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Targeting a key enzyme in cell growth: a novel therapy for cancer

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Abstract --- The enzyme ribonucleotide reductase (RR) controls the synthesis of DNA precursors and thus plays a pivotal role in cell growth. Since the free-radical-containing active-site of this enzyme can be disabled by a lone electron, low-level direct electric current should have an inhibitory effect on RR and, thus, on uncontrolled cell proliferation. This hypothesis is strongly supported by the results of several cancer electrotherapy studies reported over the years.

Introduction

Cancer is uncontrolled cell growth. For a cell to divide, it must replicate its DNA strand. The building blocks of this strand -- four bases -- are in short supply in a healthy, resting cell. However, the building blocks of a related molecule RNA are always in great abundance since RNA is needed for many cellular functions. When a cell is ready to divide, an enzyme called ribonucleotide reductase (RR) converts building blocks of RNA into those of DNA. The enzyme RR is, thus, pivotal for cell growth. Not surprisingly, the activity of this enzyme is tightly linked, much more than that of any other enzyme, to neoplastic transformation and progression (1).

A whole class of anti-cancer chemotherapeutic drugs -- hydroxy-urea being best known -- is aimed at blocking the enzyme RR (2). However, utility of such drugs is limited since inhibition of the enzymic activity is only partial and undesirable side-effects are many.

Hypothesis

A novel way of arresting the activity of this pivotal enzyme in cell growth, is suggested by the fact that the active-site of RR contains a stable tyrosyl free-radical which is essential for its activity (13). Such free-radicals can be neutralized/destroyed by free-floating electrons -- easily available in the form of direct electric current. Thus DC electrotherapy should result in inhibition of RR and cessation of malignant cell proliferation. Low-level surface DC electrotherapy would act selectively on cancerous growth since the concentration of the target enzyme RR is exponentially higher in cancerous cells, as compared to healthy quiescent cells (1).

Metastasized cancer should also be treatable by direct current electrotherapy since even in the metastatic state, irrespective of the organ micro-environment, the biochemical mechanism of cell division involving the enzyme RR, remains the same.

Experimental Evidence

The connection between low-level DC electrotherapy and deactivation of enzyme RR is being proposed for the

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time. However, use of low-level direct electric currents to treat tumor -- without any clear understanding of the underlying mechanism -- has been reported in scientific literature about ten times during the last four decades (4-13).

Three of these papers - the last one in 1985 - reported very encouraging results. For example, in some experiments, there was total regression in 60% of mice (4), an average of 88% tumor necrosis in hamsters (5), and 98% reduction in tumor mass, also in hamsters (7). (It is strange that none of these studies had any proper follow-ups.) The outcome of other studies was less positive -- almost certainly due to poor choice of parameters.

Following is a summary of these ten reports. (The electrode near the tumor is termed as 'active', the other one being called 'passive'.)

1. Humphrey et al, 1959 (4)

- ACTIVE Electrode: Cu or Zn plate with saline-solution-saturated sponge on unbroken skin over tumor.
- PASSIVE Electrode: Same, over ventral area.
- BEST RESULTS (Total regression in 60% mice): at cathode, with 3 mA at 3 V, 4.8 hours per day for 21 days.

2. Schauble et al, 1977 (5)

- ACTIVE Electrode: Silicone covered steel needle - exposed tip implanted.
- PASSIVE Electrode: Wire-mesh with electrode paste and saline-dampened sponge - over chest skin.
- BEST RESULTS (88% Necrosis): at positive electrode with 3 mA at 1.5 V, 1 hour per day for 4 days.
- NOTE: Necrosis was also observed when active electrode was made negative.

3. Habal 1980 (6)

- Poor results with 0.5 µA at 1.5 V, for 12 days continuous, using an implanted device.

4. David et al, 1985 (7)

- ACTIVE Electrode: Silicone covered Steel or Pt-Ir(70:30) needle - exposed tip implanted.
- PASSIVE Electrode: Al foil plate with conducting paste - over shaved underbelly.
- BEST RESULTS (98% Reduction in tumor mass): at either electrode, with 2.4 mA at less than 3 V, for 1 hour per day for 5 days.

5. Marino and Morris et al, 1986 (8)

- Both Electrodes ACTIVE: Insulated Pt - except for the implanted tips - at foci of tumor.
- BEST RESULTS (Total regression in 43% of primary tumors): with 2 mA at about 3 V, 1 hour per day for 3 intermittent days.

6. Morris and Marino et al, 1992 (9)

- Both Electrodes ACTIVE: Pt needles - implanted in tumor.
- BEST RESULTS (Reduction in tumor mass without improved survival): with 20 mA at 8-10 V, for 15 min. once.

7. Miklavčič et al, 1993 (10)

- ACTIVE Electrode: Pt-Ir(90:10), Au, Ag or Ti needle - tip implanted.
- PASSIVE Electrode: Same, placed subcutaneously the whole length, near tumor.
- BEST RESULTS (About 70% necrosis): at cathode, with 0.6 mA at unspecified volts, for 1 hour once.
- NOTE: "Field" electrotherapy, by placing both electrodes subcutaneously for their entire length, on either side of tumor, also produced similar necrosis.

8. Griffin et al, 1994 (11)

- ACTIVE Electrode: Au needle - implanted.
- PASSIVE Electrode: Cu plate with conducting gel - beneath the animal.
- BEST RESULTS (Regression proportional to charge passed): at anode, with 1-4 mA at 1-16 V, for 30-90 min. once.

9. Taylor et al, 1994 (12)

- ACTIVE Electrode: 4 parallel brass plates, vertically mounted, in a specially designed oesophageal tube.
- PASSIVE Electrode: Large plate with saline-soaked pad on human patient's back.
- BEST RESULTS (Oesophagus tumor of one patient regressed completely at the primary site): with 20 mA at 7 V, at each of four anodes, for 1 hour. Three treatments over 4½ month period.

10. Miklavčič et al, 1994 (13)

- ACTIVE/PASSIVE Electrodes: Au needles, placed subcutaneously the whole length, on either side of tumor.
- BEST RESULTS (Tumor growth slowed by a factor of 3): with 1.0 mA at unspecified volts, for 1 hour, applied once.
- NOTE: No correlation was observed between the amount of deposited electrode material (gold) and antitumor effect.

Discussion

Both positive and negative results of the published low-level electrotherapy studies can be adequately explained by the posited enzyme-mediated mechanism. Various aspects of these reports is being discussed in three sections:

Most Beneficial Voltage Range

Free radicals are known to be formed in a biological medium when it is subjected to any voltage in excess of 1.2 volts. Electrochemical products begin to form around 1.5 to 2 volts (8) but these products may not be significant in concentration until the voltage is raised to, say, 3 or 4 V. If the anti-tumor effect of electrotherapy is due to the disabling of the pivotal enzyme RR through free radical interactions, voltage between 1.2 to about 3 V should be most beneficial. Higher voltage, for this mechanism, would be undesirable for two reasons: (i) more and more electrons would engage in electro-chemical processes, leaving less and less electrons free or as free-radicals, and (ii) concentration of toxic electrochemical species would increase steadily. This toxicity may be as harmful as the tumor itself.

Studies 1, 2, 4 and 5 above (4,5,7,8), have reported the most positive electrotherapy results to date. Voltages in all of them was kept around 3 V or less. In study1 (4), experiments with 6 V seemed to show less benefits. When investigators of study 5 (8) employed 8-10 V in their next study, 6 (9), tumor mass was reduced again but, this time, without improved survival. Toxicity, significant now, must be targeting the host, and not the tumor. Study 8 (11) reports on toxicity in blood after treatments at 1-16 volts.

Mention must be made here of Bjorn Nordenstrom of Sweden, who has, since mid-1980s, advocated "high"-voltage (about 10 volts) electrotherapy for cancer (14). This therapy is also known as electro-chemo-therapy (E.C.T.) since it entails toxic electrochemistry. If the hypothesis about deactivation of the enzyme RR by stream of electrons is correct, then high-level direct currents suggested by Nordenstrom, for the reasons given above, should be much less beneficial than low-level currents. The last five studies (9-13), which were, partly or wholly, influenced by Nordenstrom's ideas, suggest that this is so since their outcomes were much less favorable.

Unlike Nordenstrom's modality, which is usually a one-time treatment, the low-voltage electrotherapy, due to its minimal toxicity, can be applied repeatedly. Total or almost total regression of some tumors was achieved with multiple treatments in studies 1, 4 and 5 (4,7,8). Study 3 (6) employed too feeble a current to produce any significant results. The procedure was also very invasive.

Positioning & Polarity of Electrodes

If deactivation of the enzyme RR is the dominant mechanism underlying the efficacy of electrotherapy, then it should not matter whether electrodes are implanted or on the surface -- as long as the tumor is in the path of the current. Only in study 1 (4) were both electrodes placed on unbroken skin, and it reported one of the better results. Beside being non-invasive, surface electrodes also minimize electrochemistry and its attendant toxicity.

Similar reasoning would suggest that the polarity of the electrodes is inconsequential. Almost all electrotherapy studies where beneficial results were obtained, confirm this.

Results of "field" electrotherapy experiments, where electrodes were implanted on either side of tumor (10,13) also show that polarity of electrodes is immaterial, and that electrode-electrolyte interactions are of little significance.

Electrode Metal Dissolution

If the primary mechanism of electrotherapy involves inhibition of enzyme RR, then electrode metal deposition should have little or no influence on the beneficial outcome. Study 10 (13) has clearly shown that this is so. The fact that different electrode materials produce very similar results, further indicates that electrodes act merely as electron conductors.

Conclusion

Thus, virtually all the observed facts are in accord with the proposed mechanism involving the deactivation of the free radical containing active-site of RR. Furthermore, a recent experiment has shown that the concentration of enzyme RR decreases and cell-growth ceases when direct electric current is passed through the tumor (15). The proposed hypothesis, thus, is on the verge of being proved.

This novel way of arresting cell growth can be foundation of a cancer therapy that is non-toxic, non-invasive, site-specific, low-cost and easy to administer. The current cancer treatments are called "slash, burn & poison" by oncologists themselves, and are mostly empirical in nature. The gentle electrotherapy, on the other hand, would be deductively scientific with potential to cure most cancers.

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