UNIVERSITÀ DEGLI STUDI DI SALERNO

UNIVERSITÀ DEGLI STUDI DI SALERNO
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PhD Thesis in

The Winnie-APCmin as an Innovative Tool to Investigate the Axis Between Inflammation and Colorectal Cancer

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EGLISH SUMMARY

During these last three yeas of PhD we aimed to create a new murine model of spontaneous inflammatory-induced colorectal cancer a combining the genetic susceptibility of the APC^{Min} model and the chronic intestinal inflammation of the Winnie mice. Differently from the DSS induced colitis, Winnie are murine models of spontaneous, mild and progressive ulcerative colitis that require several months to show histological sign of disease. During these years, we characterized the disease progression in Winnie. 5-week old mice show reduced body weight, watery diarrhea, but now rectal bleeding or prolapse. Importantly, histologically no distinctive sign of UC is present in the colon, but a specific molecular pathway characterized by upregulated inflammatory cytokine transcript is present.

In light of the mild inflammatory response observed in 5-wee old Winnie, it was surprising to realize that the colon of age matched Winnie-APC^{Min} mice was rich of dysplastic ACFs along the all the colon length with a gradually increase in incidence and multiplicity moving from the proximal to the distal colon tract. The Winnie-APC^{Min} molecular pathway underlines the unique molecular feature resulting from the combination of genetic predisposition and chronic inflammation. This still preliminary observation has been used to submit an experimental protocol aiming to prevent the upregulation of some of the Winnie-APC^{Min} specific genes using nutritional strategies that suppress the intestinal inflammation and/or prevent dysbiosis. Indeed, nutritional based strategies to suppress or mitigate intestinal inflammation has been one of the most important research topic of our group. For this reason, we used BMDCs as a paradigm of cells potentially affected by polyphenol exposure.

Dendritic cells respond to quercetin exposure producing secretory leukocyte protease inhibitor (SLPI). SLPI is an antimicrobial protein that is also involved in tissue repair and possess the ability to block NFkB nuclear translocation with the ultimate result to suppress inflammation. Using Slpi-KO DCs we demonstrated that Slpi induction was a necessary step following quercetin administration to suppress inflammatory cytokine secretion. Using an easy dose response experiment, we demonstrated that the administration of inorganic iron was able to block quercetin in a dose dependent manner. As quercetin is a strong iron chelating agent, we proposed that quercetin-iron chelation may result in DCs cytoplasmic loss of iron reservoir and consequent switch to an inflammatory-impaired phenotype. At the same time, nutritional intake of quercetin may contribute to sequestrate iron from the intestinal lumen, suppressing bacterial growth. This aspect was partially explored using polyphenol enriched diet administered to WT or Winnie mice. Dysbiosis is partially recovered after two weeks of 1% enriched diet. The Winnie-APCMin model will be crucial to evaluate the efficiency of the polyphenol-enriched nutritional strategies and, potentially, many different pharmaceutical approaches.