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EDITORIAL

A Novel Therapeutic Approach to Breast Cancer using a Selective Cyclooxygenase 2 Inhibitor and Adenovirus-mediated Delivery of the Melanoma Differentiation-associated Gene-7 (Ad-mda7)

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Recently, many preclinical and clinical researches have focused on the possible roles of new therapeutic modalities to enhance current treatment efficacy or to extend the current limitations against breast cancer treatment. Th melanoma differentiation-associated gene-7 (*mda-7*), now classified as a member of the interleukin (IL)-10 gene family, has attracted attentions from several investigators for its unique ability to act against various cancers including breast cancer. In addition to *mda-7*, highly selective cyclooxygenase-2 (Cox-2) inhibitors, have continuously demonstrated possible anticancer effects against various cancers even though theray with many of the inhibitors has resulted in major set backs due to complications after long-term use. However, few have performed to demonstrate the synergistic effects of these two efficient treatment options or to demonstrate preventive measures to reduce the size of tumors. We summarize important results and our experience related to the use of a selective cyclooxygenase 2 inhibitor and adenovirus-mediated delivery of *mda-7*.

Key Words : *mda-7, Celecoxib, Breast Cancer*

INTRODUCTION

Breast cancer is the most prevalent cancer among women in Western countries. Although breast cancer is not the most prevalent cancer among women in developing countries like Korea, the number of newly diagnosed patients per year has been exponentially increasing.*(1)* Similar to other malignancies, breast cancer is a systemic disease characterized by local/regional and systemic dissemination after surgery with the intention to cure. The therapeutic modalities such as systemic chemotherapy, external irradiation and hormonal therapy are used in combination for the treatment of breast cancer. However, these aggressive treatments may cause moderate to severe adverse effects in patients while achieving the therapeutic goals. Therefore, many investigators are studying methods to enhance the therapeutic efficacy of treatments while reducing the systemic burden of therapy. Among such methods, adenoviral delivery of certain proteins or genes and chemotherapeutic agents are being studied. The adenoviral delivery system is not a perfect vector for the delivery of genes and proteins, but the transfection efficiency of this vector is higher than any other vector, without compromising the host's immune defenses. The adenoviral delivery of the melanoma differentiation-associated gene 7 (Ad-mda7) was introduced to target malignant tumors, while sparing normal cells. Celecoxib, a highly selective cyclooxygenase 2 (COX-2) inhibitor, has proven to be effective for the treatment, and even for the prevention, of certain malignancies.

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MELANOMA DIFFERENTIATION-ASSOCIATED GENE-7 (MDA-7)

Malignant tumors share many characteristics such as

uncontrollable growth, repressed apoptosis and genetic abnormalities. Several steps are involved during the process of oncogenesis; some of them are beneficial to the host, but many of them are not. MDA-7 is a tumor suppressor that leads to apoptosis and cell death only for cancer cells;*(2-13)* its protein product has been identified and is referred to as IL-24.*(14, 15)* The complementary DNA (cDNA) of mda-7 was initially isolated by subtraction hybridization from a human melanoma cell line.*(16, 17)*

MDA-7 has been shown to have many anticancer properties such as cancer cell growth inhibition *(18)* and selective induction of apoptosis, only in cancer cells, *in vitro* and *in vivo*.*(19)* Expression of MDA-7 is regulated during human melanoma differentiation, during which AP-1 and C/EBP transcriptional factors are also present and play an important role.*(20, 21)* However, the expression of mda-7 has been shown to be suppressed or lost in human melanomas.*(16, 22)* The selective induction of apoptosis of mda-7 is mediated via the overexpression of the GADD family via p38 MAPK, beta-catenin, PI3K, BAX, JAK/STAT-independent pathway, JNK, and Fas. *(10, 23-26)* Furthermore, mda-7 has been shown to affect angiogenesis and vascular smooth muscle cells. *(27-30)*

CELECOXIB, A HIGHLY SELECTIVE CYCLOOXYGENASE-2 INHIBITOR

Celecoxib, one of the highly selective COX-2 inhibitors, was initially introduced to treat arthritis.*(31)* Before the recent major setbacks, related to systemic complications after long-term use for arthritis, celecoxib and other analogues were prescribed to many patients with arthritis.*(32)* In addition, celecoxib and various derivatives have been shown to be therapeutic and possibly preventive against certain cancers including colon and breast cancer.*(33-41)* The evidence to date points to celecoxib inducing apoptosis and cell cycle arrest in cancers.*(42-44)* Different from the original indications for celecoxib, its use for cancer can be temporary, which would prevent some of the long-term side effects associated with cerebrovascular function.*(45)*

Breast cancer is a malignant tumor shown to overexpress COX-2.*(46, 47)* HER-2/*neu*-positive breast cancer is associated with a poor prognosis; activator protein-1 (AP-1) along with PEA-3 is involved in the COX-2 overexpression in HER-2/*neu*-positive breast cancer.*(48)* In addition, AP-1 may play a role in reducing COX-2 transcriptional activity in HER-2/*neu*-negative MCF-7 breast cancer cells with conjugated linoleic acid.*(49)* AP-1 has been shown to be related to mda-7 gene promoter activity.*(21)* In addition, GADD153 was recently shown to mediate celecoxib-induced programmed cell death in cervical cancer, *in vitro*.*(50)* In breast cancer cells, COX-2 is known to induce IL-11 synthesis.*(51)* These findings suggest a possible synergism between COX-2 inhibition and mda-7. Celecoxib appears to be involved in the modulation of signaling pathways, such as PI3K, Akt, beta-catenin, uPA, death receptor, caspase, NFκB, p21, and p27.*(40, 41, 44, 52-59)*

ADENOVIRAL GENE DELIVERY

Many vectors have been introduced to deliver genes, proteins and other molecules into target cells or organs. Adenovirus is a vector used frequently due to its safety and reliable handling. It has been considered for possible use in humans without major systemic problems. The transfection efficiency of the adenovirus, devoid of self replication, is superior to other physiological and mechanical methods. Though some possible generalized adverse reactions, after repetitive transfection with the adenovirus are a concern, it still is a promising vehicle for transfer. Additional research is needed to enhance the expression of target molecules or genes, while decreasing possible problems without compromising its therapeutic results. The expression of mda7 can be enhanced by the adenoviral-mediated delivery of celecoxib into breast cancer cells.

COMBINATION OF AD-MDA7 AND CELECOXIB

We previously reported the combined treatment of Ad-

mda7 and trastuzumab for HER-2/*neu*-overexpressing human breast cancer cells to enhance cell death.*(60)* Other studies have also reported on the effects of the combined use of celecoxib and chemotherapeutic or hormonal agents on cancer cells.*(61-67)* However, there are no reports on the combination of a selective COX-2 inhibitor, such as celecoxib and Ad-mda7, on any type of cancer cells, except for our report on their effect on breast cancer cells.*(68, 69)* Accidentally, we observed a synergistic enhancement of mda7 expression after the transfection of Ad-mda7 combined with celecoxib (unpublished data). We noted increased tumoricidal effects, apoptosis and decreased cancer cell growth after combination treatment compared to the effects of either alone. In addition, we observed decreased prostaglandin E_2 synthesis, expression of COX-2 and Akt phosphorylation. Since Akt, a key regulator of the estrogen receptor alpha, was decreased after combined treatment, this suggested promising use of such a combination for the treatment of cancer cells.*(70)* According to our experiences, the synergistic effects were not dependent on the expression of HER-2/*neu*. This implies that the combination treatment can be used for breast cancer without being affected by HER-2/*neu* expression. The combination showed somewhat different patterns of enhanced apoptosis for HER-2/*neu*-positive and -negative breast cancer cells. HER-2/*neu*-positive breast cancer cells were affected more during the early phase of apoptosis, while the opposite findings were observed in the HER-2/*neu*-negative breast cancer cells. The effects of the combined treatment on the cell cycle differed depending on the cell type according to the expression of HER-2/*neu*. In the HER-2/*neu*-positive cells, the G_1 phase was pronounced and the S phase fraction was significantly increased after combined treatment.

RADIOSENSITIZATION

Many breast cancer patients are candidates for breast-conserving surgery rather than mastectomies.*(71, 72)* In such cases, external radiation treatment after curative surgery is frequently used to target metastatic foci with or without other treatments such as chemotherapeutic agents and hormonal agents. Many investigators have studied how to enhance the radiosensitivity of cancer cells including breast cancers. Ad-mda7 has shown radiosensitizing effects in a variety of cancer cells.*(7, 73, 74)* Aside from the known chemosensitization effects,*(75, 76)* selective COX-2 inhibitors, such as celecoxib, have also been shown to make cancer cells more susceptible to external irradiation.*(77-79)* However, a synergistic radiosensitization with Ad-mda7 and celecoxib, for breast cancer cells, has not been previously evaluated. We observed an enhanced radiosensitization with combined Ad-mda7 and celecoxib delivered prior to radiotherapy in breast cancer cells, in vitro. Although additional research is needed for confirmation of these findings this may provide a promising approach for enhancing radiation treatment.*(80)*

CONCLUSION

Ad-mda7 has unique characteristics including induction of apoptosis that targets only cancer cells. Celecoxib has shown therapeutic and preventive effects against various cancers. Our work on the combination of Ad-mda7 and celecoxib to increase the tumoricidal effects compared to the use of either alone, in breast cancer cells, requires additional study to elucidate the probable mechanisms or networks involved and to identify important signal molecules. After the accumulation of additional scientific evidence and associated data, a less toxic but more effective treatment approach with the combination of Ad-mda7 and celecoxib might be applicable to human therapy.

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