmonary disease via Nrf2 activation [45].

Studies have confirmed that eosinophils are relevant not only in allergic diseases but also in tumorigenesis, and the ability to harness their function is important in cancer therapy [46, 47]. 15d-PGJ2 and rosiglitazone significantly reduce eosinophil migration into the peritoneal cavity and downregulate eosinopoiesis [48]. 15d-PGJ2 enhances eotaxin-induced chemotaxis, shape change, and actin reorganization in eosinophils through its ligation with PPARγ [49].

B7-H1 was revealed to be directly involved in the protection of cancer cells from activated T lymphocytes [50]. The interaction of PD-1 with B7-H1 downregulates T cell proliferation and cytokine production and induces T cell apoptosis [51]. 15d-PGJ2 suppresses the interferon-γ-elicited expression of B7-H1 by inhibiting IRF-1 transcription via the Jak/STAT signaling pathway through a PPARγ-independent mechanism in mouse melanoma cells [52].

Anti-angiogenic effects of 15d-PGJ2

The creation of new blood vessels from existing ones, or angiogenesis, is essential in cancer to feed the growing cancerous tissue [53]. Tumor angiogenesis is also a key event that governs tumor progression and metastasis [54]; therefore, its targeted inhibition is an important step in the treatment of tumors. 15d-PGJ2 has been reported to have antiangiogenic effects in a variety of cancer types through various mechanisms (**Figure 4**). The production of vascular endothelial cell growth factor (VEGF) and other factors is the driving force of angiogenesis [55]. 15d-PGJ2 has been revealed to inhibit the production of angiogenic factors, such as angiopoietin-1 (Ang-1), basic fibroblast growth factor (bFGF), and VEGF in cancer cells [56-58]. Moreover, 15d-PGJ2 inhibited the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxi-

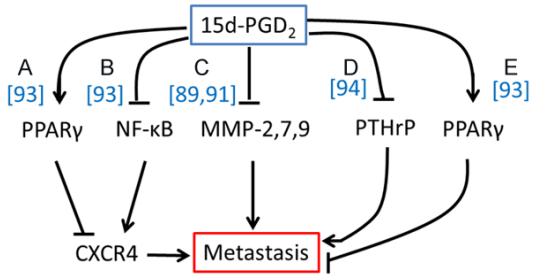

Figure 5. Mechanism of 15d-PGJ2-induced antimetastasis of cancer cells. A and B: 15d-PGJ2 inhibits the expression of CXCR4 by PPARγ and suppresses NF-κB activation; C: 15d-PGJ2 inhibits the expression of MMP-2, MMP-7, and MMP-9 in the tumor microenvironment; D: 15d-PGJ2 induces the expression of PTHrP to inhibit cancer cell metastasis; E: 15d-PGJ2 directly acts on PPARγ and thus affects tumor cell metastasis.

de synthase (iNOS), which are overexpressed in a variety of human malignant tumors and alter the expression of important angiogenesis modulators [59-63]. Many tumor cells or tumor microenvironment cell-derived cytokines such as interleukin (IL)-1β, IL-6, CCL2, IL-10, IL-12, and TNF-α also promote angiogenesis [64-66]. 15d-PGJ2 inhibits angiogenesis through the suppression of such cell cytokines. 15d-PGJ2 was reported to inhibit the expression of IL-1β, IL-6, and TNF-α in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated monocytes [67] and IL-10 and IL-12 in LPS-treated macrophages [66]. Macrophages are one of the most abundant innate immune cells within the tumor microenvironment that have been associated with tumor growth, metastasis, angiogenesis, and poor prognosis [68, 69]. 15d-PGJ2 reduced Ang II-induced expression of Egr-1 and its inflammatory gene targets (IL-1β, TNF-α, TGF-β, MCP-1, and ICAM-1) through PPARγ activation and ROS formation in macrophages [70]. The number of ECs is critical to angiogenesis, and the induction of apoptosis in proliferating ECs may be a strategy for cancer treatment. 15d-PGJ2 has been reported to act as an antiangiogenic factor by inducing EC apoptosis [71-73] and suppressing angiogenic factor-induced EC proliferation, tube-like differentiation, and VEGF receptor expression [57, 71]. Another study showed that 15d-PGJ2 induces vascular EC apoptosis through the signaling of JNK and p38 MAPK-mediated p53 activation both *in vitro* and *in vivo* [32].

15d-PGJ2-induced cell cycle arrest and p53 upregulation

Cell cycle arrest in response to DNA damage is crucial to maintain genomic integrity, and the control mechanisms that regulate this are known as cell cycle checkpoints [74]. Consideration of cell cycle checkpoints may provide more effective means for cancer treatment [75]. Several studies have confirmed that 15d-PGJ2 can induce cell cycle arrest in cancer cells. Inhibition by PPARγ ligands of growth of esophageal adenocarcinoma cells is due to the induction of apoptosis, G1 cell cycle arrest, and reduction of ornithine decarboxylase activity [76]. 15d-PGJ2 induced cell cycle arrest at the G2/M phase and apoptosis of human endometrial cancer cell lines [77]. Moreover, it was reported to strongly stimulate eukaryotic initiation factor 2 (eIF-2) phosphorylation and downregulate cyclin D1 expression through protein kinase R [78]. 15d-PGJ2 induced significant G2/M arrest and AKT inhibition by ROS-mediated inactivation of AKT [79]. Cheng et al. found that 15d-PGJ2 inhibited the growth of OC15-5 hepatic oval cells by dose-dependent arrest at G1-S [80]. Another study showed that 15d-PGJ2 is a tubulin-binding agent that destabilizes microtubules and induces mitotic arrest, leading to breast cancer cell death [81].

p53 is an important cell cycle checkpoint protein that regulates the cycle under adverse conditions [82]. 15d-PGJ2 significantly promoted p53 accumulation in both cytosolic and nuclear fractions of MCF-7 cells [83]. 15d-PGJ2 can undergo nucleophilic addition to p53, presumably at the cysteine 277 residue, rendering p53 less susceptible to proteasomal degradation and making it more stable [84]. 15d-PGJ2 also induces p53 expression through Nrf2-mediated upregulation of heme oxygenase-1 in human breast cancer cells [85].

15d-PGJ2 inhibits tumor metastasis

The metastatic spread of malignant cells to distant anatomical locations is a prominent cause of cancer-related death [86]. Metastatic cancer cells disrupt the target tissue remodeling cycle and result in target tissue destruction [87]. 15d-PGJ2, as an electrophile, is potentially anti-metastatic, exhibiting specificity for migration and adhesion pathways [88] (**Figure 5**). It has been demonstrated to significantly inhibit

the invasiveness of human breast and pancreatic cancer cells [89, 90]. Increased expression of matrix metalloproteinases (MMPs), especially gelatinases (MMP-2 and MMP-9), has been closely associated with tumor progression [89]. 15d-PGJ2 was reported to reduce MMP-2 and MMP-9 activity, thereby abrogating the invasiveness of pancreatic cancer cells and human breast cancer cells [89, 91]. Moreover, 15d-PGJ2 inhibits the proliferation and invasiveness of colon cancer cell lines, which are associated with G1 cell cycle arrest and MMP-7 synthesis downregulation, respectively [92]. The chemokine receptor 4 (CXCR4) is critical in the metastasis of colorectal cancer and its growth at metastatic sites [93]. 15d-PGJ2 can downregulate CXCR4 on cancer cells through both PPARγ and NF-κB [93]. In addition, a study confirmed that 15d-PGJ2 can dose-dependently inhibit viability, migration, invasion, and parathyroid hormone-related protein (PTHrP) production in MDA-MB-231 breast cancer cells [94].

Whether 15d-PGJ2 can control the expansion of cancer stem cells

The cancer stem cell (CSC) model claims that the initiation, maintenance, and growth of a tumor are driven by a small population of cancer cells termed CSCs [95]. CSCs possess a variety of phenotypes associated with therapeutic resistance and often cause recurrence [95]. Thus, targeting CSCs is crucial to controlling tumor growth. Up to now, direct evidence of 15d-PGJ2 regulation of CSCs is still scarce. However, studies have shown that 15d-PGJ2 could inhibit CSC function. Wang et al. found that 15d-PGJ2 inhibited the levels of stemness-related genes in bladder cancer cells [96]. The combination of an AKT inhibitor and a PPARγ agonist restricts the stem cell character of liver cancer cells and tumor growth [97]. PPARγ agonists were determined to inhibit the growth and expansion of CD133+, a CSC marker, in brain tumor stem cells [98]. These studies have indicated that PPARγ agonists are involved in the regulation of CSC-related gene expression. However, additional research is required to elucidate whether 15d-PGJ2 can affect the function of CSCs, as well as the potential therapeutic promise of agents that act on anticancer therapy.

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Disclosure of conflict of interest

None.

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