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Commentary

Is CDK9 a promising target for both primary and metastatic osteosarcoma?

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Osteosarcoma is the most common bone cancer and mainly occurs in children and young adults [1]. Although treatment of osteosarcoma has been greatly improved in recent years, the high recurrence and metastasis rates in patients underscore the need to develop new therapeutic and preventive approaches to this disease. Clinical and preclinical evidence suggest that cyclin-dependent kinases (CDKs) play an important role in cancer development and progression through regulating cell cycle progression and DNA transcription [2]. Among them, CDK9 is a transcriptional activator that is involved in promoting the release of paused polymerase II (RNAPII) into transcriptional elongation. CDK9 also phosphorylates RNAPII at the C-terminal domain, facilitates RNAPII-associated transcription, and increases the expression of genes regulating proliferation (*e.g.*, MYC) and apoptosis (*e.g.*, MCL-1). Indeed, CDK9 is frequently dysregulated in human cancers, including hematologic cancer to favor cancer cell growth and proliferation [3]. Zhang and colleagues have recently reported that CDK9 also plays an essential role in maintaining gene silencing at heterochromatic loci, resulting in the suppression of tumor suppressor genes [4]. Given its oncogenic functions in cancer, CDK9 may be as a promising target for developing anticancer therapeutic agents. Several CDK9 inhibitors, such as LDC000067 [5] and MC180295 [4] have been successfully developed and shown promising efficacy in human cancer cells *in vitro* and *in vivo*.

In *EBioMedicine*, Duan laboratory describes the potential of using CDK9 as a prognostic marker and therapeutic target for osteosarcoma [6]. This group focused on the relationship between CDK9 expression and the clinical prognosis of patients with osteosarcoma. They discovered that CDK9 is overexpressed in osteosarcoma tumor tissues and cell lines and its high expression is associated with the poor survival of patients with this disease. Of note, the CDK9 expression is significantly higher in metastatic osteosarcoma in comparison to the primary tumor. Although previous studies have linked CDK9 to cancer invasion and metastasis [7], this may be the first time to provide the clinical evidence showing a prominent role of CDK9 in metastatic osteosarcoma.

Further studies confirmed the impact of specific CDK9 inhibition in osteosarcoma cell migration *in vitro* using a CDK9-specific siRNA and a pharmacological inhibitor LDC000067. Because the pharmacological inhibition of CDK2/9 could suppress triple negative breast cancer cell migration through decreasing the phosphorylation of CDK-mediated Smad3 [8], Duan group speculated that CDK9 might promote osteosarcoma cell migration *via* Smad3 phosphorylation, which actually should be attributed to CDK2's activity. CDK9 has also been found to promote tumor growth and metastasis in cervical cancer *via* AKT2/p53 pathway [9]. Although it is plausible that CDK9/AKT2/p53 pathway may be involved in osteosarcoma metastasis, further investigation on the specific molecular mechanisms is warranted.

Interestingly, CDK9 expression level is negatively associated with the degree of chemotherapy-induced tumor necrosis in patients with osteosarcoma. Patients with higher CDK9 expression exhibited a poor response to chemotherapy, while those with low CDK9 expression showed a good response. Similar results have recently been observed in breast cancer by Schlafstein and colleagues [10]. Given the elegant experimental data, the inhibition of CDK9 could sensitize osteosarcoma cells to chemotherapy and CDK9 inhibitors could be used in combination with existing chemotherapies to open up new therapeutic strategies for osteosarcoma patients.

To demonstrate the therapeutic potential of CDK9 inhibitors in osteosarcoma, Duan group examined the effects of siRNA knockdown and pharmacological inhibition of CDK9 on osteosarcoma cell viability. As anticipated, CDK9 inhibition not only reduced the cell viability but also specifically downregulated the expression of phosphorylated RNAP11 ser2 as well as the anti-apoptotic proteins MCL-1 and BIRC5. Beyond inhibiting cell viability, CDK9 inhibition also significantly induced osteosarcoma cell apoptosis, reduced cell clonogenicity, and decreased spheroid diameter. Another key question from this work is whether the CDK9 inhibitor is effective and safe in animal models. If the safety and efficacy of CDK9 inhibitor can be further demonstrated in more clinically relevant models of osteosarcoma, these results may pave the way of CDK9 inhibitors to clinical applications.

In conclusion, the findings from Duan laboratory demonstrate the potential of using CDK9 as a prognostic marker for osteosarcoma and provide a basis for further development of CDK9 inhibitors for the treatment and prevention of osteosarcoma, especially those with metastatic diseases. Future studies are warranted to demonstrate the role of CDK9 in osteosarcoma metastasis and chemoresistance, to evaluate the *in vivo* efficacy and safety of CDK9 inhibitors, and to examine the synergistic effects of CDK9 inhibitors in combination with other chemotherapies.

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Disclosure

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References

[1] Durfee RA, Mohammed M, Luu HH. Review of osteosarcoma and current management. Rheumatol Ther 2016;3:221–43. https://doi.org/10.1007/s40744-016-0046-y.
[2] Peyressatre M, Prével C, Pellerano M, Morris MC. Targeting cyclin-dependent kinases in human cancers: from small molecules to Peptide inhibitors. Cancers 2015;7:179–237. https://doi.org/10.3390/cancers7010179.
[3] Boffo S, Damato A, Alfano L, Giordano A. CDK9 inhibitors in acute myeloid leukemia. J Exp Clin Cancer Res 2018;37(36). https://doi.org/10.1186/s13046-018-0704-8.
[4] Zhang H, Pandey S, Travers M, Sun H, Morton G, Madzo J, et al. Targeting CDK9 reactivates epigenetically silenced genes in cancer. Cell 2018;175:1244–1258.e26. https://doi.org/10.1016/j.cell.2018.09.051.
[5] Albert TK, Rigault C, Eickhoff J, Baumgart K, Antrecht C, Klebl B, et al. Characterization of molecular and cellular functions of the cyclin-dependent kinase CDK9 using a novel specific inhibitor. Br J Pharmacol 2014;171:55–68. https://doi.org/10.1111/bph.12408.
[6] Ma H, Seebacher NA, Hornicek FJ, Duan Z. Cyclin-dependent kinase 9 (CDK9) is a novel prognostic marker and therapeutic target in osteosarcoma. EBioMedicine 2018. https://doi.org/10.1016/j.ebiom.2018.12.022 Dec 19. pii: S2352–3964(18)30599–1.
[7] Shan B, Zhuo Y, Chin D, Morris CA, Morris GF, Lasky JA. Cyclin-dependent kinase 9 is required for tumor necrosis factor-alpha-stimulated matrix metalloproteinase-9 expression in human lung adenocarcinoma cells. J Biol Chem 2005;280:1103–11. https://doi.org/10.1074/jbc.M406293200.
[8] Thomas AL, Lind H, Hong A, Dokic D, Oppat K, Rosenthal E, et al. Inhibition of CDK-mediated Smad3 phosphorylation reduces the Pin1-Smad3 interaction and aggressiveness of triple negative breast cancer cells. Cell Cycle 2017;16:1453–64. https://doi.org/10.1080/15384101.2017.1338988.
[9] Xu J, Xu S, Fang Y, Chen T, Xie X, Lu W. Cyclin-dependent kinase 9 promotes cervical cancer development via AKT2/p53 pathway. IUBMB Life 2018. https://doi.org/10.1002/iub.1983.
[10] Schlafstein AJ, Withers AE, Rudra S, Danelia D, Switchenko JM, Mister D, et al. CDK9 expression shows role as a potential prognostic biomarker in breast cancer patients who fail to achieve pathologic complete response after neoadjuvant chemotherapy. Int J Breast Cancer 2018;2018:6945129. https://doi.org/10.1155/2018/6945129.