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LETTER TO THE EDITOR

Dual LOX/COX inhibitors: potential novel anti-cancer drugs

R. Vijayakrishnan

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Dear Editor,

I read with great interest the article written by Barry et al. [1]. It is encouraging to see that more studies are being conducted to investigate inflammatory pathway drugs as potential targets for cancer therapeutics. Their observation that the anti-neoplastic effect of COX-2 inhibitors is not sustainable over long periods of time is interesting. Also they found that dual inhibition of COX and LOX pathways attenuated the escape process of these tumor cells. Thus, conclusion was made that even though COX-2 inhibitors may initially downstage tumors, their use along with lipoxygenase inhibitors leads to sustained anti-tumor response.

In 2005–2007 there were lots of reports demonstrating the favorable inhibition of cancer cells to dual inhibition of COX2 and LOX enzymes. Keeping this in mind, we used the available X-ray crystal structures of the complexes of COX2 and LOX with the known inhibitors to carry out a structure-based, rational, molecular modeling approach to design a small peptide inhibitor, which is potent for both COX and LOX [2]. Since the crystal structure of 5LOX was not known, and since the active sites of human 5LOX and mammalian 15LOX are highly similar, the crystal structure of rabbit 15LOX enzyme was used. Docking studies using Discovery Studio 1.7 (Accelrys Software Inc) indicated that the designed peptide inhibited both 15LOX and COX2 with potency in the nanomolar range, which is about 1,000 times more than the known dual LOX/COX inhibitors.

Barry et al. had raised concerns of the utility of such medications bearing in mind the increased incidence of cardiovascular events with selective COX-2 inhibitors [1]. The inhibitor designed by our team also blocks the COX1 enzyme so that the unwanted cardiovascular side effects of COX2 selective inhibitors are minimized [2]. Thus, the designed small peptide inhibitor is a novel lead compound for the design of a new class of stable anti-cancer drugs.

References

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R. Vijayakrishnan (✉)
Department of Medicine, Saint Vincent Hospital,
123 Summer Street, Worcester, MA 01608, USA
e-mail: rajakrishnan.vijayak@stvincenthospital.com