MODULATION OF MYELOID DERIVED SUPPRESSOR CELLS: A NEW STRATEGY TOWARDS HYDROGEN SULFIDE ANTI-CANCER EFFECTS

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Introduction: Chronic inflammation is considered to be one of the hallmarks of tumor initiation and progression. Pro-inflammatory mediators have been shown to induce DNA damage, which contributes to genetic instability and transformed cell proliferation; to promote angiogenesis and thereby enhance tumor growth and invasiveness; and to impair myelopoiesis and hemopoiesis, which cause immune dysfunction and inhibit immune surveillance. Myeloid-derived suppressor cells (MDSCs) represent the major components of this immune-suppressive network. MDSC are a heterogeneous population of immature myeloid cells with potent immune suppressive activity. They are directly implicated in the transformation of premalignant cells and promote tumor growth and metastasis. Above all else, MDSCs cause immune suppression in most cancer patients, representing the major obstacle to cancer treatment. Thus, targeting MDSCs might be useful to prevent tumor initiation or to improve the efficacy of immunotherapy for cancer treatment. Recently, new roles of hydrogen sulfide (H_2S) in the pathophysiology of cancer have emerged. H_2S is an endogenous signaling molecule with a plethora of cellular and molecular targets. Many studies have shown that H_2S donors exert anticancer actions in vitro and *in vivo*. In this study, we investigated on the ability of the naturally occurring H_2S donors diallyl trisulfide (DATS) to modify the immune cells profile in tumor microenvironment focusing on MDSCs.

Materials and methods: The effect of H_2S on the host immune response to cancer was evaluated using a:

- *in vivo* model of colitis-associated cancer induced by infection with the intestinal bacteria Helicobacter hepaticus (Hh) of 129SvEvS6/Rag2$^{-/-}$ mice;
- *in vivo* syngeneic model of murine melanoma induced by subcutanus injection of B16F10 murine melanoma cells in C57/BL6mice.

Mice were treated with DATS by oral gavage once a day for 14days and analyzed for MDSCs composition by flow cytometry.

Results: The progressive intestinal inflammation induced by Hh in Rag2$^{-/-}$ mice went along with a significantly time-dependent increase in the frequency of MDSCs both in colon and spleen. Moreover, following Hh mouse infection, we observed a significant reduction of H_2S levels in inflamed colon that was correlate with the down-regulation of CBS protein and mRNA expression. Finally, we found that enhancement of H_2S levels in Hh-infected mice, obtained by administration of DATS (50mg/Kg), resulted in a significant reduction of inflammation in the distal part of the colon that was accompanied with a significant reduction of MDSCs in colon. In melanoma-bearing mice, DATS inhibited tumor growth and this effect was associated with a reduction in the frequency of MDSCs in the spleen, in the blood as well as in the tumor microenvironment. In addition, we found that DATS was able to inhibit immunosuppressive activity of MDSCs and to restore T cell proliferation and function.

Discussion and conclusions: H_2S donors have been proposed as novel anti-cancer drugs. In fact relatively high concentrations of exogenous H_2S could suppress cancer cells growth via various mechanisms including inhibition of cell proliferation and induction of cell death signaling, inhibition of NF-κB activation, inhibition of cancer cell metabolism. Here, we delineate a novel mechanism for the anti-cancer effect of H_2S based on its ability to inhibit immunosuppressive MDSCs accumulation and functions. Our study adds a new piece in the complex machinery that regulates MDSCs expansion and activity unrevealing an additional molecular mechanism driven by H_2S. In conclusion, these data indicate that increasing H_2S level in the body by giving H_2S donors or by stimulating its endogenous synthesis may reduce the risk of developing cancers and improve clinical responses to immunotherapy in cancer.