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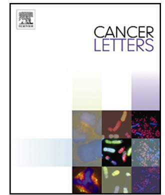

Original Articles

Metabolic reprogramming supports the invasive phenotype in malignant melanoma

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ABSTRACT

Invasiveness is a hallmark of aggressive cancer like malignant melanoma, and factors involved in acquisition or maintenance of an invasive phenotype are attractive targets for therapy. We investigated melanoma phenotype modulation induced by the metastasis-promoting microenvironmental protein S100A4, focusing on the relationship between enhanced cellular motility, dedifferentiation and metabolic changes. In poorly motile, well-differentiated Melmet 5 cells, S100A4 stimulated migration, invasion and simultaneously down-regulated differentiation genes and modulated expression of metabolism genes. Metabolic studies confirmed suppressed mitochondrial respiration and activated glycolytic flux in the S100A4 stimulated cells, indicating a metabolic switch toward aerobic glycolysis, known as the Warburg effect. Reversal of the glycolytic switch by dichloracetate induced apoptosis and reduced cell growth, particularly in the S100A4 stimulated cells. This implies that cells with stimulated invasiveness get survival benefit from the glycolytic switch and, therefore, become more vulnerable to glycolysis inhibition. In conclusion, our data indicate that transition to the invasive phenotype in melanoma involves dedifferentiation and metabolic reprogramming from mitochondrial oxidation to glycolysis, which facilitates survival of the invasive cancer cells. Therapeutic strategies targeting the metabolic reprogramming may therefore be effective against the invasive phenotype.

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Introduction

Metastasis relies on cancer cells with phenotypic plasticity to enable accomplishment of all steps in the metastatic cascade. An important example of such plasticity is the transition to an invasive (mesenchymal) phenotype, which not only facilitates dissemination from a primary tumor and extravasation at distant sites [1] but also can promote therapy resistance [2]. Invasiveness is consequently considered as a hallmark of aggressive, metastatic cancer cells, and factors involved in acquisition or maintenance of the invasive phenotype might be highly relevant targets in anti-metastasis therapy.

Malignant melanoma is one of the most aggressive forms of human cancer, and melanoma cells exhibit considerable phenotypic plasticity [3]. Comparison of melanoma cell lines with high *versus* low invasive capacity revealed that the melanocyte differentiation genes controlled by the master regulator of the lineages, Microphthalmia-associated transcription factor (MITF), were among the signature genes clearly distinguishing the two phenotypes. While highly expressed in poorly invasive cells, low expression in the counterpart indicated that invasive cells are less differentiated [4,5]. Further signifying the importance of the dedifferentiation state for melanoma aggressiveness is the observation that less differentiated melanoma cells show higher resistance to therapy [6]. Although an association between aggressiveness and invasive dedifferentiated phenotype has been acknowledged, the mechanisms involved in acquisition of such phenotype are not fully clarified. It has been reported previously that melanoma cells can switch between proliferative/differentiated and invasive/dedifferentiated phenotypes during metastasis progression [7,8]. Further, it was proposed that the tumor microenvironment plays a significant role in the

Abbreviations: DCA, dichloracetate; LDH, lactate dehydrogenase; MITF, microphthalmia-associated transcription factor; NMR, nuclear magnetic resonance; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPP, pentose phosphate pathway; TCA, tricarboxylic acid.

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regulation of the phenotype switch [7], due to a multitude of factors present in the microenvironment that may influence the malignant phenotype [9]. Among such factors are members of the S100-protein family that affect many cellular processes including cell migration and invasion [10]. A number of these proteins, such as S100A4 (also known as metastasin (Mts1) or fibroblast-specific protein 1 (FSP1)), are associated with metastasis and poor prognosis in several cancer types, including melanoma [11]. Both cancer cells and stromal cells express and secrete S100A4, actualizing the protein as an important factor in the tumor microenvironment [12–16]. Extracellular S100A4 has been shown to induce motility in several cancer types [17,18]. The protein is also known as a regulator of epithelial–mesenchymal transition (EMT), being particularly enriched in mesenchymal, stem cell-like subpopulations of carcinoma [2,19].

Metabolic plasticity has emerged as an important feature to aid cancer cells during tumor progression. Cancer cells can utilize glycolysis rather than oxidative phosphorylation even in the presence of oxygen (known as the Warburg effect) [20,21]. Aerobic glycolysis not only assures supply of energy and building blocks for fast proliferating cells but can also be beneficial for invasive, metastatic cells [22]. However, the relationship between metabolism and metastasis is poorly understood, and e.g. mitochondrial oxidation has been linked with both pro-metastatic [23] and anti-metastatic [22,24] effects. Interestingly, it has been recently shown that the main regulator of melanocyte differentiation, MITF, controls an important regulator of mitochondrial metabolism, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) [25,26]. These reports suggest interconnectivity between differentiation and metabolic pathways, and further propose that development of the invasive dedifferentiated phenotype could involve metabolic reprogramming.

In the present study, we investigated phenotype modulation induced by the pro-metastatic protein S100A4 in malignant melanoma *in vitro*, focusing on the relationship between enhanced cellular motility, differentiation status and metabolic alterations. We revealed that upon stimulation with S100A4, melanoma cells acquire the invasive dedifferentiated phenotype and simultaneously switch

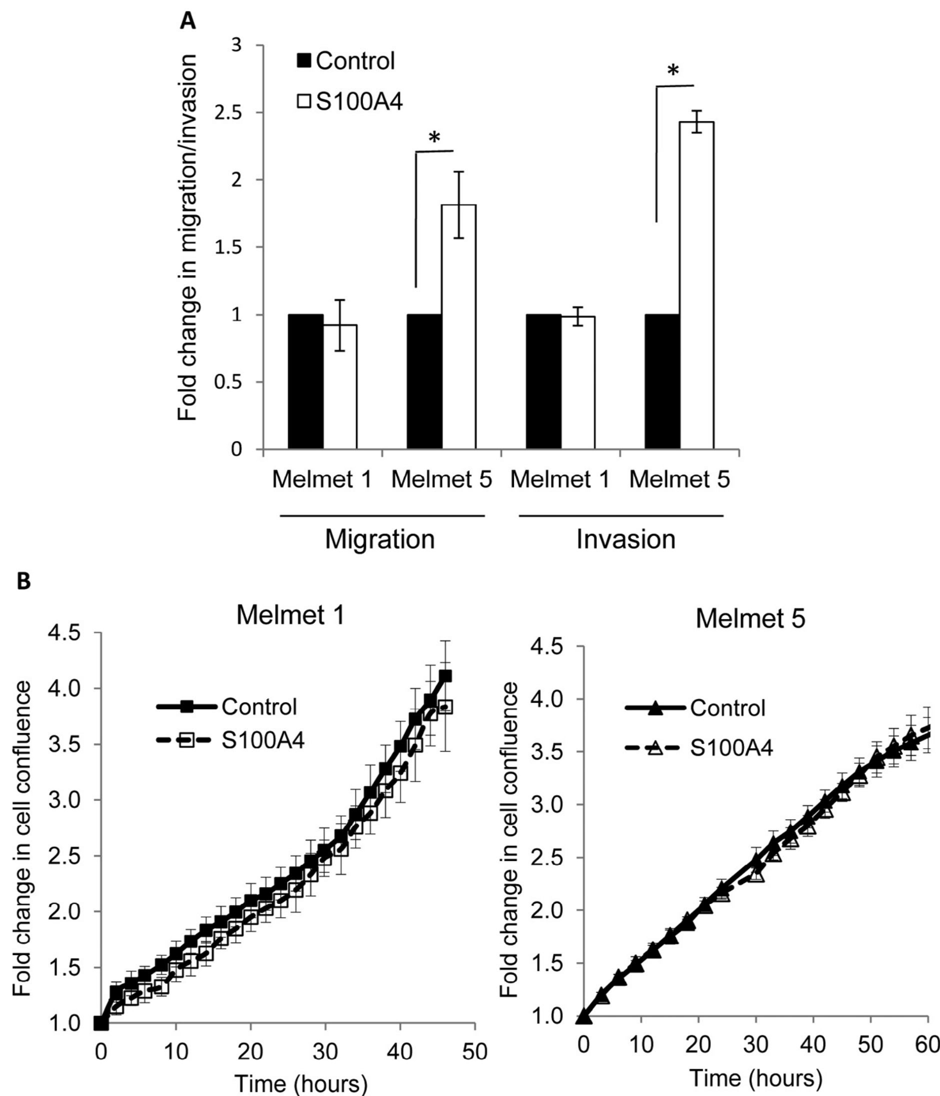

Fig. 1. S100A4 stimulates melanoma cell motility without affecting proliferation. (A) Effect of S100A4 on migration and invasion in Melmet 1 and Melmet 5 cells was evaluated in a trans-well chamber by stimulating the cells for 48 hrs, and calculating fold change in the fraction of migrated cells compared to the non-stimulated controls (where migration was set to 1). Error bars indicate SD (Melmet 1, n = 1, 3 parallel wells) and SEM (Melmet 5, n = 3); *$p < 0.05$. (B) Proliferation of melanoma cells with/without S100A4 was tracked by IncuCyte and presented as fold increase in cell confluence as a function of time. Representative graphs from at least three independent experiments are shown; error bars indicate SD (from at least 5 parallel wells) in the presented experiment.

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