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Research Article

Adiponectin Regulates the Development and Progression of MCA-Induced Sarcoma in Mice

Abstract

Background: Sarcomas are malignant tumors with low survival rates and remain refractory to the current therapeutic methods. Adiponectin plays crucial roles in many physiological responses. Studies have shown that adiponectin could regulate various tumors. However, the roles of adiponectin in sarcomas remain unknown.

Results: In this study, we found that the adiponectin-deficient mice induced by MCA develop sarcomas more rapidly and frequently than the WT mice do. With the sarcomas formation, adiponectin deficiency showed inhibiting effect on tumor growth and reduced the mortality rates of the mice with sarcomas.

Conclusions: Adiponectin inhibits the sarcomas formation, but may promote the growth of tumor after sarcomas occur.

Abbreviations

ADN: Adiponectin; MCA: Methylcholanthrene; WT: Wild Type; KO: Adiponectin Knockout Mice

Background

Adiponectin (ADN) is a type of adipocytokine and it is primarily produced by adipose tissues [1]. Studies have shown that adiponectin plays crucial roles in many physiological responses, such as inflammation and cancer [2,3]. Many reports demonstrated that adiponectin has regulatory effects on the development and progression of various tumors via different signaling pathways [4-6]. Our previous studies also explore the potential mechanism of adiponectin on pancreatic cancer [7]. However, the roles of adiponectin in sarcomas remain largely unknown. Sarcomas could occur in different tissues and can be divided into two major groups, namely, bone and soft-tissue sarcomas [8,9]. Sarcomas are malignant tumors with low survival rates and remain refractory to the current therapeutic methods [8]. Therefore, it is significant to study the development, treatment and prognosis of sarcomas. Methylcholanthrene (MCA)-induced sarcoma model is a classical animal model of sarcoma and can be used to investigate the tumor immunology [10].

In our study, we used a low-dose MCA-induced mouse sarcoma model to explore whether adiponectin can affect the development and progression of mouse sarcoma. The results indicated that adiponectin deficiency increased the tumor incidence; in addition, the occurrence of sarcoma was earlier in contrast with the wild type (WT) mice. It is worth mentioning, after the sarcomas formation, adiponectin deficiency had been shown to have the effect of suppressing tumor growth. Mortality rates of the adiponectin-deficient mice with sarcoma were lower than the rates of the WT control group. Our data suggested that adiponectin may have inhibiting effects on the sarcomas formation, whereas, promote the tumor growth during the sarcomas progression.

Materials and methods

Mice

Female wild-type C57BL/6 mice (n=10) (Academy of Military Medical Science, Beijing, China) and female C57BL/6 background adiponectin knockout mice [11] (n=7) at 6 to 8 weeks old were maintained and fed in a specific pathogen-free facility at the Experimental Animal Center of Tianjin Medical University. The care for mice and the experiments were approved by Animal Ethics Committee of Tianjin Medical University and were in accordance with the guidelines for animal care.

MCA induced tumor model

Wild-type and adiponectin knockout mice were subcutaneously injected with 25 μg of MCA emulsified in corn oil [12] in the hind flank. For tumor development, the mice were monitored every 6 days for 156 days after the MCA induction. Tumors≥0.3cm in diameter were recorded as sarcoma positive. The tumor area was determined using the following formula: $r^2 \times 3.14$, where r was radius (cm) of the tumor.

Statistical analysis

The data are presented as the mean ± SD. Statistical significance

was determined by a Student's *t* test. In the statistical comparisons, *p*-value < 0.05 was considered as a significant difference.

Results

The adiponectin-deficient mice induced by MCA develop sarcomas more rapidly and more frequently than the WT mice

In this study, the adiponectin-deficient mice and the WT mice were used to induce mouse sarcoma by low-dose MCA. The mice were monitored every 6 days after the MCA induction for 156 days to observe the tumor formation and incidence. As shown in Figure 1, tumor formation of the adiponectin-deficient mice was at day 36 after the MCA induction, however, sarcomas occurred in the WT mice was later (day 60). In addition, the tumor incidence rate of the adiponection deficiency group was 71.43%, remarkably higher than the rate of the WT group (40%). These data indicated that adiponectin may have inhibiting effects on the sarcomas formation. With the deficiency of adiponectin, the mice induced by MCA developed sarcomas more rapidly and frequently in contrast with the WT mice. This suggested that adiponectin could suppress the tumor formation of sarcomas.

Adiponectin deficiency inhibited the sarcomas growth and reduced the mortality rates of the mice with sarcomas

Next in our study, we analyzed the tumor growth, survival rates and the mortality rates of the adiponectin-deficient and the WT mice with sarcomas, respectively. Although the survival rates showed in Figure 2A did not show significant difference between the two groups of mice (P=0.3), the mortality rates of the adiponectin-deficient mice with sarcomas were lower than that of the WT control group (Figure 2B). Furthermore, considering the mean tumor maximal area, adiponectin deficiency noticeably inhibited the sarcomas growth (Figure 3). Our data implied a promoting effect of adiponectin on sarcomas progression.

Discussion

Adiponectin is involved in the development and progression of various tumors via different signaling pathways [4]. Many studies have shown that the level of adiponectin decreases in patients with prostate [13], gastric [14], breast [5] and many other cancers[6,15]. This suggests that adiponectin may have a protective role in cancer. However, whether adiponectin has regulatory effects on sarcomas

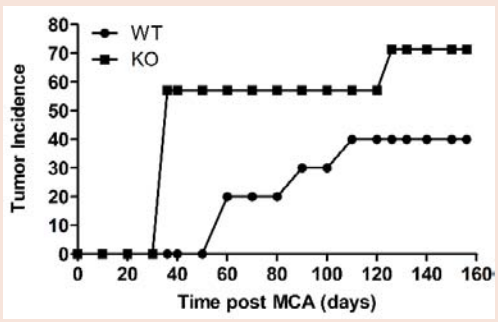

Figure 1: Tumor incidence of mice with sarcoma. Wild-type (n=10) and adiponectin knockout (n=7) mice were subcutaneously injected with low-dose MCA to induce mouse sarcomas. The tumor incidence of mice with a tumor ≥3 mm in diameter.

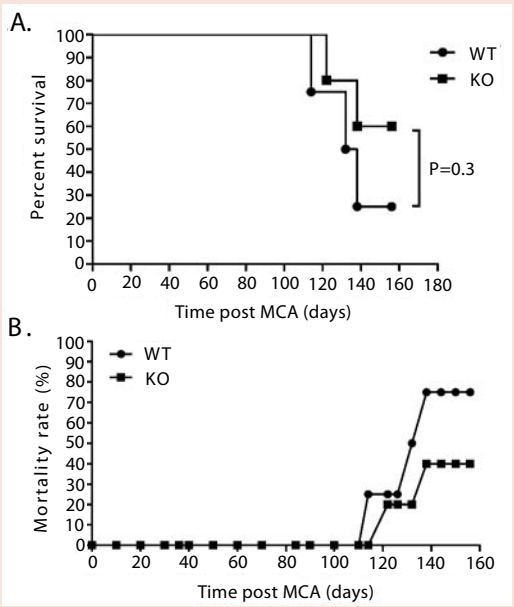

Figure 2: Survival curve and mortality rates of mice with sarcoma.
(A) The survival analysis of mice with sarcoma displayed as Kaplan-Meier curves.
(B) The mortality rates of mice with sarcoma.

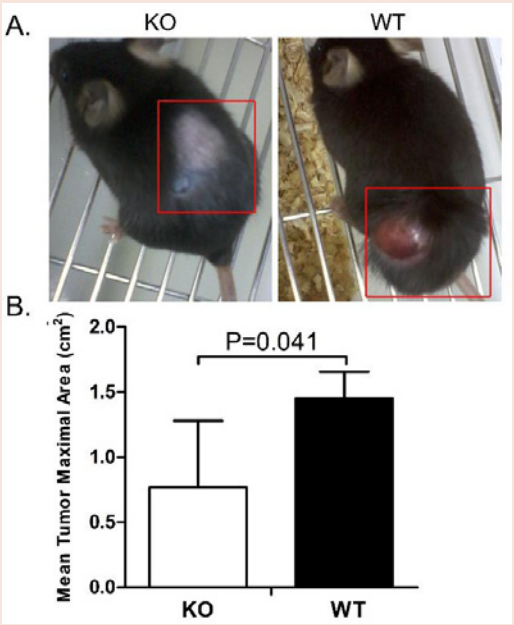

Figure 3: Tumor area of mice induced with sarcoma.
The tumor area were measured and analyzed after the sarcomas occur. (A) The sarcomas from adiponectin knockout mice and WT mice. (B) The mean tumor maximal area. The data are expressed as the mean ± SD.

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remains unclear. In our investigation, WT and adiponectin knockout mice were subcutaneously injected with a low-dose MCA to induce mouse sarcomas, and we found that the adiponectin-deficient mice develop sarcomas more rapidly and more frequently comparing with the WT mice (Figure 1). Furthermore, statistical data of the area of sarcomas measuring the tumor growth indicated that the inhibiting effect of adiponectin on sarcomas turned into facilitating effect once sarcomas occur (Figure 3). Besides, the mortality rates of the adiponectin-deficient mice with sarcomas were lower than the rates of the WT control mice (Figure 2B). These results were consistent to our previous findings that adiponectin deficiency suppressed pancreatic cancer [7]. In spite of this, the exact roles of adiponectin in cancers are controversial and need further study.

Many studies demonstrate that adiponectin could be related to inflammatory response [16,17]. Also, we previously found that adiponectin could inhibit the differentiation of dendritic cell, which plays an crucial role in immune response initiation [18]. It is well known, in human, most cancers are associated with chronic inflammation [19,20], the MCA-induced sarcoma model is a classical animal model of sarcoma for studies of tumor immunology [10,21]. During the generating process of sarcomas induced by MCA, antigens specific responses by lymphoid cells such as CD4 and CD8 cells were identified [22]. Therefore, the inhibiting effects of adiponectin on sarcomas formation may be due to its anti-inflammatory activity. However, at the later stages, a thorough research is still needed to understand the potential molecular and cellular mechanisms about facilitating effect of adiponectin on sarcomas growth.

Conclusions

In this study, the results demonstrated that adiponectin deficiency could increase the sarcomas formation, while inhibit the growth of tumor after sarcomas occur.

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