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Review Article

Dual-Specificity Protein Phosphatase 5: Recent Insights into Cancer, Inflammatory, and Neurodegenerative Diseases

Chengyun Tang[1], Gilbert Charles Morgan[1], Yedan Liu[2], Cameron Cantwell[1], David Bunn[1], Andrew Gregory[1], and Fan Fan[1]*

[1]*Physiology, Medical College of Georgia, Augusta University, Augusta, USA*

[2]*Pediatrics, The Affiliated Hospital of Qingdao University, Qingdao, China*

***Corresponding author:** Fan Fan, MD, MS, FAHA, Department of Physiology, Augusta University, Medical College of Georgia, USA

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Abstract

Dual-specificity phosphatase 5 (DUSP5) functions as a nuclear phosphatase that inactivates the extracellular signal-related kinases 1/2 in the mitogen-activated protein kinase family by dephosphorylating the tyrosine-threonine residues. This enzyme plays a pivotal role in cellular proliferation and differentiation and is implicated in various pathological contexts. This review briefly consolidates recent studies linking DUSP5 to cancer, vascular function, and neurodegenerative diseases, including Alzheimer's Disease and Alzheimer's Disease-Related Dementias. Additionally, we explore the relevance of DUSP5 in inflammatory diseases, including osteoarthritis. This review offers novel insights into the diverse roles of DUSP5, providing valuable information to unlock its therapeutic potential and contribute to the development of innovative treatment modalities for various disorders.

Keywords: DUSP5; ERK; cancer; inflammation; neurodegenerative diseases; AD/ADRD

Introduction

The mammalian genome harbors approximately 200 phosphatases [1]. The Dual specificity phosphatase (DUSP) family catalyzes the removal of phosphate groups from molecules, playing a crucial role in regulating cellular signaling pathways by counteracting the actions of kinases [2-5]. DUSP5 negatively regulates extracellular signal-related kinase 1/2 (ERK 1/2) by specifically dephosphorylating the tyrosine-threonine residues [6-10]. DUSP5 engages with ERK in a feedback loop, resulting in the deactivation by anchoring of ERK1/2 in the nucleus. This process amplifies cytoplasmic ERK activity, with the paradoxical effect of concurrently facilitating nuclear translocation [11]. This view was supported by a recent study (Figure 1) that the expression of pERK in the nucleus in primary cerebral vascular smooth muscle cells (VSMCs) was enhanced in *Dusp5* knockout (KO) rats. Additionally, DUSP5 has been reported to regulate protein kinase C (PKC) [6,12]. nuclear factor-κB (NF-κB), transforming growth factor β (TGF-β) and epidermal growth factor [13]. Tumor necrosis factor α (TNFα) [14]. Signaling pathways, involved in DNA methylation [15]. Long non-coding RNA (lncRNAs) [16-18], and microRNA modulation, 13 and is a direct target of p53 [19]. DUSP5 has been associated with significant effects on cancer [20]. Neurodegenerative diseases such as Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) [21-23]. And a range of other conditions, including ischemic stroke, hypertension, renal disease, pulmonary hypertension, osteoarthritis, and immunological diseases [24-30].

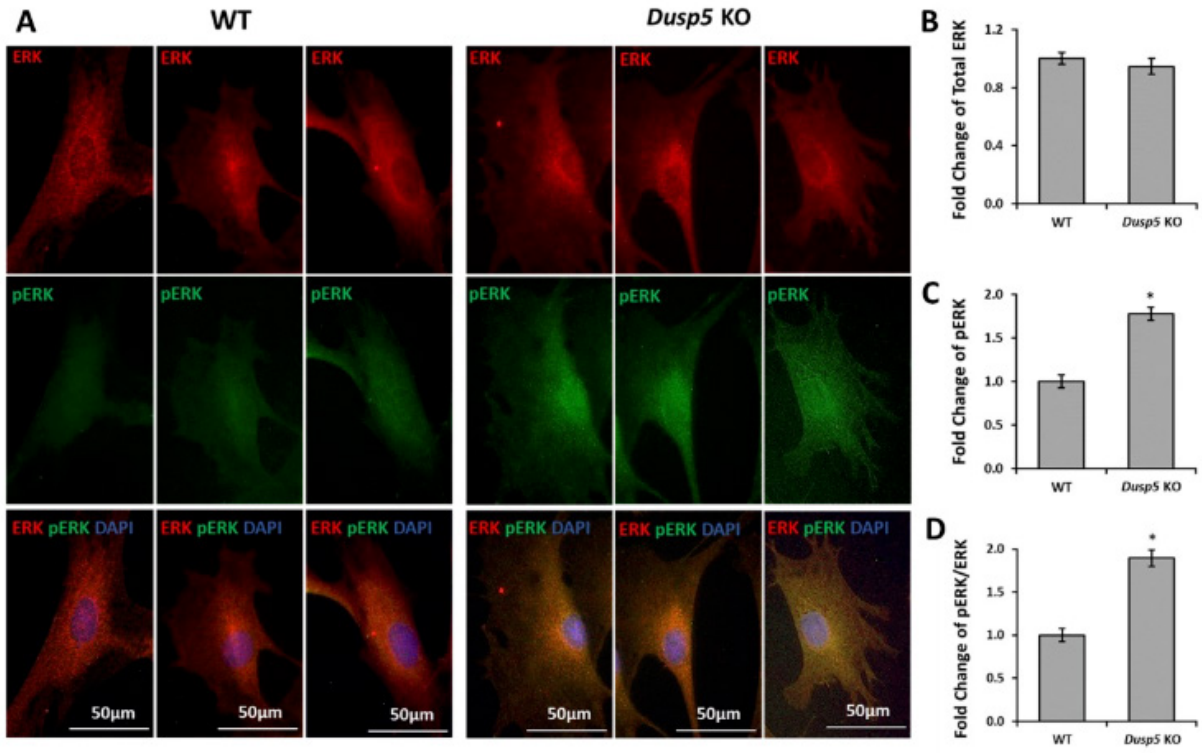

Figure 1: Enhanced expression of p-extracellular signal-related kinase (ERK) in the nucleus in primary cerebral vascular smooth muscle cells (VSMCs) in *Dual-specificity phosphatase (Dusp5)* KO rats.
(A) Representative images of total ERK and pERK expression and localization in primary VSMCs isolated from wildtype (WT) and *Dusp5* KO rats. (B) Quantitation of fold changes of the mean red fluorescence intensity in VSMC of *Dusp5* KO compared to WT rats. (C) Quantitation of fold changes of the mean green fluorescence intensity in VSMC of *Dusp5* KO compared to WT rats. (D) Quantitation of fold changes of pERK/ERK in VSMC of *Dusp5* KO compared to WT rats. Three rats of *Dusp5* KO and WT were used for primary VSMCs isolation. The experiments were replicated 3 times, with triplicate wells used in each experiment. * indicates $p<0.05$ from the corresponding value in *Dusp5* KO versus WT rats. Reprinted with permission from the Physiological Reports.

DUSP5 in Cancer

The role of DUSP5 in cancer may result from its function as a direct target of p53[19] and also may result from its enzymatic activities involving ERK and related signaling pathways[20]. DUSP5 levels are elevated in some cancers, however, reduced DUSP5 expression has been detected in some cancers.

DUSP5 and Breast Cancer

In MCF-7 cells treated with phorbol 12-myristate 13-acetate, an activator of phosphorylation, DUSP5 was specifically upregulated, and this increase was associated with the inhibition of the ERK pathway. Reduced expression of DUSP5 was observed in breast cancer during its malignant transformation [31]. Reduced expression of DUSP5 correlates with resistance to paclitaxel and is associated with an unfavorable prognosis in basal-like breast cancer [32].

DUSP5 and Cervical Cancer

The expression of DUSP5 is reduced in HeLa cell, a cervical cancer cell line, compared to normal human cervical epithelial cells. LncRNA ARAP1 antisense RNA 1 negatively regulates DUSP5 by recruiting enhancer of zeste 2 (EZH2) polycomb repressive complex 2 subunits, which may play a role in cervical tumorigenesis and imply a potential novel drug target.

DUSP5 and Colon Cancer

DUSP5 plays a crucial role in colon cancer and has been considered a novel prognostic indicator [33]. There is a significant decrease in the expression of DUSP5 in colorectal cancer [34], a negative correlation between BAF53A, a member of the ATP-dependent switching/sucrose fermentation complex, and DUSP5 has been revealed in colorectal cancer [35]. A recent investigation revealed that LncRNA ROR1-AS1 fosters the proliferation of colon cancer cells by suppressing the expression of DUSP5 through its binding to EZH2 [36]. Introducing DUSP5 expression in colon cancer cells has the capacity to inhibit growth and reduce ERK activity. Low levels of DUSP5 expression in individuals with colon cancer are associated with adverse outcomes, indicating a potential link between DUSP5 and the progression or prognosis of colon cancer. Further studies may be needed to explore the specific mechanisms through which DUSP5 influences colon cancer development and its potential as a therapeutic target in managing the disease.

DUSP5 and Gliomas

DUSP5 has been implicated in the regulation of cellular processes in gliomas. Studies indicate a potential negative influence on DUSP5 by p68 in the context of glioma invasiveness. In vitro experiments revealed that reducing p68 levels and increasing DUSP5 expression both exerted inhibitory effects on the proliferation, invasion, and migration of glioma cells [37]. Investigating the interplay between DUSP5 and gliomas could offer insights into therapeutic interventions for glioma-related conditions.

DUSP5 and Hepatocellular Carcinoma

Hepatocellular Carcinoma is the most common type of primary liver cancer. It's also the third leading cause of cancer deaths [38]. A study conducted by Liu et al. revealed that the suppression of DUSP5 in hepatocellular carcinoma cells is attributed to the recruitment of EZH2 by HOXA11 antisense RNA (HOXA11-AS) to the DUSP5 promoter region. Cumulatively, the HOXA11-AS/DUSP5 interplay facilitates the proliferation of hepatocellular carcinoma cells by modulating the cell cycle and apoptosis [18]. Upregulation of DUSP5 by endoplasmic reticulum stress results in hepatocyte death through the pancreatic endoplasmic reticulum kinase-C/EBP homologous protein pathway [39,40].

DUSP5 and Ovarian Cancer

Ovarian cancer stands as the primary cause of mortality among gynecological malignancies. In ovarian cancer, there is a significant decrease in the expression of DUSP5, and individuals with lower levels of DUSP5 expression experienced shorter survival periods. Silencing DUSP5 promotes cell proliferation, migration, and invasion of ovarian cancer cells in vitro by activating the expression and secretion of interleukin 33 (IL-33) [41]. Circular RNA_0000471 boosts DUSP5 expression by acting as a sponge for miR-135b-5p in ovarian cancer [42]. These results suggest that targeting DUSP5/IL33 and miR-135b-5p/DUSP5 axes may hold therapeutic potential in addressing key aspects of ovarian cancer progression and improving patient outcomes.

DUSP5 and Thyroid Carcinoma

DUSP5 is overexpressed in papillary thyroid carcinoma, especially in cells with BRAF V600E mutations [43]. In contrast, DUSP5 expression is reduced in thyroid follicular carcinoma in association with a high metastasis rate and is identified as a novel prognostic indicator [44].

DUSP5 and Renal Cell Carcinoma

Renal cell carcinoma is the most common kidney cancer in adults and accounts for 90–95% of kidney neoplasms [45]. Laczmanska et al. [46]. analyzed tyrosine phosphatase genes in renal cell carcinoma; they found elevated levels of DUSP1 and DUSP4 but not DUSP5 in all cancer stages. Another study by Qiu et al. [47], reported that DUSP5 expression is altered in renal cell carcinoma cell lines. Notably, they found that simvastatin, a statin medication prescribed to lower cholesterol levels by inhibiting HMG-CoA reductase, inhibited renal cell carcinoma cell viability, migration, and invasion, as well as regulated the cell cycle and induced apoptosis by promoting DUSP5 expression [47].

DUSP5 in Vascular Function

DUSP5, a negative regulator of ERK1/2 and PKC, has been reported to play roles in renal and cerebral vascular function. Increased levels of pPKC and pERK1/2 contribute to calcium influx in VSMCs, thereby promoting vasoconstriction [48,49]. A series of recent studies utilizing a *Dusp5* KO rat model demonstrated that the reduction of DUSP5 leads to eutrophic hypotrophy specifically in brain-penetrating arterioles (PAs) and renal interlobular arterioles, 7 but not in the middle cerebral arteries (MCAs) [50]. The myogenic tone is increased in cerebral and renal arterioles and MCAs. However, improved distensibility, enhanced compliance, and reduced stiffness are only observed in the arterioles in *Dusp5* KO animals, although the internal elastic lamina in the MCA showed heightened thickness and reduced fenestrations [7,50]. Primary VSMCs isolated from the MCA of *Dusp5* KO rats demonstrate increased contractility. The myogenic responses of MCA, PA, and renal arterioles are enhanced in *Dusp5* KO rats. When ERK and PKC are inhibited, both rat strains display a dose-dependent dilatory response in the MCA and PA, with a more significant impact observed in *Dusp5* KO rats [7,51]. Additionally, the autoregulation of renal and cerebral surface and deep cortical blood flow are elevated in *Dusp5* KO rats [6,7,29,50,51]. *Dusp5* KO rats exhibited a significant attenuation of hypertension-related renal damage, including proteinuria, glomerular injury, and interstitial fibrosis. These findings indicate that DUSP5 plays a significant role in influencing vascular function in both the brain and kidney, underscoring the potential therapeutic significance of targeting DUSP5 to maintain vascular homeostasis in these pathological conditions.

DUSP5 in Neurodegenerative Disease

AD/ADRD are prevalent forms of dementia, often presenting with a mix of brain pathologies [52,53]. Vascular contributions to cognitive impairment and dementia represent a significant aspect of ADRD, with hypertension and diabetes being the top risk factors [54-60]. AD is characterized by the abnormal accumulation of amyloid beta (Aβ) and hyperphosphorylated tau, leading to neuronal damage and cognitive decline [59,61-64]. Brain hypoperfusion is a causative factor in AD/ADRD-related neuronal damage, occurring earlier than Aβ and tau abnormalities and preceding dementia [65-70]. Increasing evidence indicates that vascular factors may play a role in the onset and advancement of AD/ADRD [61,71,72]. Brain hypoperfusion, linked to compromised cerebral blood flow autoregulation, impaired neurovascular coupling, weakened blood-brain barrier integrity, and neurodegeneration, represents crucial potential causal factors in AD and age-, hypertension-, and diabetes-related ADRD [73-82].

DUSPs are recognized for their pivotal involvement in the pathophysiology of neurodegenerative diseases, including AD/ADRD and Parkinson's disease [30,51]. *Dusp5* KO enhances brain hemodynamics [51] and is likely to improve brain perfusion under pathological conditions. Additionally, the genetic analysis indicated that DUSP5 is associated with late-onset AD [22], and AD APOE ε4 non-carrier patients [23]. These results imply that the role of

DUSP5 in AD/ADRD may expand to the vascular contribution that is independent of Aβ and Tau abnormalities. Supporting this perspective, Zhang et al. reported enhanced hippocampal-based learning and memory function in *Dusp5* KO rats, suggesting a potential therapeutic avenue in targeting DUSP5 deletion for addressing AD/ADRD.

DUSP5 in Inflammatory Disease

Following IL-2 stimulation, T-cells exhibit high expression of DUSP5 [83]. Lymphoid-specific overexpression of DUSP5 in transgenic mice results in diminished IL-2-dependent proliferation in T cells, and this model manifests autoimmune symptoms, coupled with arrested thymocyte development at the CD4+/CD8+ stage [84]. A study by Seo et al [85]. reported that DUSP5 plays an anti-inflammatory role in macrophages by inhibiting the ERK/NF-κB axis. In adipocytes, DUSP5 functions as an endogenous regulator in TNFα-induced inflammation and may play a role in obesity-related inflammatory phenotypes. Eosinophils exhibit high expression of DUSP5, which serves as a negative regulator of IL-33-dependent survival [86]. In *Dusp5* KO mice, T cell development remains normal, but the balance between CD8+ T cell-derived short-lived effector cells and memory precursor effector cells is altered in response to acute infection with lymphocytic choriomeningitis virus [87]. *Dusp5* KO rats exhibit attenuation of hypertension-related renal dysfunction, marked by reduced proteinuria and glomerular fibrosis. This is accompanied by lower macrophage infiltration, as evidenced by decreased monocyte chemoattractant protein-1 (MCP-1) and cluster of differentiation 68 (CD68) in the renal cortex.

DUSP5 plays an anti-inflammatory effect in many inflammatory diseases [88]. Osteoarthritis, the most prevalent form of arthritis, is characterized by structural damage to cartilage and other joint tissues [89]. Although aging and injury are causal factors, inflammation plays an essential role in the progression of this disease. Knockdown of DUSP5 in vitro enhanced IL-1β-induced inflammatory cyclooxygenase 2 (COX2) and matrix metalloproteinases in chondrocytes and decreased anti-inflammatory tissue inhibitor of metalloproteinase 3 and IL-10. 25 Moon et al. Reported that DUSP5 exhibits antiarthritic properties and attenuates bone loss by decreasing Th17 and increasing Treg cell populations and inhibiting ERK activity.

Conclusion and Future Prospects

The significance of DUSP5 is increasingly acknowledged, and it holds substantial promise as a novel drug target in various medical domains. The multifaceted roles of DUSP5 across various physiological and pathological contexts underscore its significance as a critical regulator of cellular processes. The diverse impact of DUSP5 in cancer, neurodegenerative diseases, inflammatory conditions, and vascular dysfunction emphasizes its potential as a therapeutic target. Future research avenues could explore the intricate molecular mechanisms underlying the interactions of DUSP5 with specific signaling pathways, shedding light on its precise regulatory functions. Additionally, investigating the clinical implications of modulating DUSP5 expression in specific diseases may pave the way for targeted therapeutic interventions. Moreover, understanding the crosstalk between DUSP5 and emerging molecular players, such as long non-coding RNAs and microRNAs, could unravel novel dimensions of its regulatory network. Ultimately, the full spectrum of roles played by DUSP5 is anticipated to offer the potential for the development of innovative strategies in disease intervention and the advancement of precision medicine approaches. Further studies exploring the therapeutic potential of targeting DUSP5 could contribute to the development of novel treatment modalities across a spectrum of disorders.

Author Contributions

CT and FF conceived and designed the outlines of this review; CT, GCM, and FF drafted the manuscript; CT, GCM, YL, CC, DB, AG, and FF edited and revised the manuscript; all authors approved the final version of the manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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