3-DEAZANEPLANOCIN A (DZNep), A NEW MOLECULE TO TREAT CHONDROSARCOMAS?

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Growing evidences indicate that the histone methyltransferase EZH2 (enhancer of zeste homolog 2) may be an appropriate therapeutic target in some tumors, such as lymphomas, leading to development of several EZH2 inhibitors. The first molecule identified to downregulate EZH2, and subsequently to reduce methylation on lysine 27 of histone H3 (H3K27) was the 3-Deazaneplanocin A (DZNep). Interestingly, several reports suggest that this molecule may induce death of tumoral cells without affecting normal cells. The aim of this study was to determine whether DZNep may be also efficient to treat chondrosarcomas, a bone tumor considered as radio- and chimio-resistant.

By immunohistology, we show that high grade chondrosarcomas highly express EZH2, when compared to enchondromas or chondrocytes. In vitro, DZNep induces cell death of chondrosarcoma cell lines by apoptosis, while it slightly reduces growth of chondrocytes. In addition, DZNep reduces chondrosarcoma cell migration. In vivo, DZNep reduces growth of chondrosarcoma tumor xenograft in mice, without apparent side effects on other tissues (brain, liver, heart, cartilage…). Furthermore, we showed that DZNep inhibits EZH2 protein expression and reduce H3K27me3 in some chondrosarcoma cells lines but not in others, suggesting that its antitumoral action is independent to its ability to inhibit EZH2. This hypothesis was confirmed by the fact that another EZH2 inhibitor was not able to induce apoptosis of chondrosarcoma lines whereas it strongly reduced H3K27me3.

In conclusion, these results indicate that DZNep may be an interesting molecule to treat chondrosarcomas. However, its mechanism action is still unclear, since we show that it acts independently to its ability to inhibit the methylase EZH2.