Research Article

Effect of Adjuvant Magnetic Fields in Radiotherapy on Non-Small-Cell Lung Cancer Cells In Vitro

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Objectives. To explore sensitization and possible mechanisms of adjuvant magnetic fields (MFs) in radiotherapy (RT) of non-small-cell lung cancer. Methods. Human A549 lung adenocarcinoma cells were treated with MF, RT, and combined MF-RT. Colony-forming efficiency was calculated, cell cycle and apoptosis were measured, and changes in cell cycle- and apoptosis-related gene expression were measured by microarray. Results. A 0.5 T, 8 Hz stationary MF showed a duration-dependent inhibitory effect lasting for 1–4 hours. The MF-treated groups had significantly greater cell inhibition than did controls (P < 0.05). Surviving fractions and growth curves derived from colony-forming assay showed that the MF-only, RT-only, and MF-RT groups had inhibited cell growth; the MF-RT group showed a synergetic effect. Microarray of A549 cells exposed for 1 hour to MF showed that 19 cell cycle- and apoptosis-related genes had 2-fold upregulation and 40 genes had 2-fold downregulation. MF significantly arrested cells in G2 and M phases, apparently sensitizing the cells to RT. Conclusions. MF may inhibit A549 cells and can increase their sensitivity to RT, possibly by affecting cell cycle- and apoptosis-related signaling pathways.

1. Introduction

Lung cancer is a common malignant tumor, and its incidence is rapidly growing: 64% of patients with non-small-cell lung cancer (NSCLC) need radiotherapy (RT); 45% of these patients receive primary RT. Although RT and chemotherapy together have better therapeutic effects, patients often cannot tolerate the toxicity and side effects of the combination. Optimizing treatment result is therefore critical.

Magnetic fields (MFs) are biologically effective, and their effect on tumors has been studied since the 1970s [1–5]. Although the mechanism of how MFs affect tumors is unclear, they have been shown to inhibit cancer cell growth and induce apoptosis. Magnetic fields influence charged particles. As such, they interfere with interactions among molecules and electrons in cells and possibly harm cellular functions such as DNA synthesis, thereby inhibiting cancer cell division and growth [6]. Zhang et al. reported that a 3 Hz/picosecond electromagnetic pulse can apparently inhibit growth of cervical carcinoma Hela cells by raising intercellular Ca2+ concentration, inducing apoptosis, and increasing Bax protein expression while decreasing Bcl-2 expression (thus significantly increasing the Bax/Bcl-2 ratio) [7]. Lu et al. applied a low-frequency electromagnetic field on BEL-7402 hepatoma cells and found that expression of SODD and Survivin genes was significantly downregulated [8]. Wei et al. studied effects of rotational MFs combined with 5-fluorouracil (5-FU) on cell cycle and apoptosis in SP2/0 mouse myeloma cells, and found the S phase ratio was increased [9]. Magnetic fields alone cannot induce cell apoptosis, but they can sensitize cells to 5-FU toxicity, thus facilitating 5-FU-induced apoptosis. Liu et al. claimed that strong magnetic pulses significantly inhibited growth and exacerbated apoptosis in BIU-87 bladder carcinoma cells [10], Pan et al. used microarray to measure and analyze the apoptosis-related gene-expression profile in MF-processed BEL-7402 hepatoma cells and L-02 fetus liver cells [11]. Electromagnetic field-processed cells upregulated expression...
of apoptosis-inducing genes and downregulated expression of apoptosis-inhibiting genes. Han et al. used pulse MFs to study drug resistance in HL60/ADR leukemia cells [12]. Pulse MFs could downregulate MRPI gene and protein expression, while increasing accumulation of cellular RgI23, and reverse multidrug resistance in leukemia cells.

Preliminary research showed that MFs, alone or together with chemotherapy, can inhibit tumor cell proliferation. However, few studies of MFs combined with RT in lung cancer are reported. We hypothesized that cell-cycle changes induced by MFs sensitize lung cancer cells to radiation. In this study, we designed experiments to measure the effect of adjuvant MFs in chemotherapy on colony formation, cell cycle, and apoptosis in A549 cells. Microarray was employed to elucidate the molecular and cellular mechanisms.

2. Materials and Methods

2.1. Cell Lines and Reagents. Lung adenocarcinoma cell line A549 was provided by Zhejiang Cancer Hospital. Cells were cultured in RPMI1640 media with 10% bovine serum and kept in an incubator at 5% CO₂ and 37°C to promote growth. RPMI1640 was purchased from Gibco-BRL; bovine serum was purchased from HyClon.

2.2. Magnetic Field Duration and Radiation Dose. The inhibition rate was estimated by MTT assay to determine the duration of the MF effect. Using earlier research [13], 4 Gy was chosen as the radiation dose. Cells were transferred into 96-well plates at 500 cells/well and cultured for 24 hours. Four 8-well groups of cells were exposed to 0.5 T stationary MFs for 1, 2, 3, or 4 hours. After 48 hours, 20 μL 5 mg/mL MTT was added into each well. After culturing for another 4 hours, supernatant was disposed, and 200 μL was added into each well. After another 30 minutes, when brown crystals were completely dissolved, absorbance (AB) of each well was measured by enzyme-linked immunosorbent assay with 550 nm absorption wavelength. Inhibition rate of cell growth was calculated as [(Experimental AB – background control AB)/(Control AB – background control AB)] × 100%.

2.3. Colony-Forming and Surviving Curve Assay. Cells in logarithmic growth phase were digested into single-cell suspensions, which were diluted and transferred into 25 mL culture flasks for 1, 2, 3, or 4 hours. After 48 hours, 20 μL 5 mg/mL MTT was added into each well. After culturing for another 4 hours, supernatant was disposed, and 200 μL was added into each well. After another 30 minutes, when brown crystals were completely dissolved, absorbance (AB) of each well was measured by enzyme-linked immunosorbent assay with 550 nm absorption wavelength. Inhibition rate of cell growth was calculated as [(Experimental AB – background control AB)/(Control AB – background control AB)] × 100%.

2.4. Superarray Gene Chip Assay. Cells at logarithmic growth phase were digested into single-cell suspensions, which were diluted and transferred into 75 mL culture flasks with 1 × 10⁵ cells per flask. After 24-hour adherent culturing, three flasks of cells were exposed to 0.5 T, 8 Hz MF for 1 hour, and three bottles of cells were used as controls. After another 24 hours of culturing, RNA was extracted for gene chip assays for each group.

2.5. Cell Cycle and Apoptosis Assay. Cells in logarithmic growth phase were digested into single cell suspensions, which were diluted and transferred into 25 mL culture flasks with 5 × 10⁴ cells per flask. Cells were randomly divided into four groups: controls, MF-only group (0.5 T), RT-only group (4 G), and combination group (0.5 T + 4 G). Each group provided three parallel flasks for collection at 24, 48, and 72 hours separately. Cell cycle and apoptosis rates were measured by flow cytometry with an ABC cell cycle kit (BD Biosciences) and an Annexin V-FITC apoptosis detection kit.

2.6. Data Analysis. SPSS 11.0 software was used for statistical analysis. Measurement data are expressed as mean ± standard deviation. Different groups were compared using one-way ANOVA. P < 0.05 was considered statistically significant.

3. Results

3.1. Inhibition Rates under Different Magnetic Field Durations Measured with MTT Assay. The inhibitory effect of a 0.5 T, 8 Hz stationary MF lasts for 1–4 hours, in a duration-dependent manner (Table 1). Although the inhibitory effect did not significantly differ with magnetic duration (P > 0.05), MF-treated groups had significantly greater cell inhibition than the control group (P < 0.05).

| Magnetic field duration (h) | Absorbance (OD value) | Inhibition rate (%) |
|-----------------------------|-----------------------|---------------------|
| Control                     | 1.120 ± 0.089         | 0.0                 |
| 1 h                         | 1.032 ± 0.059         | 7.9                 |
| 2 h                         | 1.025 ± 0.065         | 8.5                 |
| 3 h                         | 0.990 ± 0.087         | 11.6                |
| 4 h                         | 0.985 ± 0.098         | 12.1                |
Table 2: Upregulated genes in A549 after 1-hour exposure to MF.

| Position | Genebank | Genename | Fold change |
|----------|----------|----------|-------------|
| 138      | NM_003824| FADD     | 5.64        |
| 278      | NM_006297| XRCC1    | 4.32        |
| 89       | NM_001260| CDK8     | 3.42        |
| 225      | NM_003839| Rank     | 3.11        |
| 199      | NM_000963| Cox-2    | 2.87        |
| 261      | NM_003300| CRAFI    | 2.81        |
| 236      | NM_000043| Fas/Apo-1/CD95 | 2.56 |
| 227      | NM_003790| DR3/Apo3 | 2.52        |
| 63       | NM_053056| Cyclin D1| 2.48        |
| 62       | NM_005190| Cyclin C | 2.45        |
| 244      | NM_003809| TNFSF12/APO3L | 2.37 |
| 43       | NM_003723| Caspase 13| 2.26        |
| 44       | NM_012114| Caspase 14| 2.14        |
| 58       | NM_003914| Cyclin A1| 2.12        |
| 182      | NM_002392| Mdm2     | 2.08        |
| 61       | NM_004701| Cyclin B2| 2.08        |
| 70       | NM_004354| Cyclin G2| 2.05        |
| 48       | NM_004347| Caspase-5 | 2.03        |
| 64       | NM_001759| Cyclin D2| 2.00        |

3.2. Colony-Forming Efficiency and Surviving Curve. The colony-forming assay showed that, for RT-only groups at 2, 4, 6, 8, and 10 Gy, the CEs were 16.4%, 13.2%, 10.2%, 7.1%, and 1.2%, respectively; SFs were 0.77, 0.62, 0.48, 0.33, and 0.24, respectively. For MF-RT combined groups at 2, 4, 6, 8, and 10 Gy, CEs were 13.7%, 8.1%, 3.3%, 1.3%, and 0.4%, respectively, and SFs were 0.64, 0.38, 0.15, 0.06, and 0.02, respectively. Cell survival decreased significantly (P < 0.05) with increasing RT dose in both RT groups and combination groups. Among groups with the same RT dose, the group with adjuvant MFs had a significantly smaller SF (P < 0.05), which suggests that A549 cells are more sensitive to RT with adjuvant MFs application. Survival curves are shown in Figure 1.

3.3. Gene Chip Assay. The microarray showed that after 1-hour exposure to MFs, 19 cell cycle- and apoptosis-related genes in the A549 cells had 2-fold upregulation, and 40 genes had 2-fold downregulation (Tables 2 and 3). In particular, TNFRSF21 and CASPASE had significant upregulation, whereas expressions of ATM, p53, p57, p21, p27, TNFSF12, TNFRSF10D, BAG4, BCL2L2, Mdn2, and XRCC1–5 were downregulated.

3.4. The Alternation of Cell Cycle and Apoptosis. Flow cytometry results showed that the MF-only group had G2-M phase arrest. Percentages of MF-only cells at G2-M were 24.2% for collection at 24 hours, 28.4% at 48, hours and 18.5% at 72 hours—all significantly different from the control group. The MF-only group showed no significant difference in apoptosis index compared with the control group. Both the RT-only group and the MF-RT combination group showed significant apoptosis; however, the apoptosis index of combination group was 34.6 for collection after 24 hours, which was significantly higher than that of the RT-only group (Figure 2).

4. Discussion

Repair of DNA double-strand breaks (DSBs) and cell-cycle regulation are two important factors that influence RT sensitivity of cells. ATM plays a very important role in DSB
Table 3: Downregulated genes in A549 after 1-hour exposure to MF.

| Position | Genebank   | Gene name            | Fold change |
|----------|------------|----------------------|-------------|
| 228      | NM_003820  | TNFRSF14             | 0.03        |
| 246      | NM_006573  | TNFSF13B             | 0.09        |
| 264      | NM_004620  | TRAF6                | 0.12        |
| 96       | NM_001800  | p19-INK4D            | 0.14        |
| 232      | NM_001066  | TNFR2/p75            | 0.15        |
| 86       | NM_000075  | Cdk4                 | 0.17        |
| 90       | NM_000389  | P21/Waf1/CIP1        | 0.18        |
| 221      | NM_003844  | TRAIL-R/DR4          | 0.20        |
| 88       | NM_001799  | CDK7                 | 0.21        |
| 128      | NM_001950  | E2F-4                | 0.21        |
| 229      | NM_001192  | TNFRSF17             | 0.22        |
| 76       | NM_004358  | CDC25B               | 0.23        |
| 127      | NM_001949  | E2F-3                | 0.23        |
| 282      | NM_021141  | KU80                 | 0.26        |
| 130      | NM_001952  | E2F-6                | 0.27        |
| 135      | NM_005236  | XPF                  | 0.33        |
| 204      | NM_000321  | Rb                   | 0.34        |
| 114      | NM_000499  | CYPIA1               | 0.34        |
| 262      | NM_004295  | TRAF-4               | 0.35        |
| 122      | NM_004402  | DFF40/CPAN           | 0.36        |
| 26       | NM_004050  | Bcl-w                | 0.38        |
| 279      | NM_005431  | XRCC2                | 0.41        |
| 7        | NM_000051  | ATM                  | 0.41        |
| 17       | NM_001188  | Bak                  | 0.41        |
| 132      | NM_001983  | ERCC1                | 0.42        |
| 22       | NM_000633  | Bcl-2                | 0.42        |
| 208      | NM_003804  | RIP                  | 0.43        |
| 126      | NM_004091  | E2F-2                | 0.43        |
| 142      | NM_001924  | GADD45               | 0.44        |
| 91       | NM_004064  | p27Kip1              | 0.44        |
| 71       | NM_001239  | Cyclin H             | 0.45        |
| 27       | NM_005178  | BCL-3                | 0.45        |
| 281      | NM_003401  | XRCC4                | 0.46        |
| 256      | NM_000546  | p53                  | 0.46        |
| 129      | NM_001951  | E2F-5                | 0.48        |
| 242      | NM_003810  | TRAIL                | 0.48        |
| 125      | NM_005225  | E2F                  | 0.48        |
| 240      | NM_001561  | 4-1BB                | 0.49        |
| 224      | NM_003840  | TRAIL-R4/DcR2        | 0.49        |
| 220      | NM_000594  | TNFA                 | 0.50        |

repair and cell cycle regulation signaling pathways. ATM activates the G$_1$-S checkpoint by activating p53 and p21 genes; it activates S phase and G$_2$-M checkpoints by activating the chkl, chk2, cdc25, and cdc2 genes [14]. When ATM expression is deficient or decreased, cell cycle checkpoints are dysfunctional, and cell cycle arrest is hindered. Thus, ATM expression and activity are related to RT sensitivity of cells [15]. In a study of sensitivity of nasopharyngeal carcinoma cell CNE-1 to RT, Hui et al. found that an RT sensitizing agent, UCN-01, works by weakening the cell’s self-repair capability, and UCN-01 can only sensitize cells with p53 deficiency. Cyclin-dependent kinase inhibitor 1C (CDKN1C; p57, Kip2), which belongs to Cip/Kip family, can inhibit multiple G$_1$ cyclin/Cdk complexes and induce G$_1$ arrest, thus inhibiting cell proliferation. CDKNIA (p21, Cip1) can inhibit CDK2 or CDK4 complexes and regulate the cell cycle. CDKNIA is regulated by p53 and can arrest cell in G$_1$ phase under activating circumstances. CDKN1B (p27, Kip1), which encodes a CDK inhibitor protein, can inhibit activation of cyclin E/CDK2 or cyclin D/CDK4 complexes and arrest the G$_1$ phase as
well. TNFSF12, which belongs to TNF superfamily, can combine with the FNI4/TWEAKR cytokine receptor, thus inducing apoptosis through multiple cell death pathways, and promote endothelial cell proliferation and migration (which are related to angiogenesis). TNFRSF21, whose functional domain activates the NF-κB and MAPK8/JNK pathways, also induces apoptosis. However, TNFRSF10D does not induce apoptosis and has been shown to play an inhibitory role in TRAIL-induced cell apoptosis. BAG4 is a member of the BAG1-related protein family. BAG4 is an antiapoptosis protein; it can interact with multiple apoptosis- and cell growth-related proteins, including BCL-2, Raf kinase, steroid receptor, growth factor receptor, and heat shock protein; it combines with TNFRI and death receptor 3 to negatively regulate the downstream death signaling pathway. BCL2L2 belongs to the bcl-2 family; its expression induces apoptosis under cellular toxic environment. Mdn2 protein combines with and deactivates p53 and RB proteins, and it negatively regulates the p53 gene. X-ray repair cross-complementing gene (XRCC) is a major mediator of mammalian gene repair [16]. XRCCI, XPD, and XRCC3 proteins are the important components of BER, NER, and DSBR, respectively. XRCC1 repairs DNA single-strand breaks, induced by RT or alkyl-lation agents, and works with DNA ligase III, polymerase
beta, and poly(ADP-ribose) polymerase, involved in the BER pathway. XRCC2 and XRCC3 mediate RecA/Rad51-related proteins involved in homologous recombination to maintain chromosome stability and repair of double-strand breaks in DNA damage.

The gene chip results showed that, after MF exposure of A549 cells, the apoptosis-inducing gene TNFRSF21 was upregulated, as were several other apoptosis-related genes (e.g., ATM, p53, p57, p21, p27, TNFSF12, TNFRSF10D, BAG4, BCL2L2, Mdn2, and XRCC1–5). The upregulation of TNFRSF21 activated NF-κB and APK8/JNK pathways and induced apoptosis. Cellular sensitivity to RT is related to apoptosis rate [17]; higher apoptosis levels indicate higher sensitivity to RT, and rapidly apoptotic cells are more sensitive to RT. Conversely, downregulation of ATM and p53 increases apoptosis; downregulation of p57, p21, and p27 weakens cell-cycle arresting function, thus inducing apoptosis; downregulation of antiapoptotic genes (TNFSF12, TNFRSF10D, BAG4, BCL2L2, and Mdn2) also induces apoptosis. Downregulation of XRCC1–5 also weakens DNA repair function, thus leading to cell death and weakened proliferative capacity.

Our study showed that, for a 0.5 T, 8 Hz stationary MF, duration had no significant effect ($P > 0.05$); however, groups treated with MF had significantly greater cell inhibition than controls ($P < 0.05$). The surviving fraction and growth curve derived from the colony-forming assay showed that MF-only, 4 Gy RT-only and the MF-RT combination groups had increased cell growth; the combination group in particular showed a synergetic effect ($P < 0.01$). The microarray showed that after A549 cells were exposed for 1 hour to MFs, 19 cell cycle- and apoptosis-related genes were more sensitive to RT. The microarray showed that after A549 cells were exposed for 1 hour to MFs, 19 cell cycle- and apoptosis-related genes were more sensitive to RT. Conversely, downregulation of ATM and p53 increases apoptosis; downregulation of p57, p21, and p27 weakens cell-cycle arresting function, thus inducing apoptosis; downregulation of antiapoptotic genes (TNFSF12, TNFRSF10D, BAG4, BCL2L2, and Mdn2) also induces apoptosis. Downregulation of XRCC1–5 also weakens DNA repair function, thus leading to cell death and weakened proliferative capacity.

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