Aspirin and Salicylic Acid in the Combination with Inhibition of PI3K Promote Cell Death in Malignant Melanoma

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Aspirin (acetylsalicylic acid) and salicylic acid are anti-inflammatory drugs with several molecular targets in cells. They were also found to suppress the growth of prostate and colon cancer cells. Malignant melanoma is an aggressive skin cancer with a high death rate for which there is no effective treatment available. In my study, I tested the effect of small molecule drug combinations containing aspirin or salicylic acid on the growth and viability of B-Raf mutated malignant melanoma cell line A375. I found that the combination of aspirin/salicylic acid with LY294002, an inhibitor of the PI3K signalling pathway, leads to a significant decrease of viability of the cancer cells. The proportion of dead cells also increased when aspirin or salicylic acid was combined with Gossypol, an inhibitor of anti-apoptotic proteins of Bcl-2 family, suggesting that these proteins might limit the activity of salicylates in melanoma cells. I further investigated the mechanism of action of aspirin and salicylic acid on malignant melanoma. While cyclooxygenases COX-1 and COX-2 have been established as targets of salicylates, the fact that we have not observed any significant decrease in viability of melanoma cells treated with the combination of PI3K inhibitor and the small molecule cyclooxygenase inhibitor Celecoxib suggests that the antiproliferative effect of salicylates may not be mediated through cyclooxygenase inhibition. Interestingly, I observed a strong inhibition of phosphorylation of initiation factor 4E-binding protein 1 in melanoma cells, which would lead to the stopping of cap-dependent translation and this might limit their survival.

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