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Research Paper

Toxic Effects of Some Heavy Metals on the Structure and Stability of the Recombinant Human FGFR2b Kinase Domain

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ABSTRACT

Introduction: Fibroblast growth factor receptor type II (FGFR2b) is crucial in mediating cellular signal transduction and controlling vital biological processes such as cell growth and differentiation. The disruption or impairment of signaling pathways mediated by this particular receptor has been closely associated with the pathophysiology of various human malignancies, including breast cancer, ovarian cancer, and endometrial cancer. It has been observed that toxic heavy metals, such as lead, cadmium, and aluminum, exert their detrimental effects primarily through the alteration of established signaling pathways within the cellular environment. The primary objective of this research endeavor is to conduct a comprehensive investigation into the effects of the heavy metals lead (Pb^{2+}), cadmium (Cd^{2+}), and aluminum (Al^{3+}) on both the structural integrity and stability of recombinant FGFR2b.

Materials & Methods: Recombinant FGFR2b kinase domain was expressed in *Escherichia coli* BL21 (DE3) cells and purified using Ni^{2+}-NTA affinity chromatography. Protein integrity and activity were confirmed by PAGE analysis. Structural and stability changes of FGFR2b in the presence of Pb^{2+}, Cd^{2+}, and Al^{3+}

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were evaluated using intrinsic fluorescence spectroscopy and chemical denaturation with guanidine hydrochloride. Secondary structure alterations were assessed by far-UV circular dichroism (CD) spectroscopy, and metal–protein interactions were further analyzed using Fourier transform infrared (FTIR) spectroscopy.

Results: The analysis of intrinsic fluorescence emission and CD spectra of FGFR2b, when exposed to varying concentrations of these heavy toxic metals, indicated a gradual series of structural fluctuations that corresponded with the increased concentrations of the metals present. Furthermore, the findings from fluorescence and FTIR analysis of the protein structure demonstrated that the influence exerted by Pb^{2+} at concentrations of 100 and 500 µM was significantly more pronounced and impactful than the effects produced by the other two metals under investigation. The structure and stability of FGFR2b as a key receptor in cellular signal transduction were reduced by Pb^{2+}.

Conclusion: These results shed light on the effects of toxic heavy metals on biological functions of the cells via a change in their signaling pathways.

1. Introduction

Fibroblast growth factors (FGF) and their receptors (FGFR) play crucial roles in cell proliferation, differentiation, migration, and survival. They are essential to fetal growth, development, and regulation of angiogenesis and wound healing in adults [1]. The mammalian FGFs are involved in critical signaling pathways, and their dysregulation can result in anomalies [2]. The pleiotropic effects of FGFs are interposed through four highly conserved receptor tyrosine kinases (RTKs), namely FGF receptors 1 to 4 (FGFR1–FGFR4). The structure of FGFRs consists of three extracellular immunoglobulin (D1-D3) domains, a transmembrane region, and intracellular tyrosine kinase activity portions. The FGF/FGFR pathways significantly influence various cell behaviors and are implicated in numerous human diseases, such ascancer [3]. FGFR2, through gene amplification and abnormal activity, is a therapeutic target in cancers [4]. FGFR2 has two isoforms, FGFR2b and FGFR2c, and its locus is located at 10q26.13. FGFR2b comprises 334 aa and has a molecular weight of 38 kDa [5]. The change of FGFR2 performance by different factors such as somatic missense mutations or gene amplification results in a variety of cancers including endometrial, lung, breast, gastric, colorectal, and ovarian cancers [6].

Heavy metals, originating from industrial and agricultural sources, are major environmental pollutants. Their significant toxicity, even at low exposure levels, poses substantial risks to biological systems by disrupting signaling pathways and inducing DNA damage, oxidative stress, and structural mutations [6, 7]. The toxicological traits of Pb^{2+} and Cd^{2+} are partly accompanied by the generation of reactive oxygen species (ROS) that may activate numerous intracellular signaling pathways, especially NF- κB, JNK/SAPK/p38, as well as ERK/MAPK [7]. The induction of the transcription factor nuclear factor κB (NF-κB) by metal-triggered signaling routes may result in sustained inflammatory processes and associated conditions, such as cancer development. Research findings have illustrated that cadmium notably triggers NF-κB and the secretion of the chemokine IL-8 [8].

Despite the known roles of FGFR2b in cellular signaling and the toxicity of heavy metals in disrupting these pathways, little is known about how these metals affect the structure of FGFR2b. This study aims to evaluate the effects of lead, cadmium, and aluminum on FGFR2b using circular dichroism (CD), fluorescence, and Fourier transform infrared spectroscopy (FTIR).

2. Materials and Methods

In this study, imidazole, isopropyl β-D-1-thiogalactopyranoside (IPTG), and Ni^{2+} -NTA from Sigma (Sigma-Aldrich Co.), ampicillin and HEPES from Merck, and *Escherichia coli* BL21 (DE3) were obtained from Invitrogen. All other reagents used in this study were of analytical grade and purchased from Sigma-Aldrich Co.

2.1. Expression and purification of FGFR2b kinase domain

Recombinant pLEICS-01 vectors containing the mutated coding region of FGFR2b were transformed into the standard *E. coli* BL21 (DE3) host cells. Luria-Bertani broth and LB agar bacterial culture media supple-

mented with 100 µg/mL ampicillin were inoculated with the cells. Competent cells were prepared in the presence of calcium chloride.

Recombinant pLEICS-01 vectors containing the target gene were transformed into *E. coli* BL21 (DE3). The expression of recombinant protein was induced by 1 mM IPTG. The expressed protein was largely insoluble and prone to aggregation. Protein solubility was improved by changing in temperature of the bacterial culture from 37 ˚C to 20 ˚C. The purified protein was obtained using a Ni^{2+}-NTA column by affinity chromatography and an eluting buffer containing 50-200 mM imidazole. The fractions containing the FGFR2b kinase domain were dialyzed in 25 mM Tris-HCl, 100 mM NaCl, pH 7.5, subdivided into smaller aliquots, and stored at -80 ˚C. Functional analysis of the purified kinase domain was performed by polyacrylamide gel electrophoresis (PAGE). The concentration of protein was measured with a Nano Drop spectrophotometer using an extinction coefficient at 280 nm of 41,160 M^{-1}. cm^{-1}.

The engineered kinase domain of human FGFR2b was considered with two mutations and cloned in our previous study [9]. The mutations were created at E565A and K660E residues, selected based on associated pathologic disorders of Pfeiffer syndrome and endometrial cancer, respectively. To prove that the purified protein is in the active state, its interaction with both the wild type and mutant SH2 domains of phospholipase C (PLC) was studied using PAGE [10].

2.2. Tertiary structure of FGFR2b by intrinsic fluorescence spectroscopy

Intrinsic fluorescence measurements of purified proteins were carried out on a Cary Eclipse spectrofluorimeter (Varian, Australia), using a 10-mm short-path quartz cuvette. The photomultiplier tube (PMT) detector was set to medium voltage. Both excitation and emission slits were adjusted to a 5 nm bandpass. The intrinsic fluorescence spectra were obtained by excitation of protein (tryptophan fluorophore) at 280 nm, with the emission range of 300–450 nm at room temperature. To record the baseline of the buffer, the system was zeroed with a blank dilution (400 µL of buffer). The protein concentration of 3 mg/mL was kept fixed in each sample solution. All the spectra were gathered at the fixed concentration of FGFR2b, with a gradual increment in the concentrations of Pb^{2+} (100-1000 µM), Cd^{2+} (100-1000 µM) and Al^{3+} (100-1000 µM), with a 3-min incubation time for each increment.

2.3. Fluorescence spectroscopy and protein chemical denaturation analysis

The change in the λmax of emission (blue and red shift) of the folded native FGFR2b protein was 115 obtained by titration of guanidine hydrochloride (GnHCl) concentration (0-6 M). The excitation wavelength was set at 280 nm, and the emission spectra were recorded in the range of 300-450 nm. FGFR2b KD Chemical denaturation and λmax of emission were achieved in the GnHCl concentrations of 0, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, and 6 M, and in the presence of different concentrations of Pb^{2+} (0, 100, 150, 200,300, and 500 µM), Cd^{2+} (0, 6 and, 12 mM), and Al^{3+} (0, 0.5, and 1 M).

2.4. Secondary structure of FGFR2b by Far-UV CD spectroscopy

The Far-UV CD spectra were used for the assessment of secondary structural changes in FGFR2b KD after incubation with different concentrations of GnHCl (0, 3, 6 M) using a Jasco J-810 spectropolarimeter. Far-UV CD spectra were recorded at 25 ˚C from 190 to 260 nm using a quartz cuvette with 1-mm path length containing 15 µM protein. CD spectra were baseline-corrected with buffer, and then the sample spectra were obtained from the protein alone and its incubation with Pb^{2+} (500 µM), Cd^{2+} (12 mM), and Al^{3+} (1 M). These concentrations induced different fluctuations of protein structure as observed by fluorescence spectroscopy.

2.5. FTIR of FGFR2b

The FTIR spectroscopy was used to evaluate the type of metal interaction with FGFR2b KD using a Perkin-Elmer Spectrum RXI (Infrared spectroscopy). FTIR spectra at a fixed protein concentration, and after incubation with two concentrations of Pb^{2+} (300 and 500 µM), were recorded.

3. Results

3.1. Expression and purification of FGFR2b kinase domain region

From SDS-PAGE analysis illustrated in Figure 1, the maximum expression of recombinant protein was achieved at three to four hours post-induction. There was no contamination from other bacterial proteins that may have co-eluted with the purified protein.

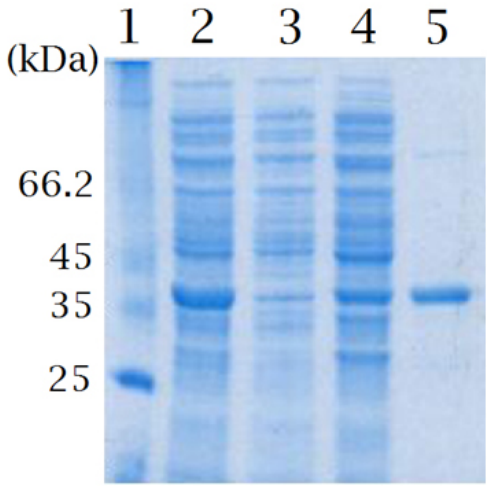

Figure 1. Purification of FGFR2b KD by affinity chromatography

Note: Lane 1: Molecular weight markers; Lane 2: Load sample; Lane 3: Flow-through; Lanes 4 and 5: Eluted samples.

3.2. Internal fluorescence analysis of FGFR2b KD-native versus denatured spectra

Two different spectra of intrinsic fluorescence of tryptophan fluorophore in Figure 2 refer to the denatured and native forms of FGFR2b. The maximum emission wavelength (λmax) of the native protein at 336 nm demonstrates a red shift toward 365 nm after incubation with 1 M GnHCl as a chemical denaturant.

3.3. Metal increment spectra of protein

The effect of different concentrations of Pb^{2+}, Cd^{2+} and Al^{3+} from 100 µM to 1000 µM were evaluated on the fluorescence emission spectra of native FGFR2b kinase domain. As can observed in Figure 3, there was not a significant change in the emission maximum wavelength of the protein with gradual increases in metal concentrations, while a gradual decrease in fluorescence intensity could be observed.

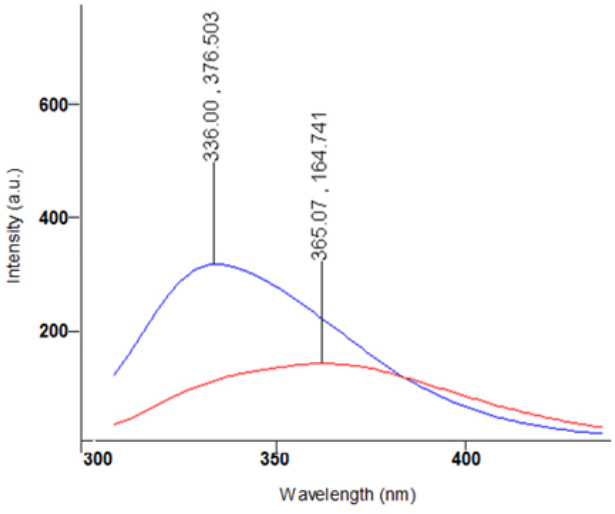

Figure 2. Intrinsic fluorescence spectra of native (solid line) FGFR2b KD and after incubation with 1 M GnHCl as a chemical denaturant (dashed line)

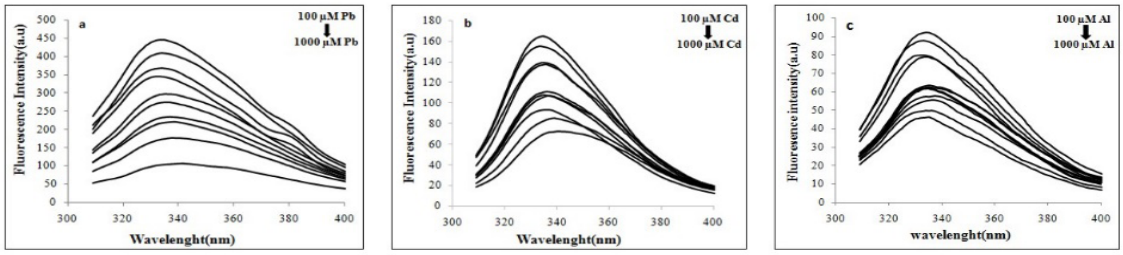

Figure 3. Fluorescence spectra of FGFR2b KD

a) Fluorescence emission spectra at differe nt concentrations of Pb^{2+}; b) Cd^{2+}, c) Al^{3+}

3.4. Protein chemical denaturation and shift in the maximum emission spectra

As mentioned above, the protein concentration was constant in all experiments, and the effect of these metals on the structural changes of the protein was evaluated at different concentrations. The tertiary structure of the protein tyrosine kinase FGFR2b was assessed in the presence of Pb^{2+} (0, 100, 150, 200, 300, and 500 µM), Cd^{2+} (0, 6, and 12 mM), and Al^{3+} (0, 0.5, and 1 M) using intrinsic fluorescence by monitoring the change in λmax of emission upon addition of GnHcl to the protein. As shown in Figures 4a, 4b and 4c, the fluorescence emission spectra of the protein were accompanied by a gradual decrease in intensity and a red shift of the spectra.

As depicted in Figures 5a, 5b, and 5c, titration of GnHcl in the presence of metals induced an observable shift in the λmax in the range of 334-340 nm. The effects of chemical denaturation and the change in maximum emission intensity with gradual increments of GnHCl in the presence of the maximum concentration of these metals, illustrated in Figure 5, demonstrate the significant change in the tertiary structure of the protein by Pb^{2+} in comparison with Cd^{2+} and Al^{3+}.

3.5. Far-UV circular dichroism spectroscopy and FTIR analysis for FGFR2b KD

The Far-UV CD spectra of the FGFR2b kinase domain, shown in Figures 6a, 6b, and 6c, were obtained using GnHcl at concentrations of 0, 3, and 6 M, and in the presence of Cd^{2+} (0, 6 mM) and Al^{3+} (0, 0.5 M). It is clear from these figures that GnHcl as a chemical denaturant altered the typical shape of the protein CD spectra with increasing concentration, but these metals did not show a significant change in the spectra. in contrast, Pb^{2+} treatment completely abolished the negative ellipticity of the protein.

The significant effect of Pb^{2+} on protein structure prompted us to perform an FTIR analysis to detect its interaction with the FGFR2b kinase domain. As illustrated in Figure 7, the FTIR analysis confirmed the substantial influence of lead ions (Pb^{2+}) on the structural composition and characteristics of the protein.

4. Discussion

Given that FGF signaling plays a crucial role in the regulation of several biological processes, including cellular differentiation and proliferation, it is reasonable to speculate that metal toxicity can affect this signaling pathway through interaction with the related receptors. Xie et al. investigated FGFR2 amplification in gastric cancer and the therapeutic potential of AZD4547, a potent ATP-competitive receptor tyrosine kinase inhibitor of fibroblast growth factor receptors (FGFR) 1–3, in patients with FGFR2-amplified gastric cancer. The study showed that AZD4547 effectively blocked the

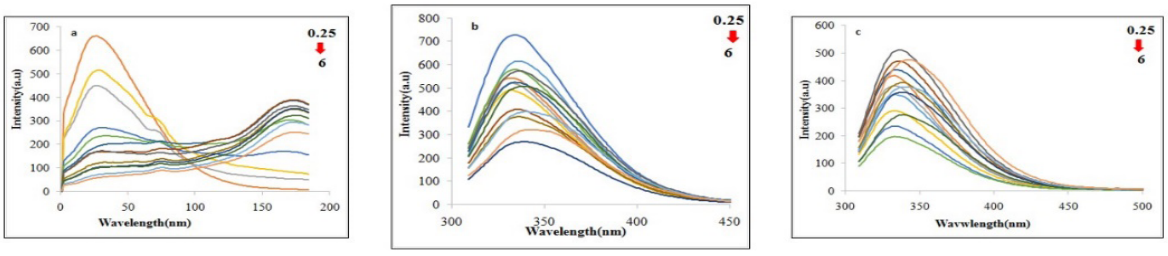

Figure 4. Intrinsic fluorescence spectra of FGFR2b with gradual addition of GnHCL (0.25-6 M) as a chemical denaturant in the presence of Pb^{2+} (500 µM) (a), Cd^{2+} (12 mM) (b), and Al^{3+} (1 M) (c)

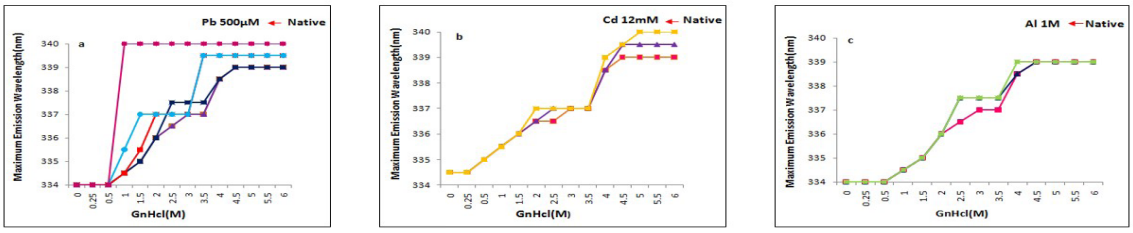

Figure 5. Red shift (334-340 nm) of maximum emission intensity of FGFR2b with gradual addition of GnHCL (0.25-6 M) as a chemical denaturant in the presence of Pb^{2+} (0, 100, 150, 200, 300, and 500 µM) (a), Cd^{2+} (0, 6, and 12 mM) (b), and Al^{3+} (0, 0.5, and 1 M) (c)

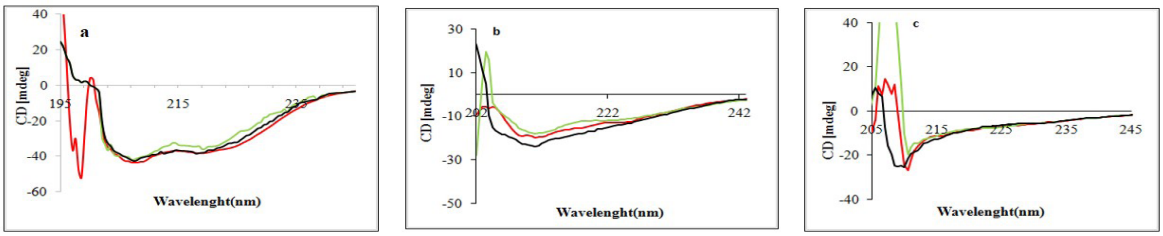

Figure 6. Far-UV CD spectra of FGFR2b in the presence of Cd^{2+} (0 and 6 mM) and Al^{3+} (0 and 0.5 M) (c), with incubation of GnHCL at 0 M (a), 3 M (b), and 6 M (c) as a chemical denaturant

phosphorylation of FGFR2 and its downstream signaling molecules, leading to apoptosis in SNU-16 cells [11].

Despite their different properties, metal carcinogens share common cancer-causing mechanisms, such as oxidative stress, blocking DNA repair, activating growth signals, and altering gene expression. These effects are mostly due to protein interactions, which are more significant than direct DNA damage, impacting DNA repair, tumor suppression, and signaling proteins [12]. This study aims to evaluate metal interactions and protein structural changes using three techniques: fluorescence, CD, and FTIR spectroscopies. Fluorescence spectroscopy is a sensitive method for characterizing protein structure, particularly through the intrinsic fluorescence of tryptophan residues, which serve as intrinsic labels for proteins [13]. FTIR is one of the oldest and well-

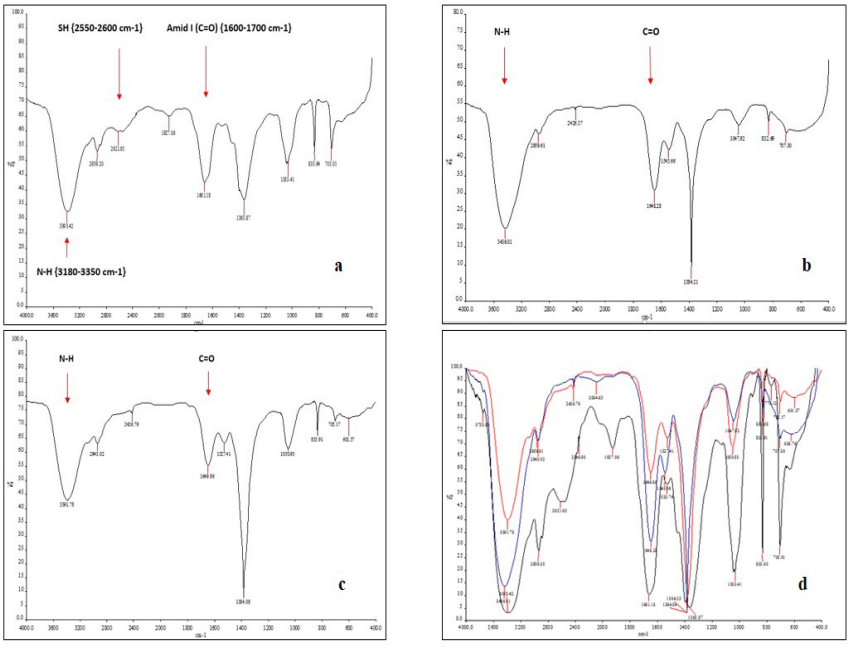

Figure 7. FTIR spectra of FGFR2b in the presence of different concentrations of Pb^{2+} (0 µM) (a),(300 µM) (b), and (500 µM) (c)

established experimental techniques for the analysis of chemical bases and secondary structure of polypeptides and proteins [14]. In addition, circular dichroism (CD) is recognized as a valuable technique for examining the regular structure of proteins in solution and provides important information about the secondary structure of biological macromolecules [15]. The analysis of CD spectra can therefore yield valuable information about the secondary structure of biological macromolecules.

These techniques were used to study the effects of heavy metals, such as lead, cadmium, and aluminum, on the FGFR2b kinase domain [16]. In this way, different concentrations of metals, with a fixed protein concentration, were investigated for their effects on the structure and stability of protein. The amount of heavy metals in the human body is often found in biological fluids, such as blood, plasma, and urine. These metals are derived from workplaces or environments where people are exposed to them, leading to damage to cells and important proteins [17].

These heavy metals and their complexes can induce undesirable biological effects; for example, Pb^{2+} can inhibit enzyme activity through coordination with sulfhydryl groups (SH). The clearest manifestation of this interaction is the impairment of the porphyrin metabolism in humans, which is associated with related disorders [18]. The activity of FGFR2b KD was confirmed by its interaction with both the wild-type and mutant SH2 domains of phospholipase C (PLC). Thus, in this case, the complexation of Pb^{2+} with this substrate can induce its toxic effects or act as a metabolite interfering in a signaling pathway [10, 16].

As it can observed from Figures 5a, 5b, and 5c, the chemical denaturation of FGFR2b KD followed a three-stage process. This type of denaturation emphasizes the cooperativity of unfolding, and the two sigmoidal shapes of denaturation may be related to the two domains of the protein. As shown in Figure 5c, Pb^{2+} at its higher toxic concentration induced a rapid co-destruction of the two protein domains and reduced its stability without transition through an intermediate state. In a study conducted by Apostoli et al, the effects of Pb^{2+} on anion channel membrane proteins of RBCs were confirmed. In that study, the concentration of Pb^{2+} at 60.6 µg/100 mL in workers' blood showed a significant decrease in the band of channels observed on SDS-PAGE [19].

Various studies have examined the toxic effects of Pb^{2+} at the cellular and molecular levels, especially in neuronal signaling pathways. It has been shown that Pb^{2+} can accumulate in the brain when its concentrations in the blood increases. Astroglia are the most susceptible cell type for Pb^{2+} accumulation and storage in the central nervous system (CNS) [20]. One potential mechanism implicated in Pb^{2+} toxicity is its capacity to trigger oxidative stress in blood and various tissues, thus contributing to poisoning through disruption of the intricate balance between pro-oxidants and antioxidants in mammalian cells. Numerous researchers have proposed a potential role of ROS in Pb-induced toxicity, whereby Pb leads to elevated levels of the lipid peroxidation marker malondialdehyde (MDA) and reduces the activities of key antioxidant enzymes, such as glutathione peroxidase (GPx) and superoxide dismutase (SOD), in the brains of rats [21].

ERK1/2, known as extracellular signal-regulated kinase 1/2, plays a crucial role in the formation of long-term potentiation (LTP), and the presence of Pb^{2+} can disrupt LTP by interfering with ERK and other signaling molecules. Basic fibroblast growth factor (bFGF) is a neurotrophic factor that helps protect neural cells from toxins, potentially through the MEK1/ERK signaling pathway [20]. In addition, chronic exposure to Al significantly diminishes the activities of protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) and reduces the expression levels of extracellular signal-regulated kinases (ERK1/2) [22]. Additionally, Al^{3+} can impact the expression and processing of amyloid precursor protein receptor in Alzheimer's disease. Researchers have observed that Al(mal)3 affects PKC enzyme activity and NMDAR expression through mGluR1, pointing to aluminum's role in synaptic plasticity and providing insights into complex neurotoxic mechanisms [23]. Also, Cd^{2+} can disrupt cellular PKC, which ultimately alters the phosphorylation of various transcription factors, leading to activation of target gene expression [24]. Bimonte and his colleagues demonstrated that Cd^{2+} can modify the expression and pattern of estrogen and androgen receptors in breast cancer cell lines, potentially leading to carcinogenic microenvironment [25].

The use of infrared spectroscopy allows the analysis of protein conformation in a diverse range of environments. As shown in the Figure 7, the specific absorption bands of protein infrared spectra between 400 and 4000/cm, in the presence of 300 and 500 µM Pb^{2+}, showed a significant change in the shape, position, and intensity of FTIR bands in comparison with the sole protein. The peak of the native protein at 1527.4/cm, assigned to random coil, shifted to 1546.6 and 1533.7/cm, and increased markedly at Pb^{2+} concentrations of 300 and 500 µM.

Although the magnitude of the anti-parallel β-sheet (1286.2/cm, shifted here to 1384.2/cm) did not change in the native and Pb^{2+}-incubated protein, the peak at 1649.8/cm (shifted to 1648.2 and 1661.1/cm), which is assigned to α-helix and β-turn, increased markedly after incubation of the protein with Pb^{2+}. Thus, this trend can be interpreted as an increase in β-turn structure at the expense of α-helical structure in the presence of Pb^{2+}.

5. Conclusion

This study investigated the impact of heavy metals, including lead (Pb^{2+}), cadmium (Cd^{2+}), and aluminum (Al^{3+}), on the structure and stability of the FGFR2b kinase domain. The results showed that these metals can alter the protein's structure and reduce its stability. Specifically, Pb^{2+} at higher concentrations leads to the rapid degradation of both protein domains, decreasing its stability without transitioning through an intermediate state. These findings highlight the toxic effects of heavy metals on protein structure and their potential influence on biological processes, such as cancer and neurological diseases. However, the study is limited to the structural level of the protein, and the effects of these metals on cellular function and metabolic processes have not been fully explored. Further studies are needed to better understand these effects in living biological systems.

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Compliance with ethical guidelines

No animals were used in this study, and ethical approval was not required. Standardized protocols and procedures were followed.

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

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Authors' contributions

Conceptualization: Nematollah Gheibi; Experiments: Maryam Toudehrousta; Data analysis: Dariush Ilghari, Hossein Piri, and Majid Sirati-Sabet; Writing the original draft: Maryam Toudehrousta, Roqaye Katfayazi, and Nematollah Gheibi; Review and editing: Nematollah Gheibi, Hossein Piri, Dariush Ilghari, Majid Sirati-Sabet, Maryam Toudehrousta, Roqaye Katfayazi, and Saeideh Gholamzadeh Khoei; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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