Disruption of Sphingolipid Biosynthesis in Hepatocyte Nodules: Selective Proliferative Stimulus Induced by Fumonisin B_1.

[1]**Van der Westhuizen, L.**, [1]Gelderblom, W.C.A., [1]Shephard, G.S. and [2]Swanevelder, S.

[1]PROMEC Unit, Medical Research Council; [2]Biostatistics Unit, Medical Research Council, Tygerberg, 7505, South Africa.

Fumonisin B_1 (FB_1), a food borne mycotoxin predominantly produced by *Fusarium verticillioides*, inhibits ceramide synthase, a key enzyme in the sphingolipid biosynthetic pathway. The role of this sphingolipid disruption in the development of hepatocyte nodules were investigated. Male Fischer 344 rats were subjected to cancer initiation (FB_1-containing diet or diethylnitrosamine [DEN] by i.p. injection) and promotion (2-acetylaminofluorene with partial hepatectomy [2-AAF/PH]) treatments followed by a secondary FB_1 dietary regimen. Sphinganine (Sa) and sphingosine (So) levels were measured by high-performance liquid chromatography in control, surrounding and nodular liver tissues of the rats. The disruption of sphingolipid biosynthesis by the secondary FB_1 treatment in the control rats was significantly ($p<0.05$) enhanced by the 2-AAF/PH cancer promotion treatment. The nodular and surrounding Sa levels returned to baseline following FB_1 initiation and 2-AAF/PH promotion. When comparing the groups subjected to the secondary FB_1 treatment, the initiation effected by FB_1 was less ($p<0.01$) sensitive to the accumulation of Sa in the nodular and surrounding tissues than DEN initiation and the 2-AAF/PH control treatment. In contrast, the So level of FB1 initiation was marginally increased in the nodules compared to the surrounding liver after 2-AAF/PH promotion and significantly ($p<0.05$) higher with the secondary FB_1 treatment. Although the FB_1-induced hepatocyte nodules were not resistant to the disruption of sphingolipid biosynthesis, the nodular So levels were increased and might provide a selective growth stimulus possibly induced by bio-active sphingoid intermediates such as sphingosine 1-phosphate.