

Mechanism of Gallium-67 Accumulation in Inflammatory Lesions

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Multiple factors contribute to the accumulation and retention of gallium-67 in inflammatory lesions. Adequate blood supply is essential. Gallium-67, mainly in the form of transferrin-Ga-67 complex, is delivered to the inflammatory lesions through capillaries with increased permeability. At the site of inflammation, some Ga-67 is taken up by leukocytes and bacteria when they are present. In addition, Ga-67 may also bind to lactoferrin and bacterial siderophores. Multiple contributing factors often coexist at any given inflammatory lesion. The nature and intensity of the inflammation affects the relative contribution of these factors. Thus, there may be situations in which all the contributing factors are present, but in such a low intensity that they escape clinical detection by Ga-67 scans. On the other hand, there may be situations in which one or more contributing factors are missing, such as in patients with agranulocytosis, while they are readily detected by Ga-67 scans.

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Since the first demonstration of gallium-67 accumulation in inflammatory lesions in 1971 (1,2), Ga-67 citrate has been widely used for the detection of inflammation. Accumulation of Ga-67 has been demonstrated in acute as well as in chronic inflammatory lesions of bacterial and nonbacterial origins (1-5). Because of the clinical utility of Ga-67 citrate scans in the detection of tumors and inflammatory lesions, there has been considerable interest in the mechanism of Ga-67 accumulation (6-9). This review analyzes our current knowledge of the mechanism of Ga-67 accumulation in inflammatory lesions.

Pathology of inflammation

Knowledge of the pathology of inflammation is important in understanding the mechanism of Ga-67 accumulation in inflammatory lesions. Inflammation is a nonspecific response of tissue to injury. The agents that injure tissues and therefore evoke the inflammatory response include living agents such as bacteria, and non-living agents such as physical or chemical agents. Regardless of the nature of the injurious agent or the site

of its occurrence, the basic character of the immediate inflammatory response is almost always the same. Acute inflammation is characterized by three vascular events: (a) vasodilatation and changes in blood flow, (b) increase in vascular permeability with exudation of plasma, and (c) emigration of neutrophilic leukocytes (10). Clinically, it is accompanied by the classic features of heat, redness, swelling, pain, and loss of function. An abscess is a localized collection of pus surrounded by inflamed tissue heavily infiltrated with neutrophils.

The persistence of the injurious agent for weeks to years provides a continuous stimulus for an inflammatory response. Chronic inflammation is characterized by a proliferative rather than an exudative response, with a predominantly mononuclear cell infiltration (macrophages, lymphocytes and plasma cells). The proliferation is chiefly fibroblastic and vascular (10). Thus, in acute inflammatory lesions, there are increased vascular permeability with exudation of plasma, and neutrophilic infiltration. Depending on the nature of the injurious agent, there may be microorganisms, cellular products, and cell debris. In contrast, chronic inflammatory lesions are infiltrated with predominantly mononuclear cells. In addition, there is evidence that vascular permeability is also abnormal (11). In the subsequent sections, factors contributing to the accumulation of Ga-67 in inflammatory lesions are reviewed.

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Transport of Ga-67 in circulation

After intravenous injection of carrier-free Ga-67, more than 99% of the radioactivity present in the circulation is in the plasma with the rest being associated with white blood cells (12,13). Earlier studies revealed that most Ga-67 present in the plasma was protein-bound (13-16). However, the degree and the nature of Ga-67-binding was not clear. In 1980, Vallabhajosula et al. (17) and Tsan et al. (18), using ultrafiltration, demonstrated that almost 100% of Ga-67 present in normal plasma was protein-bound. In addition, Vallabhajosula et al. (17) using affinity chromatography, clearly demonstrated that Ga-67 in normal plasma was almost exclusively bound to transferrin. The uncertainty of the degree and nature of Ga-67-binding in earlier studies (13-16) was in part due to the techniques used such as electrophoresis which produced artifact (17).

In addition to transferrin, at least two other proteins, lactoferrin and ferritin, present in plasma have been shown to bind Ga-67. At neutral to acid pH, lactoferrin has a higher affinity to Ga-67 than transferrin (19). The affinity of ferritin to Ga-67 is lower than that of transferrin, although under certain conditions, transfer of Ga-67 from transferrin-Ga-67 complex to ferritin has been demonstrated (20). Whether lactoferrin or ferritin plays a role in the transport of Ga-67 in circulation is not clear. However, the plasma concentrations of lactoferrin (0.4-2.2 $\mu\text{g/ml}$) (21) and ferritin (0.01-0.25 $\mu\text{g/ml}$) (22) are at least three orders of magnitude lower than that of transferrin (2 mg/ml) (23). It is most likely that under normal circumstance, lactoferrin and ferritin do not contribute significantly to the plasma transport of Ga-67. Their role in pathological conditions associated with elevated plasma levels of lactoferrin or ferritin, such as infection or iron overload (22,24) needs further investigation.

Since in circulation Ga-67 binds to transferrin, the plasma level of unsaturated iron-binding capacity (UIBC), which is a measure of apotransferrin, greatly affects the binding of Ga-67, its plasma clearance, and tissue distribution (25-27). At normal UIBC, the large excess of apotransferrin relative to trace amount of Ga-67 favors the complete binding of Ga-67 as described above. However, in conditions with low UIBC, such as iron overload (27) or intravenous injection of agents, such as iron dextran (28), scandium (29) or gallium (30) all of which bind transferrin, free Ga-67 does exist in circulation. Scheffel and Tsan (27) have shown that in normal rabbits with serum UIBC of $306 \pm 27 \mu\text{g/dl}$, more than 99% of Ga-67 present in the plasma was protein bound, whereas in iron-overloaded rabbits with serum UIBC of $95 \pm 28 \mu\text{g/dl}$, only 84-96% of the radioactivity in the plasma was protein-bound.

Increased vascular permeability

Increased vascular permeability and the expanded

extracellular space at the site of inflammation are important in the accumulation of Ga-67. In fact, this factor alone is able to accumulate Ga-67. Histamine causes obvious dilatation of capillaries and increases the permeability of venules to plasma proteins (10). Tzen et al. (31) have demonstrated that intramuscular injection of histamine causes focal accumulation of intravenously injected Ga-67. Furthermore, a variety of radiopharmaceuticals, including Tc-99m diethyltetraaminepentaacetic acid (DTPA), Tc-99m pertechnetate, and Tc-99m minimicrosphere, accumulate at the site of inflammation (9). Kadir and Strauss (32) have also successfully scanned the patients with inflammatory bowel disease with Tc-99m DTPA.

Leukocytes

Acute inflammatory lesions are characterized by neutrophilic infiltration, whereas chronic inflammatory lesions are infiltrated with predominantly mononuclear cells. Earlier studies (33-36) suggested that accumulation of Ga-67 at site of acute inflammation was due to uptake of Ga-67 by neutrophils. This conclusion was based on the observation that (a) neutrophils took up Ga-67, (33-36) and (b) leukopenic animals showed either no localization or delayed localization of Ga-67 at experimental inflammatory lesions (36). However, this earlier hypothesis is incorrect due to the following reasons: (a) accumulation of Ga-67 at inflammatory lesions in neutropenic patients has been repeatedly described in the literature (36-38), (b) analysis of the abscess contents, either sterile or bacterial abscess, reveals that the majority of Ga-67 is in the noncellular fraction (12,39,40), and (c) Ga-67 accumulated in inflammatory lesions of agranulocytic animals (40) and patients (41) in whom no neutrophils were found in the circulation or at the site of inflammation. Thus, neutrophils are not essential for accumulation of Ga-67 in inflammatory lesions. Nonetheless, neutrophils may contribute to the accumulation and retention of Ga-67.

Neutrophils, lymphocytes, and monocytes, but not red blood cells, accumulate Ga-67 (11,33-36,39,42). Several studies (34,35,39) have consistently demonstrated that neutrophils take up more Ga-67 than lymphocytes. The mechanism of Ga-67 uptake by neutrophils has been studied in detail. Tsan et al. (39) showed that Ga-67 uptake by neutrophils in the absence of serum or transferrin was temperature-dependent and insensitive to metabolic inhibitors. Half of the neutrophil-associated Ga-67 could be removed by trypsin but not by neuraminidase. These results are consistent with the hypothesis that the plasma membrane serves as a diffusion barrier and Ga-67 only binds to the surface of the plasma membrane. When this membrane permeability barrier was disrupted as in nonviable neutrophils, Ga-67 uptake increased markedly (12,39,43). A similar phenomenon has been shown in several other cell types (43). Different

results were obtained by Weiner et al. (44) who showed that the majority (75%) of Ga-67 associated with neutrophils was in the cytosolic fraction, with 36% of the total radioactivity being bound to lactoferrin, which was present in the secondary granules of neutrophils. The reason for this discrepancy is not clear. However, in the study of Weiner et al. (44), Ga-67 uptake by neutrophils varied widely, ranging from 1.74 nCi/10⁷ cells to 130.0 nCi/10⁷ cells (n = 10), a 75-fold variation. This is in marked contrast to the study of Tsan et al. (39) in which Ga-67 uptake by neutrophils ranged from 1,000 cpm/10⁷ cells to 3,342 cpm/10⁷ cells (n = 16), a 3.5-fold variation. In addition, in the study of Weiner et al. (44), up to 9% of their neutrophils were nonviable at the start of their experiments. Thus, it is quite possible that the high intracellular Ga-67 content in Weiner's study is due to the uptake of Ga-67 by nonviable neutrophils in which the plasma membrane permeability barrier has been disrupted, allowing diffusion of Ga-67 into the cells.

The mechanisms of Ga-67 uptake by lymphocytes has also been studied. Merz et al. (45) showed that Ga-67 uptake by phytohemagglutinin (PHA)-stimulated lymphocytes was much higher than that of unstimulated cells. About 50% of the radioactivity associated with lymphocytes, either unstimulated or stimulated with PHA, could be removed by trypsinization without affecting the viability of cells. This suggests that as in the case of neutrophils (39), Ga-67 binds to the surface of lymphocyte plasma membrane (45). The effect of transferrin on Ga-67 uptake by lymphocytes or neutrophils has never been studied. Ga-67 is also taken up by monocyte-macrophages (11,42). However, there has been no study on the mechanism of Ga-67 uptake by this cell type.

Bacteria

Bacteria are present at the site of infection and may contribute to Ga-67 uptake. Menon et al. (46) demonstrated that Ga-67 was significantly taken up by a number of microorganisms. The mechanism of Ga-67 accumulation by bacteria is complex. Menon et al. (46) using *Staphylococcus aureus*, have demonstrated that in the absence of siderophore, Ga-67 uptake by *S. aureus* involves two separate processes. One is insensitive to temperature or metabolic inhibitors. This process probably operates through non-specific binding of Ga-67 to components of *S. aureus*. The second process is not inhibited by metabolic inhibitor, but it is temperature sensitive and is inhibited by high concentrations of stable gallium. This component of Ga-67 uptake is most likely due to facilitated diffusion (46). Using *Ustilago sphaerogena*, Emery and Hoffer (47) demonstrated that in the presence of a siderophore, diferriferrichrome, Ga-67 formed Ga-67-siderophore complex and was taken up by the microorganism in an active transport process indistinguishable from that of ferrichrome. Siderophores

(Greek term for iron bearer) are small molecule metal chelates (molecular weight about 500 to 1,000 daltons) with extremely high affinity for ferric iron. Microorganisms produce siderophore to effectively bind and transport iron through a receptor-mediated transport mechanism (48,49).

Gallium-binding proteins

Neutrophils and bacteria are the main cellular components of acute infectious inflammatory lesions and are capable of accumulating Ga-67. However, analysis of inflammatory exudate, either sterile or bacterial in origin, reveals that the majority of Ga-67 is not associated with the cells (12,39,40). Exactly how Ga-67 is present in the noncellular fraction of inflammatory exudate is not known. However, a number of gallium-binding molecules is present in the inflammatory exudate and may contribute to the accumulation and retention of Ga-67 at the site of inflammation.

Transferrin is present in the inflammatory lesions (50) due to leakage of plasma protein via increased vascular permeability. Intramuscular injection of a high concentration (4 mg/ml) of apotransferrin causes local accumulation of intravenously injected Ga-67 but not Tc-99m DTPA, suggesting that accumulation of Ga-67 under this circumstance was not due to increased vascular permeability (31). However, it is unlikely that the concentration of transferrin at the site of inflammation would reach such a level (50) that it would directly cause the accumulation of Ga-67.

Lactoferrin is present at a high concentration in the secondary granules of neutrophils (51,52). It is bactericidal when not saturated with iron. Hoffer et al. (19) have shown that apolactoferrin binds Ga-67 avidly. Lactoferrin is present in inflammatory exudate due to secretion of lysosomal contents by stimulated neutrophils (53,54) or as a result of cell death. Tzen et al. (31) demonstrated that intramuscular injection of a high concentration (4 mg/ml) of apolactoferrin caused marked focal accumulation of intravenously injected Ga-67 but not Tc-99m DTPA. These results suggest that lactoferrin may play an important role in the accumulation of Ga-67 in inflammatory lesions (8,31). However, binding of Ga-67 to lactoferrin in inflammatory exudate has never been demonstrated. In addition, it is currently not known whether the concentration of lactoferrin present at the site of inflammation is sufficient to cause accumulation of Ga-67. Recently, patients with neutrophil-specific granule deficiency, thus lacking lactoferrin, have been described (55,56). These patients show neutrophil dysfunction and suffer from recurrent infections (55,56). Further studies of these patients will clarify the role of lactoferrin in the uptake of Ga-67 by neutrophils and the accumulation of Ga-67 in inflammatory lesions.

As mentioned above, bacteria produce siderophores

to effectively bind and transport ferric iron. At the site of bacterial infection, siderophores may be present and may play a role in the accumulation and retention of Ga-67.

CONCLUSION AND AREAS OF FUTURE RESEARCH

Considerable evidence suggests that the mechanism of Ga-67 accumulation in inflammatory lesions is complex. The earlier concept of Ga-67 accumulation being due to uptake of Ga-67 by neutrophils present at the site of inflammation (33-36) is no longer acceptable. Multiple factors contribute to the accumulation of Ga-67 in inflammatory lesions. Adequate blood supply is essential; at areas with no blood supply such as the center of a large abscess, there is no Ga-67 accumulation because Ga-67 cannot be delivered. Gallium-67, mainly in the form of transferrin-Ga-67 complex, is delivered to the inflammatory lesions through capillaries with increased permeability. At the site of inflammation, some Ga-67 is taken up by leukocytes and bacteria when they are present. In addition, Ga-67 may also bind to lactoferrin and bacterial siderophores. All these factors contribute to the accumulation and retention of Ga-67 at the site of inflammation (9).

One question frequently asked is which factor is most important in the accumulation of Ga-67 in inflammatory lesions. Unfortunately, there is no clear answer to this question. However, it should be pointed out that multiple contributing factors often coexist at any given inflammatory lesion. In addition, the nature and intensity of the inflammation also affects the relative contribution of various factors. Thus, there may be situations in which all the contributing factors are present but in such a low intensity that they escape clinical detection by Ga-67 scans. On the other hand, there may be situations in which one or more contributing factors are missing, such as in patients with agranulocytosis (40,41), while they are readily detected by Ga-67 scans.

The above scheme is primarily based on studies of Ga-67 accumulation in acute inflammatory lesions; whether it is applicable to chronic inflammatory lesions such as chronic granulomatous inflammation requires further investigation. Areas of future research include (a) study of patients with neutrophil-secondary granule deficiency to clarify the role of lactoferrin in the uptake of Ga-67 by neutrophils and the accumulation of Ga-67 in inflammatory lesions, (b) the mechanism of Ga-67 uptake by monocyte-macrophages, (c) using animal models of chronic granulomatous inflammation (11,57) to study the mechanism of Ga-67 accumulation in chronic granulomatous inflammatory lesions.

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