

Original Article

Naturally Produced Extracellular Matrix Inhibits Growth Rate and Invasiveness of Human Osteosarcoma Cancer Cells

V. Ivanov, S. Ivanova, M.W. Roomi, T. Kalinovsky, A. Niedzwiecki, and M. Rath

Dr. Rath Research Institute, Cancer Division, 1260 Memorex Drive, Santa Clara, CA 95050

Abstract

Enhanced supplementation with certain naturally occurring nutrients and vitamins has been associated with a reduction in occurrence and progression of human cancer. The exact mechanisms of this action are still under investigation. Extracellular matrix (ECM) plays a key role in the development of cancer. Therefore, we studied whether nutrients could exert anticancer effects through alteration of ECM biological properties. Confluent cultures of normal human dermal fibroblasts were allowed to produce and deposit ECM during a 7 d incubation period in the presence of tested compounds. Subsequently, fibroblasts were removed and the growth rates of freshly placed cultures of human osteosarcoma cells (lines U2-OS, MMNG, or SK.ES1) on pre-formed ECM were assayed in plain cell growth medium. In addition, ECM was deposited by fibroblasts on the upper surface of a porous plastic membrane and the subsequent migration of osteosarcoma cells to the other side was assayed in non-supplemented medium. The results demonstrated that the ECM produced by normal fibroblasts treated with a mixture of ascorbic acid, lysine, proline, arginine, cysteine, and green tea polyphenols significantly reduced the growth rate and invasive activity of osteosarcoma cells in contrast to the non-supplemented control. The changes in ECM properties were accompanied by significant changes in ECM protein and glycosaminoglycan composition as assayed immunochemically. We conclude that anticancer effects of nutrients involve beneficial changes in ECM biological properties. The role of ECM components in ECM-dependent regulation of tumor cell activities is discussed.

Key Words: Osteosarcoma; ECM; proliferation; invasion; collagen; green tea extract; ascorbic acid; MMP-9.

Introduction

Osteosarcoma, the most common bone cancer and the sixth most common cancer in children, demonstrates aggressive, rapid growth and metastasis. Approximately 20% of children diagnosed with osteosarcoma have an advanced stage of osteosarcoma that has metastasized to the lungs, brain, and other bones (1). For decades, standard treatment for osteosarcoma has consisted of surgery (amputation or limb salvage surgery) and chemotherapy, which focus

on cancer cell destruction, but do not address metastasis. Radiation and chemotherapy have not only been ineffective in providing a cure, but also indiscriminately attack all cells—causing cellular damage and destruction of the body's connective tissue.

Cancer cells form tumors and spread by degrading the extracellular matrix (ECM) through various matrix metalloproteinases (MMPs). The activity of these enzymes correlates with the aggressiveness of tumor growth and invasiveness of the cancer. Rath and Pauling (2) postulated that nutrients such as lysine and ascorbic acid could act as natural inhibitors of ECM proteolysis and, as such, have the potential to modulate tumor growth and expansion. These nutrients can

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Aleksandra Niedzwiecki, 1260 Memorex Drive, Santa Clara,
CA 95050. E-mail: a.niedz@drath.com

