Letter to the Editor

Molecular Cancer Research

"MPNST Epigenetics"—Letter

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In the July 2019 issue of *Molecular Cancer Research*, Korfhage and Lombard reviewed the implication of Polycomb repressive complex 2 (PRC2) alterations as drivers of malignant peripheral nerve sheath tumors (MPNST) development (1). PRC2 is a chromatin-modifying complex whose function is often altered in cancers by a variety of genetic mutations (2).

In this article, Korfhage and Lombard discussed the implication of the different PRC2 core components in MPNST pathogenesis. They highlight the striking observation that while two core PRC2 subunits (SUZ12 and EED) are recurrently found mutated in MPNSTs, mutations in EZH2, the main PRC2 enzymatic subunit, are never found (3). The authors discussed evidence suggesting that EZH2, in addition to its canonical function as a chromatin modifier, can participate in noncanonical functions in several cancers such as prostate and breast cancer. Such PRC2-independent functions, the authors hypothesized, could explain why the enzyme is not found altered in MPNST.

In a recent study (4) that was published just a few weeks before the Korfhage and Lombard review, we specifically addressed this question. Through genetic and pharmacologic analyses, we unambiguously establish that EZH2 is functionally inert in the context of SUZ12-mutated MPNST-derived cells, thereby excluding a PRC2-independent function. In the absence of SUZ12, EZH2 remains bound to EED but loses its interaction with all other core and accessory PRC2 subunits. In addition, we showed that EZH1 can largely compensate for loss of EZH2, explaining why EZH2 is not found mutated in this tumor type. Our results indicate how context-dependent redundancies between the two enzymatic subunits of the PRC2 can shape tumor-type–specific mutation patterns in chromatin regulators. Efforts to target PRC2-deficient MPNSTs pharmacologically will need to take into account these context-dependent specificities of PRC2.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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