Oncogene

2022 Apr;41(18):2638-2650.
doi: 10.1038/s41388-022-02279-w. Epub 2022 Mar 30.

Selective histone methyltransferase G9a inhibition reduces metastatic development of Ewing sarcoma through the epigenetic regulation of NEU1

Daniel J García-Domínguez[1,2], Nabil Hajji[3], Roser López-Alemany[4], Sara Sánchez-Molina[5], Elisabet Figuerola-Bou[5], Francisco J Morón Civanto[6], Santiago Rello-Varona[4], Eduardo Andrés-León[7], Adrián Benito[8], Hector C Keun[8], Jaume Mora[5], Óscar M Tirado[4], Enrique de Álava[#9,10,11], Lourdes Hontecillas-Prieto[#12,13]
Affiliations expand

- PMID: 35354905
- PMCID: PMC9054661
- DOI: 10.1038/s41388-022-02279-w

Enlace web del artículo: https://pubmed.ncbi.nlm.nih.gov/35354905/

Free PMC article

Abstract

Ewing sarcoma (EWS) is an aggressive bone and soft tissue tumor with high susceptibility to metastasize. The underlying molecular mechanisms leading to EWS metastases remain poorly understood. Epigenetic changes have been implicated in EWS tumor growth and progression. Linking epigenetics and metastases may provide insight into novel molecular targets in EWS and improve its treatment. Here, we evaluated the effects of a selective G9a histone methyltransferase inhibitor (BIX01294) on EWS metastatic process. Our results showed that overexpression of G9a in tumors from EWS patients correlates with poor prognosis. Moreover, we observe a significantly higher expression of G9a in metastatic EWS tumor as compared to either primary or recurrent tumor. Using functional assays, we demonstrate that pharmacological G9a inhibition using BIX01294 disrupts several metastatic steps in vitro, such as migration, invasion, adhesion, colony formation and vasculogenic mimicry. Moreover, BIX01294 reduces tumor growth and metastases in two spontaneous metastases

mouse models. We further identified the sialidase NEU1 as a direct target and effector of G9a in the metastatic process in EWS. NEU1 overexpression impairs migration, invasion and clonogenic capacity of EWS cell lines. Overall, G9a inhibition impairs metastases in vitro and in vivo through the overexpression of NEU1. G9a has strong potential as a prognostic marker and may be a promising therapeutic target for EWS patients.

Conflict of interest statement

The authors declare no competing interests.

Figures

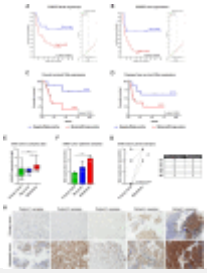

Fig. 1. *EHMT2* /G9a overexpression correlates with...

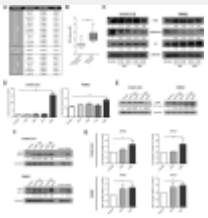

Fig. 2. EWS cell lines showed a...

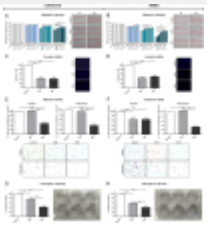

Fig. 3. Inhibition of G9a via BIX10294...

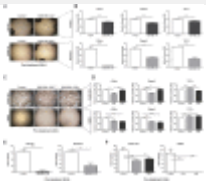

Fig. 4. BIX10294 treatment inhibited capacity for...

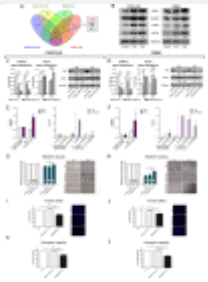

Fig. 5. NEU1 is differentially overexpressed upon...

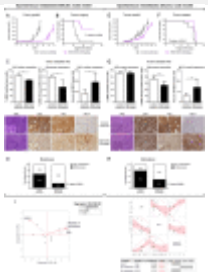

Fig. 6. Inhibition of G9a via BIX01294...

Similar articles

- KDM5A and PHF2 positively control expression of pro-metastatic genes repressed by EWS/Fli1, and promote growth and metastatic properties in Ewing sarcoma.

  McCann TS, Parrish JK, Hsieh J, Sechler M, Sobral LM, Self C, Jones KL, Goodspeed A, Costello JC, Jedlicka P.Oncotarget. 2020 Oct 27;11(43):3818-3831. doi: 10.18632/oncotarget.27737. eCollection 2020 Oct 27.PMID: 33196691 **Free PMC article.**

- The EWS/FLI Oncogene Drives Changes in Cellular Morphology, Adhesion, and Migration in Ewing Sarcoma.

  Chaturvedi A, Hoffman LM, Welm AL, Lessnick SL, Beckerle MC.Genes Cancer. 2012 Feb;3(2):102-16. doi: 10.1177/1947601912457024.PMID: 23050043 **Free PMC article.**

- Targeting the epigenetic readers in Ewing sarcoma inhibits the oncogenic transcription factor EWS/Fli1.

  Jacques C, Lamoureux F, Baud'huin M, Rodriguez Calleja L, Quillard T, Amiaud J, Tirode F, Rédini F, Bradner JE, Heymann D, Ory B.Oncotarget.

2016 Apr 26;7(17):24125-40. doi: 10.18632/oncotarget.8214.PMID: 27006472 **Free PMC article.**

- Therapeutic opportunities in Ewing sarcoma: EWS-FLI inhibition via LSD1 targeting.

  Theisen ER, Pishas KI, Saund RS, Lessnick SL.Oncotarget. 2016 Apr 5;7(14):17616-30. doi: 10.18632/oncotarget.7124.PMID: 26848860 **Free PMC article.** Review.

- Functional Role of G9a Histone Methyltransferase in Cancer.
  Casciello F, Windloch K, Gannon F, Lee JS.Front Immunol. 2015 Sep 25;6:487. doi: 10.3389/fimmu.2015.00487. eCollection 2015.PMID: 26441991 **Free PMC article.** Review.

See all similar articles

References

1. 1. Grunewald TGP, Cidre-Aranaz F, Surdez D, Tomazou EM, de Alava E, Kovar H, et al. Ewing sarcoma. Nat Rev Dis Prim. 2018;4:5. doi: 10.1038/s41572-018-0003-x. - DOI - PubMed
2. 1. Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol. 2010;11:184–92. doi: 10.1016/S1470-2045(09)70286-4. - DOI - PubMed
3. 1. Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley MC, et al. Ewing sarcoma: current management and future approaches through collaboration. J Clin Oncol. 2015;33:3036–46. doi: 10.1200/JCO.2014.59.5256. - DOI - PubMed
4. 1. Steeg PS. Targeting metastasis. Nat Rev Cancer. 2016;16:201–18. doi: 10.1038/nrc.2016.25. - DOI - PMC - PubMed
5. 1. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Jr, Kinzler KW. Cancer genome landscapes. Science. 2013;339:1546–58. doi: 10.1126/science.1235122. - DOI - PMC - PubMed

Show all 51 references

MeSH terms

- Animals
- Cell Line, Tumor

- Epigenesis, Genetic
- Gene Expression Regulation, Neoplastic
- Histone Methyltransferases / metabolism
- Humans
- Mice
- Neoplasm Recurrence, Local
- Neuraminidase / metabolism
- Neuraminidase / therapeutic use
- Oncogene Proteins, Fusion / genetics
- Proto-Oncogene Protein c-fli-1 / genetics
- Proto-Oncogene Protein c-fli-1 / metabolism
- RNA-Binding Protein EWS / genetics
- Sarcoma, Ewing* / drug therapy
- Sarcoma, Ewing* / genetics
- Sarcoma, Ewing* / pathology

Substances

- Oncogene Proteins, Fusion
- Proto-Oncogene Protein c-fli-1
- RNA-Binding Protein EWS
- Histone Methyltransferases
- NEU1 protein, human
- Neu1 protein, mouse
- Neuraminidase

Related information

- GEO Profiles
- Gene
- Gene (GeneRIF)
- MedGen
- Nucleotide
- Nucleotide
- Nucleotide (RefSeq)
- Nucleotide (RefSeq)
- Nucleotide (Weighted)
- Protein
- Protein (RefSeq)
- Protein (Weighted)
- Taxonomy via GenBank

LinkOut - more resources

- **Full Text Sources**
  - Europe PubMed Central
  - Nature Publishing Group
  - PubMed Central
- **Medical**
  - Genetic Alliance