Structural Basis for Potent Inhibition of COX by Resveratrol-A Natural Product in Wine

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Non-steroidal antiinflammatory drugs block the cyclooxygenase activity of prostaglandin-H synthase, also known as cyclooxygenase (COX), the enzyme that mediates biosynthesis of eicosanoids from arachidonic acid. Two enzyme isoforms have been identified: COX-1 which is constitutively expressed, and COX-2, which is inducible. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytoalexin found predominantly in grapes and it has both antiinflammatory and cancer chemopreventive activity. One of the mechanisms of action of resveratrol is believed to be mediated through potent inhibition of COX-1 and COX-2 activity. We have determined the x-ray structure of COX-1 co-crystallized with resveratrol to 2.9 Å resolution using synchrotron radiation (BioCARS beamline 14-BM-C) to determine the binding mode of resveratrol in the active site. Using the crystal structures of COX-1/resveratrol and COX-2/flurbiprofen complexes, we performed computational docking studies of resveratrol and its two (3- and 4'-) sulfate metabolites using Dock 4.0.1. Our results indicate that the computed free energy values of binding for each of the docked resveratrol analogs are commensurate with their experimentally determined inhibition constants (K_i). However, the computational modeling results were unable to predict the selectivity in binding of resveratrol and its metabolites to the two enzymatic isoforms most probably due to the slight differences in binding affinities of these molecules for COX-1 or COX-2. This research is funded by grants from the National Cancer Institute (NIH: R03 CA92744-02 and 5 P01 CA48112-10).

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