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Mini-review

Fluoxetine and reversal of multidrug resistance

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Abstract

This review centers on recent findings with respect to modulating cancer multidrug resistance (MDR) with the well-known antidepressant fluoxetine (prozac). The MDR phenomena and mechanisms are discussed, including the roles of ABC transporters as MDR-pumps and the potential involvement of cancer stem cells. The three generations of MDR reversal agents (chemosensitizers) are reviewed, introducing the concept of single-pump and multi-pump agents. The current status of chemosensitization is summarized, pointing-out the need for additional agents and outlining experimental criteria for testing novel candidates. Major in vitro and in vivo findings are summarized showing that fluoxetine is a chemosensitizer of the multi-pump type, and proposing it be considered a fourth-generation chemosensitizer. In concluding, we contemplate future prospects of modulating MDR in the clinic.

Keywords: Multidrug resistance (MDR); ABC transporters; Chemosensitizers; Fluoxetine; Chemotherapy

1. Introduction: tumors, multidrug resistance (MDR) and the ABC superfamily of transporters

This review focuses on recent findings with respect to reversal of multidrug resistance (MDR) by a veteran drug in use for a non-cancerous indication[1]. Chemotherapy, a major treatment for cancer patients-primary for leukemias and inoperable solid tumors, adjuvant and neoadjuvant for operable solid tumors-often fails the patients due to inherent or acquired multidrug resistance (MDR) [1–8]. MDR is a multi-factorial phenomena and the term itself has seen multiple use. It is used as a general term to describe the resistance to many different chemotherapeutic drugs, irrespective of the operating mechanisms [4]. It is also used, as in the present context, to describe the specific mechanism operated by extrusion pumps. In this case, the same mechanism confers resistance to a wide repertoire of drugs-from among anthracyclines, vinca alkaloids, anthracenes, tubulin polymerizing agents and others-that have very little in common with one another [1,2,4].

The one common feature among these drugs is a sufficient degree of lipophilicity-some more and some

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[1] For reviews on the various aspects of MDR in cancer chemotherapy, from the phenomena itself, through its molecular biology aspects to the clinical situation, the reader is referred to several recent excellent reviews [1–5].

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less-that allows the drug to diffuse across cell membranes (influx and efflux). In the case of drug-sensitive tumor cells, as illustrated in Fig. 1A, influx is expected to be dominant, due to the direction of the driving force (i.e. the electrochemical gradient of the drug across the cell membrane). In a drug-sensitive tumor cell the drug can, thus, accumulate to a sufficient level that culminates in cell death (Fig. 1A).

An entirely different situation exists in MDR tumor cells, due to over expression of extrusion transporters from the ABC superfamily [1–5,8–10]. As illustrated in Fig. 1B, these transporters actively pump the chemotherapeutic drug out of the cell, reducing intracellular drug doses below lethal thresholds. Among the ABC transporter sub-families that perform in mammalian cells as MDR extrusion pumps, the most prominently proteins identified and investigated are: P-glycoprotein; the multidrug resistance-associated proteins (MRP) of which the most studied is MRP1; MXR (also named BCRP and ABCP) [1–5,8–10]. Under a recently-introduced nomenclature ABCB1 replaces p-glycoprotein, MRP1 is named ABCC1 with other MRP's given consecutive numbers, and MXR is named ABCG2 [1–5,8–10]. The homology shared by these different families of pump proteins is relatively modest, and there are differences in substrate specificities, yet they function similarly in terms of active drug extrusion [1–5].

It has been long-recognized that clinical MDR appears in two modes, inherent (intrinsic) and acquired [1–5]. Extensive investigations into the origins of each mode shed light on the phenomena, but complete molecular understanding is still into the future. Recent findings from the stem cell arena have direct bearing on the present issues. Among them: the high levels of ABC transporters, in particular ABCG2 in normal stem cells; the recognition of cancer stem cells; the retention of ABC transporters in cancer stem cells [11,12]. The presence of cancer stem cells (irrespective of their minute share in tumors) that intrinsically and consistently over-express ABC transporters, contributes to, or complicates (depending on the point of view) our understanding of cancer biology, drug resistance and the inherent vs. acquired modes of MDR. The roles of cancer stem cells in cancer recurrence and in drug resistance-intrinsic and acquired-needs further studies. It is, however, quite clear, that the presence of cancer stem cells and their impact on MDR should become a major factor in designing strategies of cancer therapy that attempt to overcome drug resistance.

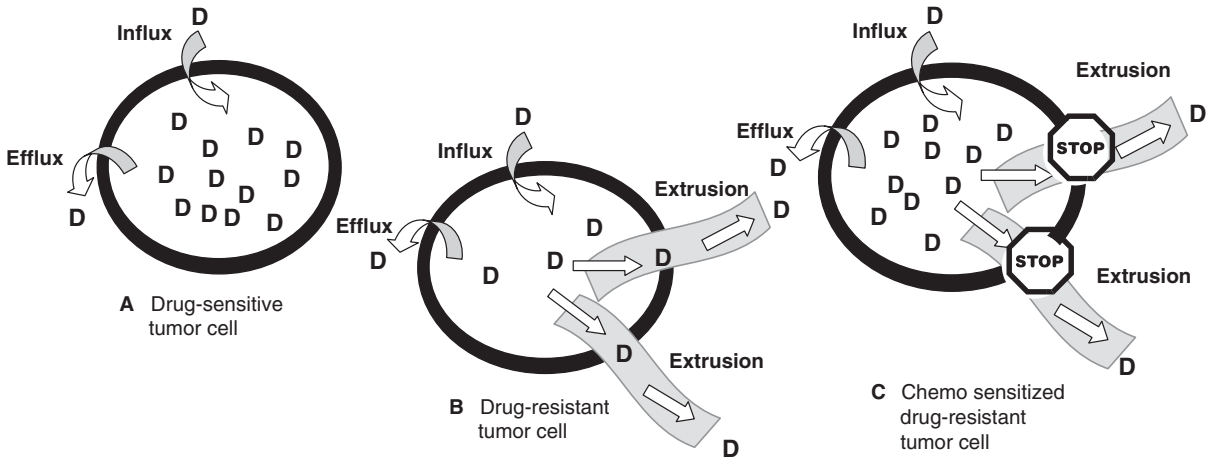

Fig. 1. Schematic representation of drug efflux and drug accumulation in drug-sensitive and in drug-resistant tumor cells. (A) A drug-sensitive tumor cell. Drug molecules-D-diffuse across the cell membrane. Influx > efflux due to the direction of the drug's electrochemical gradient, allowing sufficient drug accumulation inside the cell. (B) A drug-resistant tumor cell. In addition to drug diffusion across the cell membrane (influx and efflux), intracellular drug is pumped out of the cell by the extrusion pump (represented as the wide gray ribbons), severely reducing the drug's intracellular accumulation. (C) A chemosensitized drug-resistant tumor cell. Pumping is reduced/halted, allowing drug to accumulate inside the cells by diffusion alone, similar to the case of a drug-sensitive tumor cell.

The broad specificity, or rather the non-specific nature, of the MDR pumps carries the implication that MDR is among clinical problems that refuse to disappear, for a combination of reasons. Any small anticancer drug that operates inside the cell is at risk of MDR-pump-mediated extrusion from the cell. A case in point is imatinib (Gleevec or Glivec), one of the new generation of anticancer drugs directed against new targets inside the tumor cells [13–15]. Hopes that this drug will not be prone to extrusion were muted upon findings that this drug is a substrate and a partial inhibitor of ABCB1 [13–15]. In addition, combination treatments of conventional chemotherapeutic drugs (prone to MDR) together with new anticancer drugs seem to be significantly more effective than the new drugs alone [6,7,16,17]. The relationship between cancer stem cells and MDR while still needs further investigation, as discussed above, adds to the implication that MDR is here to stay. Consequently, while pursuit of anticancer drugs that are not substrates of MDR pumps is of high priority, continued efforts are also needed to develop ways and means of overcoming MDR.

2. MDR reversal by chemosensitization

Drug resistance mediated by the extrusion pumps is, essentially, a problem that holds the key to its resolution. In the most direct and naive view, simply arresting the pump action should lead, as illustrated in Fig. 1C, to re-instating drug accumulation inside the MDR tumor cell to levels similar to those of a drug-sensitive tumor cell (Fig. 1A). That, in turn, should lead to demise of MDR tumor cells that would be similar to the response of drug-sensitive tumor cells.

Several different names have been given to an agent capable of pump arrest: chemosensitizer, MDR reversal agent, MDR modulator, pump-inhibitor (usually specifying the pump protein such as in 'Pgp inhibitor'). The first three names indicate the desired phenomena, while the latter term, pump-inhibitor, implies a specific mechanism of overturning MDR and should be used with caution.

The on going search for chemosensitizers that can be applied in the clinic is into its third generation. First-generation chemosensitizers were found among drugs already approved for other indications, such as verapamil, cyclosporin A and progesterone [18–23]. Valid and available until today as in vitro benchmarks for the search and development of new chemosensitizers, dose-related adverse effects and toxicity, in some cases compounded by solubility limitations, prevented their progress into the clinic [18–23].

Second and third generation chemosensitizers, some of which are in clinical trials [24–29] were drawn from chemical derivatization of first-generation molecules and from combinatorial chemistry designed for the most against ABCB1. Prominent examples are VX-710, PSC833, XR9051, XR9576, MS-209, GF120918, R101933, LY335979 and OC144-093 (ONT-093) [24–35]. These advanced-generation chemosensitizers are more potent and less toxic than first-generation compounds, yet some are still prone to adverse effects, poor solubility, and unfavorable changes in pharmacokinetics of the anticancer drugs [24–35].

Among chemosensitizers under investigation, some are single-pump, namely specific to a single type of pump protein. For example, PSC833, XR9576, GF120918, LY335979 and OC144-093(ONT-093) for ABCB1 [24–31]; MK571 and probenecide for ABCC1 [36]; pheophorbide and FTC for ABCG2 [37,38]. Other chemosensitizers are multi-pump, namely capable of addressing more than one type of pump protein. For example, verapamil, Cyclosporin A and MS-209 are chemosensitizers for ABCB1 and ABCC1 while Biricodar (VX-710) is a chemosensitizer for ABCB1, ABCC1 and ABCG2 [30,39].

The diversity among pump proteins, the well-known heterogeneity of cells in a given tumor (including the cancer stem cells) as well as patient-to-patient variability in responses to the same treatment-indicates that clinical resolution of MDR will require treatment with more than one chemosensitizer. This realization carries several implications: the search and development of additional chemosensitizers should continue along with the hope that chemosensitizers currently in clinical trials will succeed all the way to the clinic. Multi-pump chemosensitizers, if they mature into the clinic, will have distinct self-explanatory advantage over single-pump ones.

Given the above-discussed need for additional chemosensitizers, we find it in place to contemplate what it takes to qualify a candidate molecule as an

effective chemosensitizer for which, furthermore, pump inhibition is the single or major mechanism. Starting in vitro, we propose that a candidate molecule should meet three criteria, one functional and two mechanistic.

The functional criterion is simply cell demise: treatment of a given MDR tumor cell line with a combination of the candidate chemosensitizer and a chemotherapeutic drug, should significantly enhance cell demise, compared to similar treatment with drug alone.

The mechanistic criteria are drug efflux and drug accumulation. Incubating MDR cells with a chemotherapeutic drug, with and without the candidate chemosensitizer, should result in higher intracellular drug accumulation in the latter case. Efflux of a chemotherapeutic drug from those MDR cells, preferably under unidirectional conditions, should be significantly faster in the absence of the chemosensitizer candidate, than when it is present. If a candidate chemosensitizer meets all three criteria, there is merit in expanding the evaluation (for the same triplicate criteria) in several directions: testing, in the same cell line, a battery of drugs drawn from those known to be substrates of the given MDR pump; testing the battery of MDR drugs with additional MDR cell lines; testing, pending availability and relevant only in the case of acquired-MDR, parent drug-sensitive cell lines. Needless to say, comparative studies to known chemosensitizers, used as benchmarks, can lend further support to evaluation of the candidate molecule. Several elegant tools for evaluation of chemosensitizer-mediated efflux and accumulation have been developed making use of probe molecules that are substrates of MDR pumps [40–41]. We suggest that such probe molecules be considered as additional (rather than standalone) valuable tools for examining a candidate chemosensitizer, as they cannot replace the combination of functional and mechanistic studies defined above, performed with actual MDR drugs.

3. Fluoxetine as a chemosensitizer of the multi-pump category

Psychotropic drugs, among them antidepressants that are SSRI agents such as fluoxetine (Prozac) and others, have been investigated for additional therapeutic indications, including cancer [42,43]. The potential of fluoxetine as an anticancer drug is inconclusive. Some of the studies indicate fluoxetine (and other SSRI agents) inhibit tumor proliferation whereas other studies imply it induces tumor promotion [42,43]. We wish to emphasize the dose range: when fluoxetine was investigated for its potential as an anticancer drug, it was tested at doses similar or higher than those used for its antidepression indication.

This review also examines the potential of fluoxetine in cancer treatment, but not as an anticancer drug-rather as a chemosensitizer, potentiating tumor response to anticancer drugs. On its face, fluoxetine belongs among first-generation chemosensitizers (as defined in Section 2 above) namely drugs approved for other non-cancer indications and found to act as MDR modulators. Yet, one critical factor sets fluoxetine apart from other first-generation members and indicates it may merit a separate category, possibly fourth-generation chemosensitizers. As our recent findings [44,45] summarized below will show, unlike the first-generation chemosensitizers and unlike the activities discussed in the first paragraph of this section, fluoxetine exerts its ability to chemosensitize MDR cells at low safe doses, well below its human safety range.

3.1. In vitro studies

Starting with the in vitro triplicate criteria-cytotoxicity, efflux and accumulation-defined in Section 2 above, fluoxetine was tested in ABCB1/MDR tumor cells, in ABCC1/MDR tumor cells and in drug-sensitive tumor cells. Test drugs were doxorubicin, mitomycin C, paclitaxel and vinblastine (VIN). The multi-pump chemosensitizers verapamil and cyclosporin A, shown to affect the ABCB1 and the ABCC1 proteins, were used as benchmarks.

3.1.1. In vitro criterion 1: cytotoxicity

Two measures are useful for evaluation of whether a chemosensitizer candidate meets the in vitro cytotoxicity criterion: IC_{50}, the drug concentration that generates 50% inhibition of cell proliferation which, in the case of MDR, is obviously measured in absence and presence of a

fixed chemosensitizer-candidate concentration. RF, the fold change in drug sensitivity, calculated from the ratio of IC_{50} in absence, to that in presence, of the candidate.

Fluoxetine, verapamil and cyclosporin doses were kept to the range of 5–20 μM, where these agents themselves did not affect cell viability. Fluoxetine had no effect on the response of drug-sensitive cells to chemotherapeutic drugs. RF values-obtained for the human breast cancer and colon cancer lines MCF7 and HT29 and the mouse leukemia line P388/WT-were in the range of 0.9–1.1 for doxorubicin, mitomycin C and vinblastine [44]. For doxorubicin, mitomycin C and paclitaxel, fluoxetine-induced RF values in the inherent-ABCC1 cell lines PANC-1 (human pancreatic adenocarcinoma) and T98G (human glioblastoma), were in the range of 10–80 [45]. RF values obtained with the benchmarks verapamil- and cyclosporin A, for the same drugs and cell lines were (for the most) in the range of 2–7 with two exceptions that did not exceed a RF of 19 [45].

Fluoxetine's candidacy as a chemosensitizer for the ABCB1 pump-protein was tested with doxorubicin, mitomycin C and vinblastine, in the following cell lines: B16F10.9 (mouse melanoma), D122 (subline of mouse Lewis lung carcinoma), C-26 (mouse colon carcinoma), NCI/ADR-RES (human breast carcinoma formerly named MCF7/ADR) and P388/ADR (mouse leukemia). Similar to the ABCC1 cell lines, verapamil-induced (spot tested) RF values were 2–3, and fluoxetine-induced RF values were 40–60 for mitomycin C, 20–70 for doxorubicin and 15–70 for vinblastine [44].

3.1.2. In vitro criterion 2: drug efflux

Drug efflux from drug-sensitive cells was rather slow. For example, complete depletion of intracellular doxorubicin from MCF7 cells, under unidirectional flux conditions, takes more than 7 h and is unaffected by verapamil or by fluoxetine [Peer and Margalit, unpublished data]. Drug efflux from inherent and acquired MDR cells, whether the pump-protein is ABCB1 or ABCC1, was found to be rather fast. For example, under unidirectional flux conditions it took only 1–2 h for complete depletion of such cells from intracellular doxorubicin, mitomycin C, paclitaxel or vinblastine [44,45]. As expected, the benchmarks verapamil and cyclosporin A slowed-down drug efflux, usually increasing the time span for complete depletion up to 3–5 h [44,45]. Fluoxetine showed a similar trend, extensively slowing-down the efflux, thereby increasing the time for complete depletion, to the range of 8–12 h, close to that of drug-sensitive cells [44,45].

3.1.3. In vitro criterion 3: drug accumulation

Measuring accumulation with actual drugs and with the fluorescent substrate Rhodamine-123, the benchmarks were found to increase intracellular drug accumulation compared to cells exposed to drugs alone. This effect was found in inherent and acquired MDR cells, whether the pump-protein was ABCB1 or ABCC1 [44,45]. In cell lines where the benchmarks increased drug accumulation by 0.2–2 fold, fluoxetine acted similarly and was usually 1.4–3.0 fold better than the benchmarks [45]. In cell lines where the benchmarks increased drug accumulation by 1–10 fold, fluoxetine also acted similarly and was 10–100 fold better than the benchmarks [44, Peer and Margalit, unpublished data]. Interestingly, chemosensitizer-induced increases in accumulation for benchmarks and for the fluoxetine were higher in ABCB1 than in ABCC1 cells. This, however, could be due to differences in experimental designs and methodologies, and will require additional studies to determine whether this is a technical or an intrinsic issue.

3.2. In vivo studies

Following the in vitro findings, fluoxetine was studied in several syngeneic and nude mouse tumor models, with doxorubicin as the test drug. Several parameters were unique to these studies: fluoxetine was given at the low dose of 0.04 mg/kg body which is well below human safety limits; it was administered orally in the drinking water; it was given continuously from tumor inoculation until termination of the experiment. Most of the efforts were on efficacy, but it was first verified that fluoxetine did not alter the drug's pharmacokinetics, a problem encountered with some previous-generation chemosensitizers [44]. Biodistribution was also tested, showing that while fluoxetine generated a 12 fold increase in doxorubicin accumulation in the lung tumors, it had no effect on

drug accumulation in liver, spleen and kidneys of the tumor-bearing mice[44].

The mouse tumor models tested were [44,45]: A C-26 (inherent ABCB1) solid tumor in the footpad of BALB/C mice; a B16F10.9 (inherent ABCB1) model of lung metastatic disease in C57BL/6 mice, P388/WT (drug-sensitive) and P388/ADR (acquired ABCB1) models of peritoneal ascites in BDF_1 mice; two human xenograft models of subcutaneous (flank) solid tumors in athymic nude mice-NCI/ADR-RES (acquired ABCB1) and PANC-1 (inherent ABCC1). These models provide for experimental designs testing tumor progression (the syngeneic models) and tumor regression (the human xenograft models). All models in which the inoculated tumor cells showed MDR characteristics in vitro, continued to act as such in vivo. In the drug-resistant in vivo models, therapeutic responses and survivals of mice treated with doxorubicin alone were not different than control groups treated with saline or fluoxetine alone [44,45]. In the one model of drug-sensitive cells (P388/WT), therapeutic responses and survival of the doxorubicin-treated group were significantly better than the controls, and addition of fluoxetine to the drug treatment was not different than drug alone [44].

In all the MDR in vivo models combination treatment of-doxorubicin (by intravenous injection in all cases, except intraperitoneal injections in the NCI/ADR-RES model) and fluoxetine (orally, as descried above)-generated therapeutic responses that were distinctly and significantly different from those generated by control treatments and, as already discussed above, treatment with drug alone. The combination treatment slowed down tumor progression (C-26 and P388/ADR models), reduced lung metastatic burden (B16F10.9 model) and generated almost-complete tumor regression (PANC-1 and NCI/ADR-RES models) [44,45]. The combination treatment increased life spans in all cases. Survival was found to increase by 2–3 fold in the cases where such an evaluation was possible in the course of the study (C-26 and the P388/ADR models) [44]. Survival was even higher in all other models, where termination of the experiment was required at a time point in which all control and drug-alone animals were dead while 50–100% of the animals receiving combination treatment were still alive [44,45].

3.3. Conclusions

In summary, fluoxetine met all three in vitro criteria for acting as a chemosensitizer. We emphasize all three, as one criterion alone may be inconclusive. An example is seen in accumulation studies of a model ABCB1-substrate performed for a series of SSRI agents and known chemosensitizers, where fluoxetine was placed in a low-response group [46]. Fluoxetine also acted as a chemosensitizer in vivo, with relatively good in vitro-in vivo correlation. The data indicate it belongs to the category of multi-pump chemosensitizers, showing capability of reversing MDR generated by two major pump proteins ABCB1 (P-glycoprotein) and ABCB1 (MRP1) [44,45]. As to its mechanism of action, the data generated so far indicates that fluoxetine acts as a pump inhibitor, but future studies are required to determine whether this is the only, or a major, mechanism by which fluoxetine modulates MDR. Future studies will also show whether fluoxetine's multi-pump ability is limited to ABCB1 and ABCC1, or extends to additional members of the MRP family and/or to ABCG2.

4. Future prospects

Two aspects, discussed in previous sections of this review, stand out when contemplating the future prospects of clinical MDR reversal. The need to provide cancer patients and their physicians with an arsenal of clinically-approved chemosensitizers that will address the different MDR pump-proteins. The need to fully understand the involvement of cancer stem cells in clinical MDR, and whether the same means will suffice to modulate resistance of the cancer cells and of the cancer stem cells.

While the early generations of chemosensitizers did not progress into approved clinical modalities, several directions hold promise to improve the situation. One is the direction taken in pursuing third-generation chemosensitizers [24–35], with the hope that some clinically-approved chemosensitizers will emerge from molecules that are currently in clinical trials. Knowledge and understanding of the pump proteins in the arenas of biochemistry,

molecular biology and theoretical biology is continuously increasing. It is anticipated that these strides will enable the design, synthesis and testing of additional chemosensitizer candidates, of the single-pump and of the multi-pump types.

At the same time we argue that the approach pioneered by the first-generation chemosensitizers, namely exploring the chemosensitization potential of drugs already approved for other (non-cancer) indications, not be abandoned. The proposal that fluoxetine be considered a fourth-generation chemosensitizer was made earlier in this review, based on its distinct difference from the first-generation molecules, by reversing MDR at low and safe doses. We find this a critical distinction, as it may make the difference with respect to the potential for reaching the clinic. To merit consideration as a fourth-generation chemosensitizer, we propose a candidate follow the blueprint outlined in this review, testing limited to sufficiently low and safe dose ranges, starting from the three in vitro criteria discussed in Section 3, progressing thereafter to the in vivo arena.

In closing our view is that, despite the complexity and the multifactorial nature of cancer MDR, encouraging prospects do exist with respect to maturation of for third and fourth generation chemosensitizers into established clinical modalities. Especially if clinical trials with chemosensitizer candidates will focus, through the advent of pharmacogenomics and the increased understanding of MDR, on patient populations that are suitable potential responders to the tested novel treatment.

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