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LETTER TO THE EDITOR

Pro-inflammatory S100A9 Protein: a Double-Edged Sword in Cancer?

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Calgranulins, S100A8 (calgranulin A), S100A9 (calgranulin B), and S100A12 (calgranulin C), belong to the S100 family of calcium-binding proteins that are expressed in a number of cells, particularly in human neutrophils. They act *via* two receptors, the receptor for advanced glycation end products (RAGE) and toll-like receptor 4 (TLR4), to stimulate pro-inflammatory responses [1, 2]. The S100A12 gene is located between S100A8 and S100A9 in the human genome, whereas it is not present in the murine genome [3].

We enjoyed reading the article published by Bennett et al. in *Inflammation*. The authors reported that S100A9 levels in bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF) were significantly elevated compared to healthy controls. They noted that S100A9 can be used as a prognostic biomarker in IPF [4]. S100A9 has also been shown to be associated with the development of IPF [5]. In addition to lung diseases, S100A9 is over-expressed in many cancer types such as lung cancer [6]. Although S100A9 contributes to the pathogenesis of different cancers, the data provides evidence that it may also inhibit the growth of cancer cells. Therefore, it must be taken into account that S100A9 could exert suppressive effects and this alludes to its controversial role in a number of cancers, including colon cancer.

p53, a tumor suppressor gene that regulates the cell cycle is involved in apoptosis and prevents angiogenesis. p53 binds to the promoter of the gene encoding S100A9 through p53BS (p53-binding sites) and activates transcription of the *S100A9* promoter. In fact, S100A9 has been shown to trigger p53-dependent apoptosis in the human colon cancer cell line HCT116 [7]. S100A9 also induces apoptosis in the human cervical cancer cell line CaSki [8] and human monocytic leukemia cell line THP-1 [9]. In the latter study, it was also noted that TLR4 may be involved in the induction of apoptosis by S100A9. It has been well established that S100A9 contributes to colon tumorigenesis *via* interaction with its receptor (RAGE) [10, 11]. The relationship between S100A9 and colon cancer has been studied in the context of the inflammatory microenvironment [12]. Of interest, expression of S100A9 was not shown in human colon cancer cell lines; however, there was a correlation between its expression in colon cancer tissues and stromal inflammatory cells. Among different cancer cell lines studied, only colon cancer cell lines were able to absorb S100A9 which led to the induction of apoptosis. The data emphasized the importance of the antitumor effects of S100A9 released from inflammatory cells into the colon cancer microenvironment and suggested its potential therapeutic value. Moreover, it has been demonstrated that regulation of S100A9 is involved in the development of colitis-associated cancer [13]. In this case, chitinase 3-like 1 (CHI3L1), expressed and secreted by a number of cells such as macrophages and neutrophils in response to inflammation, mediates its anti-apoptotic effects by downregulating S100A9 in the colonic microenvironment. Taken together, at least in the case of colon cancer, these observations reinforce the idea that low levels of pro-apoptotic S100A9 in the tumor microenvironment could promote tumor initiation and progression. What is emphasized here is the fact that cancer studies should consider both antitumor and pro-tumor functions of S100A9. Future research should aim to clarify the complex role of S100A9 in inflammation-associated tumorigenesis.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no conflict of interest.

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