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S100A8 and S100A9 in inflammation and cancer

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Abbreviations:
DMBA, 7,12-dimethylbenz(a) anthracene
TPA, 12-O-tetradecanoylphorbol-13-acetate
SCC, squamous cell carcinoma
AP-1, activator protein-1
NF-κB, nuclear factor-κB
JNK, Jun N-terminal kinase
AGEs, advanced glycation end-products
RAGE, receptor of advanced glycation end-products

ABSTRACT

Calprotectin (S100A8/A9), a heterodimer of the two calcium-binding proteins S100A8 and S100A9, was originally discovered as immunogenic protein expressed and secreted by neutrophils. Subsequently, it has emerged as important pro-inflammatory mediator in acute and chronic inflammation. More recently, increased S100A8 and S100A9 levels were also detected in various human cancers, presenting abundant expression in neoplastic tumor cells as well as infiltrating immune cells. Although, many possible functions have been proposed for S100A8/A9, its biological role still remains to be defined. Altogether, its expression and potential cytokine-like function in inflammation and in cancer suggests that S100A8/A9 may play a key role in inflammation-associated cancer.

1. Introduction

During the past decade, cancer research has generated a complex picture of dynamic genetic and epigenetic changes within the genome of transformed cells influencing the expression and function of numerous proto-oncogenes and tumor suppressor genes implicated in regulatory circuits governing cell proliferation, differentiation, and homeostasis. Emerging evidence indicates that tumorigenesis is a multistage process bearing analogy to classical evolution and leading to progressive conversion of normal cells into cancer cells. Hanahan and Weinberg suggested that the vast majority of cancer cell genotypes is the consequence of six essential alterations in cell physiology that result in malignant growth including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion

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of programmed cell death, unlimited replication potential, sustained angiogenesis, and tissue invasion/metastasis [1]. In addition, solid cancers are not only autonomous masses of transformed tumor cells, but also consist of multiple cell types including adjacent fibroblasts and epithelial cells, innate and adaptive immune cells, as well as cells from the blood and lymphatic vasculature, which create a tumor-specific microenvironment. Recent studies on mouse tumor models and numerous clinical observations have provided new insights in the molecular mechanisms of communication between tumor and stromal cells and in the role of soluble factors and direct cell–cell adhesion during each stage of cancer development [2–7].

Chemically induced skin carcinogenesis represents one of the best-established *in vivo* models to study the multistage nature of tumor development and to design novel therapeutic concepts for human epithelial neoplasia [8,9]. This tumor model is generated first by single application with the mutagen 7,12-dimethylbenz(a)anthracene (DMBA), which leads to frequent HA-Ras mutations of initiated keratinocytes. Tumor promotion is achieved by repeated subsequent treatment with phorbolesters, such as 12-O-tetradecanoylphorbol-13-acetate (TPA) resulting in benign papillomas, some of which spontaneously progress into malignant squamous cell carcinomas (SCC). Compelling experimental evidence argues for an important contribution of gene regulatory networks controlled by the transcription factor AP-1 in neoplastic transformation of keratinocytes and skin cancer development. AP-1 is mainly composed of Jun and Fos protein dimers and mediates gene transcription in response to many physiological and pathological stimuli, including cytokines, growth factors, stress signals, bacterial and viral infections, as well as oncogenic stimuli [10,11]. Studies in genetically modified mice and in cell culture models have highlighted a crucial role for AP-1 in numerous cellular events, such as proliferation, differentiation, and survival, which are involved in normal development and neoplastic transformation [12]. The requirement of AP-1-mediated gene transcription that leads to tumor promotion in response to TPA has been extensively studied in the mouse epidermal JB6 model [13,14]. Moreover, detailed analysis of genetically modified mice with impaired JNK/AP-1 function revealed that changes in the gene regulatory network depending on JNK signaling and AP-1 activity are key features of multistage skin carcinogenesis *in vivo* [15–18]. NF-κB is another important transcription factor that has been identified as an essential player in neoplastic transformation of keratinocytes [13,14]. NF-κB collectively describes a family of dimeric transcription factors consisting

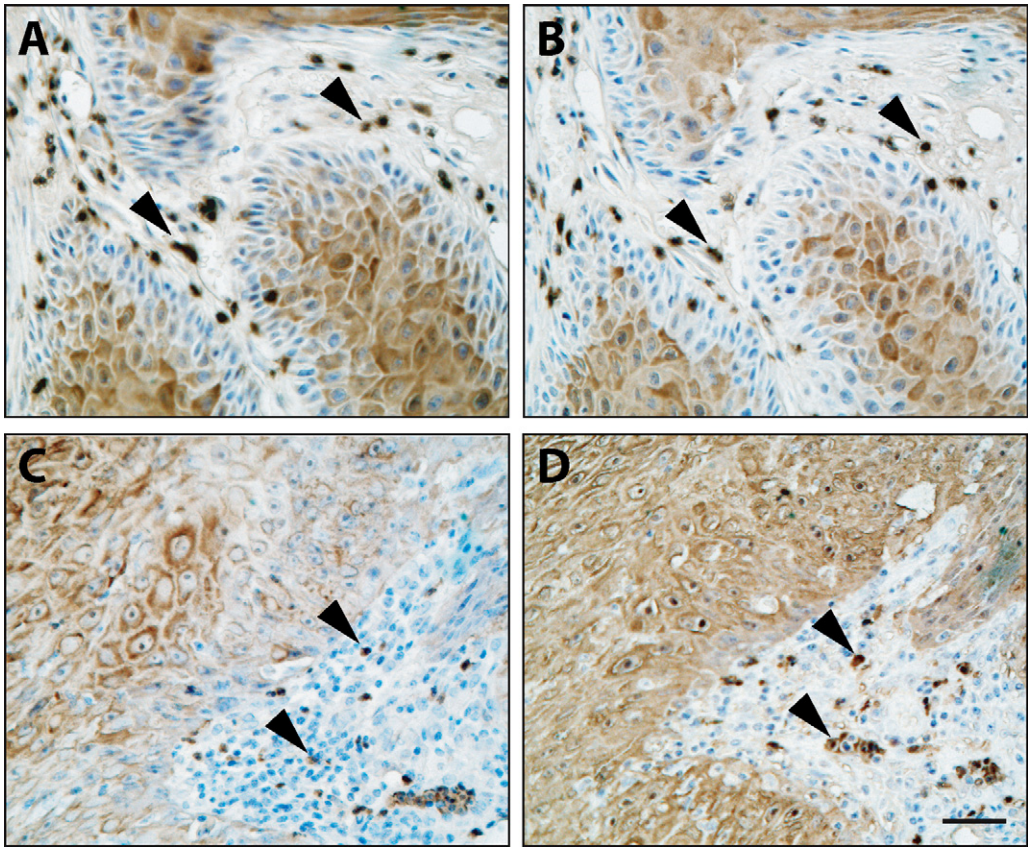

Fig. 1 – S100A8 and S100A9 expressions are restricted to different cellular compartments of mouse and human skin tumors. Representative images showing S100A8 (A and C), and S100A9 expression (B and D; stainings in brown) by immunohistochemistry on parallel tissue sections of mouse papilloma derived from the chemically induced skin carcinogenesis model (A and B) and tissue sections of human cutaneous SCC (C and D). Both proteins are strongly and coordinately expressed in tumor cells of the differentiating compartment and in distinct stromal cells (arrowheads).