TARGETING S100B-P53WT PROTEIN-PROTEIN INTERACTION WITH PENTAMIDINE: A NOVEL APPROACH TO CONTRAST CHRONIC INFLAMMATION-INDUCED COLON CANCER DRIFT

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Colorectal cancer (CRC) is one of the most common cancer and the fourth leading cause of cancer death worldwide (Arnold et al., 2016). Several studies have suggested a strictly association between CRC and intestinal chronic inflammation. Indeed, an increased incidence of colon adenocarcinoma has been observed in patients affected by intestinal bowel disease (IBD), which are more sensitive to tumorigenic drift because of their extensive state of chronic inflammation (Jess et al., 2012). In this scenario, the enteroglial-derived S100B protein displays a prominent role in both chronic inflammation perpetuation, via Receptor for Advanced Glycation End products (RAGE) interaction triggering lipid peroxodation, promoting p38 MAPK phosphorilation and NF-κB nuclear traslocation, and cancer promotion through the tumor suppressor p53wt protein inhibition (Lin et al., 2004). It can be assured that molecular targeting of S100B protein activity may be an innovative approach of intervention against CRC, as already seen for melanoma (Hartman et al., 2013). In this context, pentamidine, an old antiprotozoal drug, appears an intriguing candidate because of its capability to block S100B-p53wt protein-protein interaction (Charpentier et al., 2008), exerting a dual antinflammatory and antitumoral activity.

Aim of this study is to investigate the role of S100B protein in human sporadic colon cancer in correlation with chronic inflammation states and healthy subjects, at testing whether the S100B-p53wt interaction might potentially be a therapeutic strategy in CRC treatment.

Human colonic surgical specimens were used to assess biochemical analysis and composed the following groups: 1) control group, collected from control subjects undergoing colonscopy for CRC screening; 2) peritumoral group, peritumoral areas from patients diagnosed for CRC; 3) UC group, collected from patients with diagnosed UC; 4) tumoral group, tumoral areas from the same patients diagnosed for CRC. In a second set of experiments, specimens composing the same experimental groups were collected and cultured with or without pentamidine 5 μM for 24 h and then biochemical analysis were performed. Finally, surgical specimens deriving from control group were cultured and exposed to S100B at increasing concentration (0.005-5 μM) given alone or exposed to S100B 5 μM in the presence of pentamidine (0.005-5 μM) for 24 h and then underwent to biochemical analysis. All patients received and signed an informed consent and all procedures were approved by the Ethical Committee of the University of Naples “Federico II”.

Our results show that S100B, iNOS, RAGE, pp38 MAPK, NF-κB, AQP4 and PCNA protein expression, MPO and MDA concentration and nitrite, S100B, VEGF and IL-6 significantly increase with injury severity, starting from peritumoral and UC groups up to tumoral group in comparison with control group. Interestingly, p53wt and bax protein expression significantly decrease with severity of the injury increasing versus control subjects.

Pentamidine exposure didn't affect S100B protein expression and release but, due to its ability to inhibit S100B action, is able to significantly reduce the expression and release of all described mediators, as well as to induce a marked upregulation of p53wt and bax protein expression in the different experimental groups.

Similar results were observed in surgical specimens from control subjects following exposure to exogenous S100B in presence/absence of pentamidine, in a concentration-dependent fashion.

These results show that inhibition of S100B-p53wt connection by pentamidine might represent a novel therapeutic approach to block S100B hypersecretion and to counteract carcinogenic drift restoring p53wt activity.

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