INVITED COMMENTARY

Emerging Roles for Radiometabolic Therapy of Tumors Based on Auger Electron Emission

Preliminary reports suggest some therapeutic efficacy (however limited) after administration of high doses of the ^{111}In-labeled somatostatin analog [^{111}In-diethylenetriaminepentaacetic acid (DTPA)-D-Phe^{1}]-octreotide (^{111}In-octreotide) in patients with unresectable, somatostatin receptor–positive neuroendocrine tumors (*1–5*). The γ emission energy of ^{111}In causes minimal cell damage (*6*), so these radiobiologic effects have been reasonably attributed to the low-energy Auger and conversion electron emissions of this radionuclide. Because of the short ranges of these low-energy electrons ($\leq$1 μm), the findings imply that the complex formed on the cell membrane is internalized on binding of radiolabeled octreotide to the somatostatin receptors, with subsequent translocation of the radiopharmaceutical across the cytoplasm either into or in close proximity to the cell nucleus.

The article by Tiensuu Janson et al. (*7*) in this issue of *The Journal of Nuclear Medicine*, examining in patients the treatment of neuroendocrine tumors with ^{111}In-octreotide, provides the first in vivo experimental evidence for the translocation of this radiopharmaceutical to the cell nucleus. This work complements earlier in vitro studies based on the incubation of tumor cells with the same radiolabeled agent (*8*) and ongoing clinical trials with ^{111}In-octreotide (*1–5*). Through findings that support the hypothesis of nuclear localization as the basis of the therapeutic effect of this radiotracer, the investigators significantly contribute to our understanding of the mechanisms of its cellular uptake and subcellular localization and give new impetus to attempts at radiometabolic therapy of tumors based on Auger electron emitters.

The use of ^{111}In-octreotide for the treatment of neuroendocrine (and other) tumors raises some questions about the appropriateness of the Auger emission approach. Although many studies have shown that the decay of low-energy, electron-emitting isotopes within the nuclei of mammalian cells is highly toxic (*9–13*) and therapeutically efficacious in experimental animal models (*14,15*), the transfer of these experimental results to human clinical trials has so far been limited (*16–18*). Any therapeutic approach based on Auger electron–emitting radionuclides must take into consideration the major biophysical factors underlying the radiobiologic effects of Auger electron emission. In Figure 1, the 3 red schematic targetlike stars superimposed on the electron microscopy structure of a single neuroendocrine tumor cell symbolize the ionization range produced by the Auger electrons emitted during the decay of ^{111}In. The scale of this representation is roughly approximate in terms of cell diameters. Ionizations are highest in the immediate locality of the decaying atom, but they extend approximately 1 μm in every direction. The positions of the 3 stars correspond to 3 different phases of an internalization process such as that shown by Tiensuu Janson et al. (*7*) for ^{111}In-octreotide. The location on the cell membrane (right upper corner of Fig. 1) symbolizes binding of the tracer to the somatostatin receptors, whereas subsequent internalization of the receptor–ligand complex and translocation of radioactivity through the cytoplasmic compartment and into the nucleus are indicated by the other 2 stars. This schematic representation clearly shows that effective (desired) radiotoxicity caused by Auger electrons occurs only when the low-energy, short-range electrons produced by radioactive decay are within the cell nucleus or very close to it. Moreover, radiotoxicity is limited to the single cell that has incorporated radioactivity, because no cross-fire effect ensues with Auger electrons. By contrast, α particles (e.g., emitted during the decay of ^{211}At) and high-energy β particles (e.g., emitted during the decay of ^{131}I) have a range that roughly corresponds to few (~5–7) and many (~50–250) cell diameters, respectively. When radioactive decay leads to the emission of high-energy α or β particles, the location of the decaying atom within the cell nucleus is not an absolute prerequisite for effective radiotoxicity. The implication is that radioactivity heterogeneously deposited in a given tissue will generate a cross-fire effect that involves not only the single tumor cell that has bound or incorporated the radiopharmaceutical but also nearby cancerous cells nested within the range of the emitted particles. These highly penetrating ionizing particles can also induce radiotoxicity in normal tissues surrounding tumors, a situation not seen with Auger electron–emitting radionuclides when confined only to their intended targets. In all such radionuclide-based therapies, normal tissues must not accumulate radioactivity in amounts that can induce unacceptable systemic radiotoxicity.

The observations reported by Tiensuu Janson et al. (*5,7*), as well as results obtained by other investigators, consistently indicate that somatostatin analogs such as octreotide are indeed adequate carrier molecules for bringing radionuclides into the cell nucleus of neuroendocrine tumors (*19–23*), a fundamental criterion for any desired radio-

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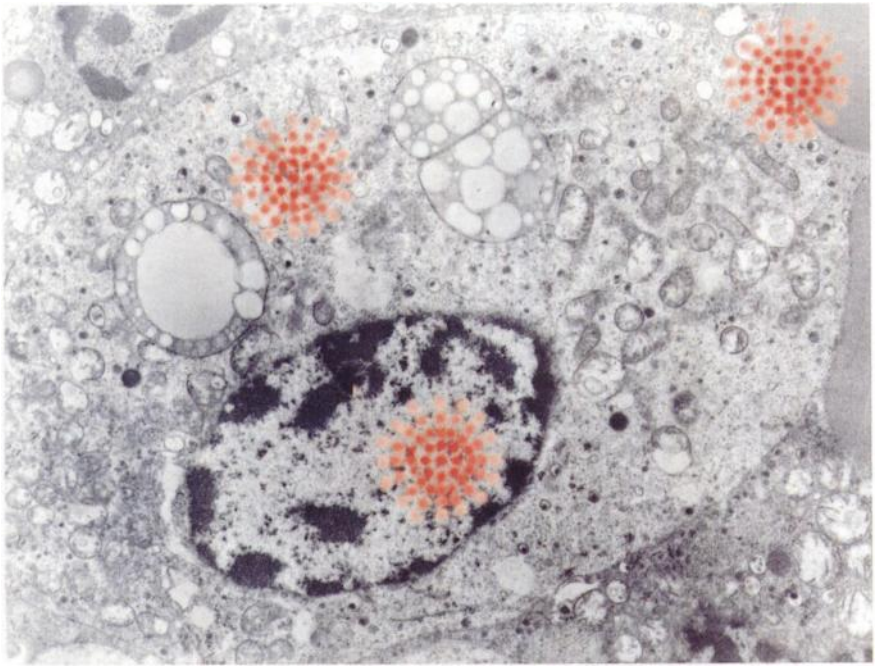

FIGURE 1. Schematic representation of ionization ranges (targetlike red stars) produced by Auger electrons and conversion electrons emitted during decay of ^{111}In, superimposed on ultrastructural image of neuroendocrine tumor cell. Size of ionization range is scaled to size of cell. Locations of red stars correspond to 3 phases of internalization: binding of radiolabeled somatostatin analog to specific receptor on cell membrane (right upper corner), translocation of radioactivity across cytoplasmic compartment, and final location within cell nucleus (mid lower portion of figure). Ultrastructure of cell shows main features of neuroendocrine tumor cells: neurosecretory granules (dark organelles scattered throughout cytoplasm), disrupted mitochondria (particularly in portion of cell to right of nucleus), dilated vacuoles (abnormal lysosomes, directly above nucleus), and condensed nuclear chromatin.

toxicity based on Auger electron emission. Once the Auger electron–emitting radionuclide is located in the cell nucleus, its physical half-life and residence time within the targeted cell nucleus must be sufficient to provide the number of decays required to sterilize the tumor, generally 5 logarithms of cell kill.

This outline of the fundamental features relating to the radiobiologic effects of low-energy Auger electrons, high-energy electrons, and α particles gives rise to other questions about the therapy of neuroendocrine tumors with radioactive analogs of somatostatin. In particular, is Auger electron emission the optimal choice for such treatment? The most crucial factor for tumor therapy based on Auger electron emitters is the fraction of tumor cells actually incorporating radioactivity after the systemic administration of a labeled somatostatin analog; this factor is a consequence of the lack of crossfire effect. The somatostatin analogs used in this therapeutic approach have 3 characteristics that make them appropriate. First, they have a low molecular mass (~1400 Da), thus diffusing in tissue much more easily than, for example, monoclonal antibody tracers used for tumor-targeting purposes. Second, expression of somatostatin receptors on the cell membranes of neuroendocrine tumors is much more widespread and homogeneous (among cells and cell nests), as shown by autoradiographic analysis (*24*) and immunohistochemical analysis (*25*), than is the expression of, for example, conventional tumor-associated antigens. Third, the internalization of ^{111}In-octreotide by virtually all tumor cells has been shown by ultrastructural autoradiography (*7*). Therefore, some therapeutic efficacy in the treatment of neuroendocrine tumors with somatostatin analogs labeled with Auger electron–emitting radionuclides is expected. Homogeneous expression of somatostatin receptors is also a good prognostic factor when the therapeutic approach is based on radionuclides emitting higher energy particles, such as is currently being pursued by other groups (*26,27*).

Is ^{111}In the optimal Auger electron emitter for the therapy of neuroendocrine tumors? Some basic considerations relating to the physics of Auger electron emission and to radiochemistry are important here. With respect to the physics, several Auger electron–emitting radionuclides are suitable in principle for use in tumor targeting. They include halogens (^{125}I, ^{123}I, ^{80m}Br, and ^{77}Br) and metals (^{201}Tl, ^{195m}Pt, ^{193m}Pt, ^{114m}In, ^{111}In, ^{99m}Tc, ^{67}Ga, ^{55}Fe, and ^{51}Cr). Among these, ^{195m}Pt exhibits the highest Auger electron yield, with an average of 33 electrons emitted per decay versus 21 electrons for ^{125}I, 11 electrons for ^{123}I, 8 electrons for ^{111}In, and even smaller numbers (between 7 and 4) for ^{77}Br, ^{67}Ga, ^{55}Fe, and ^{99m}Tc, to mention just a few of these potential candidate radionuclides (*13,28*). The amount of energy deposited per decay in a 5-nm sphere is correspondingly much higher for ^{195m}Pt (2000 eV) than for ^{125}I (1000 eV), ^{123}I (550 eV), and ^{111}In (450 eV) (*13,28*). However, platinum is not available in carrier-free form, and cost-related considerations and physical or chemical considerations restrict the choice to ^{111}In and to the 2 iodine radionuclides. Among these, ^{125}I has a greater number of electrons emitted per decay. Because this radionuclide also has a longer half-life (60 d), the total number of decays taking place during its residence within the targeted cells will be greater. Consequently, this radionuclide also seems to be a better choice than ^{111}In for the therapy of neuroendocrine tumors based on somatostatin analogs labeled with Auger electron–emitting radionuclides.

Radiochemical consideration favors ^{125}I as well. Current attempts at tumor therapy with radiolabeled somatostatin

analogs rely on either DTPA chelate chemistry (such as ^{111}In-octreotide) or recently developed DOTA chelate chemistry (such as [^{90}Y-DOTA-D-Phe^1-Tyr^3]-octreotide, in which DOTA stands for 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid). The DOTA conjugate, labeled with either ^{90}Y or ^{125}I, appears to possess even better tumor-targeting properties than the original DTPA conjugate octreotide (*23,29–31*). Good internalizing properties are also shared by other recently developed somatostatin analogs constructed for radioiodination (*22*). Previous concerns about the suitability of iodine radionuclides for stable labeling of somatostatin analogs (*32*) are not justified in the case of ^{125}I, because much less autoradiolysis occurs with this radionuclide (even at very high specific activity) than with ^{131}I.

From the available experimental evidence, we believe that targeting of neuroendocrine tumors with radiolabeled somatostatin analogs meets the criteria for successful therapy based on Auger electron emission. Despite the somewhat encouraging results reported so far with ^{111}In as a source of Auger electrons, radiochemical and radiobiologic considerations point to ^{125}I as the radionuclide of choice for such an approach, provided that analogs with high receptor affinity and long intracellular residence times are used for carrying the radionuclide into the cell nucleus. Given all these prerequisites, this approach may lead to the first successful clinical attempt at tumor therapy based on Auger electron emission. A recent article published by Hornick et al. (*33*) provides further evidence, based on an in vitro experimental model, for an efficient translocation and binding to cell nuclear structures of radiolabeled somatostatin analogs in tumor cells bearing somatostatin receptors on their cell membranes.

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