Inhibition of SIRT1 Deacetylase Uncouples Anti-Inflammatory and Chemo-Preventive Actions of NSAIDs

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Cancer incidence is projected to increase due to several causes, including the increased ageing of population, novel strategies for prevention are therefore needed to lower the social/economic impact of this disease. Several epidemiological, clinical and experimental studies established non-steroidal anti-inflammatory drugs (NSAIDs) as promising chemo-preventive agents for many cancers. However, their use in chronic treatments is limited by gastrointestinal, renal and cardiovascular side effects mainly due to the inhibition of cyclooxygenase (COX) isozymes; still lacking is a clear positive risk-benefit balance to justify the treatment of relatively healthy, at risk population. Furthermore, the development of novel safer chemo-preventive NSAIDs is hampered by the lack of a clear picture concerning the mechanism of their anti-neoplastic effects. Inhibition of COX has been proposed as the mechanism underlying their anti-neoplastic activity; however, several lines of evidence challenged this view, among them the antitumor activity of non-COX inhibitory metabolites, enantiomers and derivatives are perhaps the most convincing. All these researches described a very heterogeneous and elusive picture, which is not yet providing a clear molecular target alternative to COX entailing the anti-neoplastic activity of NSAIDs. The aim of the present study was to investigate a novel direct target of NSAIDs, which may provide a biochemical explanation of the multiplicity of the COX-independent effects ascribed to NSAIDs and their metabolites, enantiomers and derivatives.

Previous data showed that aspirin treatment promotes p53 acetylation at residue K382 in the MDAMB 231 breast cancer cell line (Alfonso et al., Int. J. Oncol. 2009). We initially tested by western blot analysis, whether other NSAIDs and exisulind, a metabolite of sulindac that does not display anti-inflammatory properties, had the same effect on p53 acetylation. This treatment was able to increase acetylation and the expression of p53 target genes in vitro and in vivo in the breast of mice exposed to a genotoxic agent. These and other results demonstrated that all NSAIDs with anti-cancer properties were able to induce p53 acetylation and transcriptional activation both in cell lines and in the mouse mammary tissue in vivo. Sulindac sulfone displayed the same activity suggesting that p53 acetylation was induced by a COX-independent mechanism of action. To demonstrate the clinical relevance of this mechanism, we have analysed breast cancer specimens from individuals that were intraoperatively treated with ketorolac or opiates as alternative analgesic treatments during the anaesthesia procedure. Previous epidemiological studies demonstrated that intraoperative treatment with ketorolac was associated with a decreased risk of early relapse and longer survival of patients (Forget et al., Anesth. Analg. 2010). The results of our western blot analysis showed that ketorolac treatment produced an increased p53 acetylation suggesting that this mechanism could be elicited also in human and might be linked with the previously reported chemopreventive effect. Taken together, our data disjoined the COX-dependent anti-inflammatory from the chemo-preventive SIRT1-dependent activity of

NSAIDs thus prompting us to design novel molecules displaying anti-neoplastic activity without the COX-dependent side effects, which are currently hampering the use of NSAIDs as chemopreventive agents.

Alfonso et al. (2009). Int J Oncol. 34, 597-608.

Forget et al. (2010). Anesth Analg. 110, 1630-1635.