Mechanism of Gallium-67 Accumulation in Tumors

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Neoplasms are characterized by increased perfusion, increased permeability of their capillary beds to macromolecules, and a delay in new lymphatic vessel growth. These lead to the increased entry and residency time of macromolecules in the interstitial space of tumors. Multiple factors contribute to the localization of ^{67}Ga in tumors. Adequate blood supply is essential; at areas with no blood supply such as the necrotic center of a large tumor, there is no ^{67}Ga accumulation. Gallium-67, mainly in the form of transferrin-^{67}Ga complex, is delivered to the tumor through capillaries with increased permeability. In tumors, some ^{67}Ga is taken up by tumor cells; some may also be taken up by inflammatory cells when they are present. Gallium-67 binding proteins, such as lactoferrin or ferritin, may also contribute to the accumulation and retention of ^{67}Ga in tumors; however, their roles are less clear. The intensity of these various factors determine their relative contribution and the degree of ^{67}Ga accumulation in tumors.

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Since the first demonstration of gallium-67 (^{67}Ga) accumulation in neoplastic lesions in 1969 (*1*), the mechanism of ^{67}Ga localization in tumors has been extensively studied (*2–4*). These studies are usually done in the following two systems: (a) in vitro, by measuring ^{67}Ga uptake by tumor cells in culture, and (b) in vivo, by studying ^{67}Ga uptake by tumors implanted subcutaneously or intramuscularly in animals.

The in vitro system has the advantage of being simple and reproducible. However, since in vitro conditions are different from those of the tumors in an in vivo situation, observations made in a tissue culture system may not be applicable to the in vivo situation. On the other hand, the in vivo system has the disadvantage of being complex with the variables being studied difficult to control. In addition, tumors are usually implanted subcutaneously or intramuscularly, which is not the origin of the tumor. Whether these implanted tumors represent the natural condition of tumors remains unclear. Nonetheless, considerable information exists in the literature to allow meaningful and rational conclusions to be drawn. This review analyzes the current knowledge of the mechanism of ^{67}Ga accumulation in tumors.

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Regional Pathophysiology of Neoplasms

Knowledge of the pertinent pathophysiology of tumors is important in understanding the mechanism of ^{67}Ga accumulation in tumors. Neoplasms, like inflammatory lesions, are characterized by increased permeability of their capillary beds to macromolecules (*5,6*). This is largely due to neovascularization and the large intercapillary pores associated with the new growth of capillary beds. The total perfusion to tumors is often increased in comparison to surrounding normal tissue. Moreover, there may be a delay in new lymphatic vessel growth. These factors lead to the increased entry and residency time of macromolecules in the interstitial fluid space of tumors (*5,6*).

Transport of ^{67}Ga in Circulation

This subject has been recently reviewed (*7*). Briefly, after i.v. injection of carrier-free [^{67}Ga]citrate, >99% of the radioactivity present in the circulation is in the plasma, the rest being associated with white blood cells (*8,9*). Using ultrafiltration, it has been demonstrated that almost 100% of ^{67}Ga present in normal plasma is protein bound (*10,11*). In addition, using affinity chromatography, Vallabhajosula et al. (*11*), have clearly

shown that ^{67}Ga in normal plasma is almost exclusively bound to transferrin. Like Fe^{3+}, ^{67}Ga binds to the two specific metal binding sites of human transferrin; however, its binding constants (log k_1 = 20.3 and log k_2 = 19.3) are considerably lower than those of Fe^{3+} (log K_1 = 22.8, log k_2 = 21.5) (*12*). When ^{67}Ga-labeled human transferrin is subjected to dialysis against normal saline in vitro, significant dissociation occurs (*10*).

In addition to transferrin, other iron-binding proteins in plasma, such as lactoferrin and ferritin have been shown to bind ^{67}Ga. At physiologic pH, lactoferrin has a higher affinity for ^{67}Ga than transferrin (*13*). The affinity of ferritin towards ^{67}Ga is lower than that of transferrin, although under certain conditions transfer of ^{67}Ga from the transferrin-^{67}Ga complex to ferritin has been demonstrated (*14*). The role of lactoferrin and ferritin in the transport of ^{67}Ga in the circulation is not clear. Their plasma concentrations, i.e., 0.4–2.2 μg/ml for lactoferrin (*15*) and 0.01–0.25 μg/ml for ferritin (*16*) are at least three orders of magnitude lower than that of transferrin (2 mg/ml) (*17*). It is most likely that under normal circumstances, lactoferrin and ferritin do not contribute significantly to the plasma transport of ^{67}Ga. Their role in pathologic conditions associated with elevated plasma levels of lactoferrin or ferritin such as infection or iron overload (*16,18*), however, needs further investigation.

Since in circulation ^{67}Ga binds to transferrin, the plasma level of unsaturated iron-binding capacity (UIBC), which is a measure of apotransferrin, greatly affects the binding of ^{67}Ga, its plasma clearance, tissue distribution, and body retention (*19–22*). Bradley et al. (*19*) noted that ^{67}Ga uptake in soft tissues and tumors was decreased, while urinary excretion of ^{67}Ga was increased, when the plasma unsaturated iron-binding capacity (UIBC) in tumor-bearing rats was reduced by whole-body irradiation. In contrast, an increase in UIBC in iron deficient rats elevated the ^{67}Ga body retention, especially in the liver and spleen, while tumor uptake remained unchanged (*20*). Similar changes in ^{67}Ga biodistribution and excretion patterns due to alteration in the serum UIBC have been reported by others (*21,22*).

Factors Affecting the Accumulation of ^{67}Ga in Tumors

Increased capillary permeability. Increased capillary permeability and the expanded extracellular space of tumors play an important role in the accumulation and retention of radiopharmaceuticals, including ^{67}Ga, in tumors. As early as the late 1950s, iodine-131 human serum albumin was found to localize in certain tumors (*6,23,24*). The currently widely used brain scanning agent, technetium-99m diethylenetriaminepentaacetic acid (DTPA), an extracellular agent, also takes advantage of the breakdown of the blood-brain barrier in brain lesions including neoplasia (*5,6*). Tzen et al. (*25*) have shown that intramuscular injection of histamine which increases capillary permeability, causes focal accumulation of intravenously-injected ^{67}Ga.

Tumor cells. A variety of tumor cells accumulate ^{67}Ga and may contribute to the localization of ^{67}Ga in tumors. The mechanism of ^{67}Ga uptake by tumor cells has been studied in detail. Several mechanisms have been proposed.

Hayes et al. (*21,26,27*) suggest that ^{67}Ga enters tumor cells, presumably by simple diffusion, as a result of the hyperpermeability of the tumor cell plasma membrane. There is no direct evidence, however, for this hypothesis. On the other hand, English et al. (*28*) have shown that several types of tumor cells do not significantly accumulate ^{67}Ga unless the plasma membrane permeability barrier is disrupted as in nonviable cells.

Anghileri et al. (*29–31*) suggest that tumor cell ^{67}Ga uptake is due to competition of binding by ^{67}Ga to calcium and magnesium-binding sites. The calcium and magnesium-binding sites in their system, however, are poorly defined. In addition, ^{67}Ga is present in trace amount (carrier-free), it is difficult to imagine that ^{67}Ga will compete favorably with calcium or magnesium which are present in much higher concentrations in the cells. Clinically, there is poor association between ^{67}Ga uptake and calcium content in tumors, e.g., neuroblastoma, which are frequently calcified, exhibit a low incidence of ^{67}Ga localization (*3*).

Hoffer et al. (*13*) propose that binding of ^{67}Ga by lactoferrin present in some tumors is responsible for ^{67}Ga accumulation. High lactoferrin content in some tumors has been previously described (*32*). Hoffer et al. reported that two patients, one with Hodgkin's disease and one with Burkett's lymphoma, had increased ^{67}Ga uptake in the tumor tissue subsequently found to contain lactoferrin (*33*). However, the binding of ^{67}Ga to lactoferrin in tumors has not been demonstrated. Furthermore, since lactoferrin is present inside the cells, one has to account for the transfer of ^{67}Ga across the cell membrane.

Using a tissue culture system, Sephton and Harris (*34,35*) observed that human transferrin enhanced ^{67}Ga uptake by a number of tumor cell lines and proposed that ^{67}Ga accumulation in tumors was due to transferrin mediated uptake by tumor cells. As an extension of this hypothesis, Larson et al. (*36*) proposed that there were transferrin receptors in tumor cell surface which were responsible for the internalization of transferrin-^{67}Ga complex. Enhancement of ^{67}Ga uptake by tumor cells in culture occurs at low concentrations (<0.1 mg/ml) of human transferrin (*34–37*). Studies using higher concentrations of transferrin have repeatedly shown an inhibition of ^{67}Ga uptake (*36–38*). The actual concentration of transferrin in the tumor interstitial fluid is not known. It is important to point out that tumor cells do take up ^{67}Ga in the absence of transferrin (*34–39*).

A number of in vivo studies have been done attempting to elucidate the role of transferrin on the tumor uptake of ^{67}Ga, however, the results are conflicting. Increased plasma transferrin as determined by UIBC either reduced tumor uptake of ^{67}Ga (*21*) or had no effect (*20*). Similarly, a reduction of serum UIBC either reduced tumor ^{67}Ga uptake (*19*) or had no effect (*21*). Conflicting results have also been reported for the effect of preincubation of ^{67}Ga with serum proteins on ^{67}Ga tumor uptake. Larson et al. (*40*) and Wong et al. (*41*) found enhanced ^{67}Ga uptake when ^{67}Ga was preincubated with serum (*40*) or apo-transferrin (*41*). This was interpreted as binding of ^{67}Ga to transferrin played an important role in the in vivo tumor uptake of ^{67}Ga. Vallabhajosula et al. (*42*), on the other hand, did not observe a difference in tumor uptake between ^{67}Ga preincubated with human transferrin and [^{67}Ga]citrate. Since after i.v. injection of [^{67}Ga]citrate 99% of the tracer is bound to plasma transferrin (*8,11,22*), it seems unlikely that pre-incubation of ^{67}Ga with serum or transferrin before injection would substantially increase the binding of ^{67}Ga to serum transferrin to account for the observed effects. These in vivo studies are difficult to interpret since, as mentioned earlier, the status of iron saturation of plasma transferrin profoundly affects the plasma level, body retention, and organ distribution of intravenously injected ^{67}Ga. Recently, Scheffel et al. (*37*) have shown that transferrin at concentrations which enhance ^{67}Ga uptake by hepatoma cells in culture, have no effect on the hepatoma uptake of ^{67}Ga in an isolated, perfused rat liver with implanted hepatoma.

Much effort has been made to determine the intracellular localization of ^{67}Ga, however, the results of these studies are conflicting. Swartzendruber et al. (*43*) have shown that intracellular ^{67}Ga present in normal and neoplastic tissue is localized in the cytoplasm within lysosome-like bodies. Brown et al. (*44*) termed the lysosomal bodies "^{67}Ga binding granules" (GBG) and showed a correlation between lysosomal enzyme activity and ^{67}Ga concentration. Further investigations by the same group (*45*) describe microvesicles, which probably represent rough-surfaced endoplasmic reticulum, as being the major site of ^{67}Ga binding in Morris hepatoma cells in contrast to normal liver cells in which ^{67}Ga is mainly localized in the much larger GBG-lysosomes. Other investigators working with Ehrlich ascites cells (*46*) or Yoshida sarcoma cells (*47*), have not found an association of ^{67}Ga with lysosomes.

Within the intracellular organelles, ^{67}Ga is apparently bound to macromolecules. Hayes et al. (*48*) reported that the majority of ^{67}Ga present in extracts from tumors and livers is associated with two macromolecules having molecular weights of ~120,000 and 45,000 daltons. The 45 kd protein is a glycoprotein which can be saturated by small amounts of stable gallium. Clausen et al. (*9*), on the other hand, have found about one-third of ^{67}Ga activity in tumors is bound to ferritin (MW ~450 kd), while the remainder is associated with lower molecular weight proteins. Gallium-67 incorporation into the ferritin fraction of normal hepatocytes has been described by Hegge (*49*); however, Samezima et al. (*50*) reported that in rat liver cells no significant association of ^{67}Ga with ferritin occurs. Aulbert et al. (*51*) report that ^{67}Ga in tumors is bound to a protein with MW of 85-90 kd, which they assume to be transferrin. It is possible that the ^{67}Ga binding protein found by Aulbert et al. is lactoferrin instead of transferrin since these two proteins have similar molecular weights.

Studies of subcellular distribution of ^{67}Ga require disruption of cells and subsequent fractionation and separation. In vitro transfer of ^{67}Ga from transferrin to lactoferrin (*13*) as well as from transferrin to ferritin (*14*) have been demonstrated. Thus, ^{67}Ga may translocate during cell disruption and subsequent separation procedures. The results of these studies may reflect the relative affinity of ^{67}Ga to various cellular components or macromolecules rather than the actual localization of ^{67}Ga in intact cells.

Inflammatory cells. Some tumors are infiltrated with neutrophils and/or mononuclear cells. Since these inflammatory cells accumulate ^{67}Ga (*52–55*), they may contribute to the localization of ^{67}Ga in some tumors. The mechanism of ^{67}Ga by these inflammatory cells has been recently reviewed (*7*).

Gallium-67 binding proteins. Theoretically, the presence of ^{67}Ga binding molecules in the interstitial fluid of tumors may contribute to the accumulation and retention of ^{67}Ga in tumors. Transferrin, lactoferrin, and ferritin all have been identified in tumors (*4,32,33,51*). However, the binding of ^{67}Ga to lactoferrin or ferritin present in the interstitial fluid of tumors has never been demonstrated. In addition, whether these proteins are present in the tumor interstitial fluid in sufficient quantity to affect ^{67}Ga uptake is not clear.

Acid pH. The pH of the interstitial fluid of tumors is slightly acidic as compared with the normal tissue. It has been suggested that the reduced pH in tumors may contribute to the accumulation and retention of ^{67}Ga in tumors, since low pH promotes dissociation of ^{67}Ga from transferrin-^{67}Ga complex (*13,56*). However, exactly how this may contribute to ^{67}Ga tumor uptake is not clear. As mentioned earlier, tumor cells can take up free ^{67}Ga as well as transferrin-^{67}Ga complex.

CONCLUSION

Considerable evidence suggests that the mechanism of ^{67}Ga accumulation in tumors is complex. Multiple factors contribute to the localization of ^{67}Ga in tumors: (a) adequate blood supply is essential, at areas with no blood supply, such as the necrotic center of a large

tumor, there is no ^{67}Ga accumulation; (b) ^{67}Ga, mainly in the form of transferrin-^{67}Ga complex, is delivered to the tumor through capillaries with increased permeability; (c) in tumors, some ^{67}Ga is taken up by tumor cells, some may also be taken up by inflammatory cells when they are present; (d) ^{67}Ga binding proteins such as lactoferrin or ferritin, may also contribute to the accumulation and retention of ^{67}Ga in tumors; however, their roles are unclear. The intensity of these various factors determine their relative contribution and the degree of ^{67}Ga accumulation in tumors.

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