Immunospecific Saturable Clearance Mechanisms for Indium-111-labeled Anti-Melanoma Monoclonal Antibody 96.5 in Humans

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ABSTRACT

Liver uptake of $^{111}$In-labeled monoclonal antibodies (MoAb) remains a significant problem in radioimaging studies to date. To determine if the observed liver uptake of an $^{111}$In-labeled anti-melanoma antibody 96.5 ($^{111}$In-96.5) was dependent on the presence of hepatic antigen or on recognition of circulating murine antibody, escalating doses of an unlabeled nonimmunoreactive MoAb (NIR-MoAb) were administered to 18 patients with metastatic malignant melanoma either 1 or 24 h prior to an infusion of 1 mg of $^{111}$In-96.5. The number of metastases imaged, pharmacokinetics, and the ratio of radioactivity (expressed as average counts/pixel) in liver (L), spleen (S), bone (B), and kidney (K) compared to blood pool (heart = H) were examined. Results were prospectively compared with data from six patients who received immunoreactive unlabeled 96.5 prior to $^{111}$In-96.5. Increasing dose or changes in the preinfusion time of NIR-MoAb had no significant effect on the biodistribution of $^{111}$In-96.5. In contrast, patients who received unlabeled, immunoreactive 96.5 prior to $^{111}$In-96.5 infusion demonstrated a significant drop ($P < 0.001$) in the liver:heart ratio of radioactivity ($2.81 \pm 0.35$ (SEM)) compared to patients receiving the identical dose of NIR-MoAb ($10.35 \pm 1.33$). Significant decreases in spleen:heart and bone:heart ratios were also observed. Pharmacokinetic studies showed that the volume of distribution ($V_d$) and the plasma $t_1/2$ both decreased when 96.5 was administered compared to NIR-MoAb. In addition, a 4-fold increase in clearance $X$ time was obtained after 96.5 antibody was administered compared to NIR-MoAb.

MATERIALS AND METHODS

Monoclonal Antibodies. Production and purification of the melanoma-specific MoAb, 96.5, has been described previously (20). It is an IgG2a murine MoAb which binds to a $M_r$ 97,000 antigen found on over 85% of human melanoma cell lines and fresh biopsy samples (21). A second MoAb, designated NIR-MoAb, was produced from a fusion and subcloning identical to those of 96.5 but was found to be nonreactive with a variety of normal tissues and malignant cells including melanoma. Currently, it has not been shown to react with any known antigen. Type-specific antisera confirmed it to be a MoAb of the IgG2a subclass, identical to 96.5. Both antibodies were produced in large quantities in ascites from BALB/c mice and purified using sodium sulfate fractionation and DEAE chromatography. MoAb 96.5 was conjugated to the cyclic anhydride of DTPA using a modification of a previously published technique (22). For clinical use, 1 mg DTPA-coupled 96.5 was mixed with 5 mCi $^{111}$In in citrate buffer, and after $^{111}$In chelation, the reaction was terminated by neutralizing buffer (3). Unmodified MoAbs (96.5 and NIR-MoAb), 96.5 covalently coupled to $^{111}$In, and buffer were supplied in kit form by Hybritech, Incorporated. The purity of the $^{111}$In-MoAb preparation was greater than 95% as determined by thin layer chromatography. The immunoreactivity of $^{111}$In-96.5 conjugate as determined by the percentage of radiolabeled antibody which bound to SK Mel-28 cells was greater than 95% as determined by thin layer chromatography. The immunoreactivity of $^{111}$In-96.5 conjugate as determined by the percentage of radiolabeled antibody which bound to SK Mel-28 cells was greater than 70%.

INTRODUCTION

Numerous immunoscintigraphy trials using radiolabeled murine MoAbs reactive with tumor-associated antigens have been published to date (1). These studies have demonstrated that tumors in humans could be successfully imaged but that the sensitivity and specificity of the technique were dependent on variables such as tumor size (2–4), MoAb specificity (5, 6), whether whole antibody or fragments were used (7), tumor permeability (8), the presence of anti-murine globulins (9), and the radioisotope (10). Antibody affinity, immunoreactivity, structure or ionic strength (11, 12), and the degree to which antigenic cross-reactivity with normal tissues could influence specific clearance of immunoreactive antibody which may cross-react with tissue antigens.

Several investigators have shown that the mass of antibody administered can also significantly affect tumor imaging and biodistribution of radiolabeled conjugates (3, 4, 14–18), although this has not been a universal finding (19). In previous imaging trials using $^{111}$In-96.5, it was noted that tumor imaging improved significantly as the amount of unlabeled MoAb was increased relative to labeled MoAb (3, 18). Based on changes in plasma half-life and the volume of distribution of radiolabeled 96.5 at time 0, it was postulated that large doses of unlabeled MoAb could partially saturate nonspecific (or specific) receptor sites in liver and/or other organs thereby affecting the quantity of radiolabeled MoAb which eventually reached tumor sites (13, 18).

To determine prospectively whether non-target uptake of $^{111}$In-labeled MoAb could be blocked by the administration of an unlabeled MoAb, melanoma patients were given increasing doses of either a nonimmunoreactive MoAb (NIR-MoAb) of IgG2a subclass identical to 96.5 or immunoreactive 96.5 prior to $^{111}$In-96.5. The data presented below suggest that blocking of non-tumor uptake of $^{111}$In-96.5 occurred when unlabeled immunoreactive MoAb was administered prior to $^{111}$In-96.5, but not following infusions of NIR-MoAb.

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2 To whom requests for reprints should be addressed, at Department of Clinical Immunology and Biological Therapy, Box 41, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston TX 77030.

3 The abbreviations used are: MoAb, monoclonal antibody; NIR-MoAb, nonimmunoreactive monoclonal antibody; $^{111}$In-96.5, indium-111-labeled anti-melanoma monoclonal antibody 96.5; DTPA, diethylenetriaminepentaacetic acid.

4 Hybritech, Incorporated, personal communication.
o gram, complete blood count, platelet count, serum chemistries, and urinalysis were also performed; patients with abnormal renal function, defined as a serum creatinine greater than 1.5 mg/dl or hepatic function, defined as a serum bilirubin greater than 1.5 mg/dl, were not eligible for study. Patients were not routinely skin tested prior to receiving MoAb in view of the lack of predictability of this test (3).

**Study Design.** Three patients per group were given either 9, 19, or 39 mg of unlabeled, unconjugated (i.e., without DTPA) NIR-MoAb as a 1-h infusion in 100 ml of normal saline (“chase”) followed either 1 h (9 patients) or 24 h (9 patients) later by a rapid infusion of 1 mg of $^{111}$In-labeled 96.5 ("pulse"). To compare the possible blocking effect of unlabeled NIR-MoAb to that of unlabeled 96.5 (i.e., tumor-specific, immunoreactive MoAb), six additional patients were given 19 mg of unlabeled 96.5 followed by 1 mg of $^{111}$In-96.5 either 1 h (3 patients) or 24 h (3 patients) later as above. The concentrations of unlabeled antibody used were those previously determined to be optimal for imaging (3). At 72 and 144 h following administration of 1 mg of $^{111}$In-96.5, gamma camera digital scans were acquired using a GE model 400 camera (Milwaukee, WI) and the images were stored in an on-line computer (GE Starcamera, Milwaukee, WI). Scans were initially interpreted in a blinded fashion by a single nuclear medicine physician (L. M. L.).

**Method of Comparing Relative Uptakes of $^{111}$In-labeled 96.5 in Various Organs Relative to Heart and Liver.** Regions of interest were drawn on digital images taken 72 h after injection over posterior bones (B = lumbar spine), posterior kidneys (K), and posterior spleen (S). These were compared to regions of interest drawn over the anterior liver (L) and anterior heart (H = blood pool) using average counts/pixel in the 7-minute images. A matrix format of 512 x 512 was used. Organ distribution was expressed as a ratio of average counts/pixel in the spleen, kidney, and spine to that of the heart blood pool or the liver.

**Pharmacokinetics: Radiological Methods for $^{111}$In Measurement.** To determine the plasma half-life of $^{111}$In, heparinized blood samples (5 ml) were collected during $^{111}$In-96.5 infusion, at the end of infusion (time 0), and at 1, 5, 10, 30, 60, 70, 120, 180, 320, and 720 min after infusion. An aliquot (0.5 ml) of the $^{111}$In-96.5 solution was also obtained to serve as a standard and isotope decay control. Plasma was obtained by centrifugation and samples were analyzed for radioactivity as described previously (23). Pharmacokinetic parameters were also obtained as described previously (23).

**Statistical Methods.** Differences between two or more groups were analyzed using Student's t test or two way analysis of variance, respectively. Differences in tumor imaging were analyzed using $\chi^2$ analysis.

**RESULTS**

**Biodistribution of $^{111}$In-96.5 following Infusions of Unlabeled MoAb.** The biodistribution of $^{111}$In-96.5 in various organs with respect to heart (blood pool) in patients given $^{111}$In-96.5 either 1 or 24 h following 9, 19, or 39 mg of NIR-MoAb was compared. There was a large amount of radioactivity in liver compared to spleen, bone, and kidney as shown by the high liver/blood pool (L/H) ratios compared to ratios of other organs to blood pool (P < 0.05) (Table 1). This finding was consistent at both the 1- and 24-h time points and did not vary with dose of NIR-96.5 administered. Likewise, the S/H ratio was increased slightly (P = 0.06) over B/H and K/H ratios; however, preadministration of escalating doses of NIR-MoAb had virtually no effect at blocking liver uptake of $^{111}$In-96.5.

In contrast to what was observed with NIR-MoAb, preadministration of unlabeled immunoreactive MoAb 96.5 significantly decreased radioactivity in liver with respect to blood pool (Fig. 1). Six patients receiving 19 mg unlabeled 96.5 either 1 h [3 patients] or 24 h [3 patients] prior to $^{111}$In-96.5 had a significantly decreased L/H ratio [2.81 ± 0.8 (SEM)] compared to the 6 patients who had received 19 mg NIR-MoAb at either 1 h [3 patients] or 24 h [3 patients] prior [10.35 ± 1.33; P < 0.001]. There was no significant difference in L/H ratios depending on whether 96.5 was given 1 h (3.14 ± 0.068) or 24 h (2.47 ± 0.18; P not significant) prior to $^{111}$In-96.5. Significant decreases in S/H (1.09 ± 0.09 versus 2.52 ± 0.39) and B/H (0.50 ± 0.05 versus 1.07 ± 0.11) ratios were also noted with preinfusion of 19 mg 96.5 compared to 19 mg NIR-MoAb (P < 0.025). No significant differences in K/H ratios were seen (Fig. 1). There were no differences noted in S/H, B/H, or K/H ratios comparing a 1-h "pulse" to a 24-h "pulse" of $^{111}$In-96.5.

The significant decrease in L/H ratio of $^{111}$In-96.5 following unlabeled 96.5 was due to a significant decrease in relative counts/pixel in liver (37.2 ± 4.8) and in the heart blood pool (33.7 ± 3.7). In contrast, the average counts/pixel in liver were increased (151.7 ± 25.5; P < 0.025) in the heart (17.4 ± 2.5; P < 0.025) in patients receiving NIR-MoAb followed by $^{111}$In-96.5. The decrease in relative counts in liver with respect to other organs seen with preadministration of 19 mg 96.5 also resulted in significantly higher S/L (0.493 ± 0.054) and B/L ratios (0.223 ± 0.030) of $^{111}$In-96.5 than that seen with preadministration of 19 mg NIR-MoAb (S/L = 0.290 ± 0.05; B/L = 0.122 ± 0.02; P < 0.025). The differences in biodistribution of $^{111}$In-96.5 observed following infusion of tumor-specific immunoreactive MoAb versus

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**Table 1 Biodistribution of $^{111}$In-96.5 following preadministration of increasing doses of NIR-MoAb**

<table>
<thead>
<tr>
<th>NIR-MoAb</th>
<th>$^{111}$In-96.5</th>
<th>L/H&lt;sup&gt;a&lt;/sup&gt;</th>
<th>S/H</th>
<th>B/H</th>
<th>K/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-h pulse</td>
<td>19</td>
<td>7.9 ± 0.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.4 ± 0.9</td>
<td>1.6 ± 0.6</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>9.0 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0 ± 0.6</td>
<td>0.8 ± 0.07</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>24-h pulse</td>
<td>19</td>
<td>14.9 ± 2.9</td>
<td>1.6 ± 0.13</td>
<td>0.85 ± 0.13</td>
<td>0.85 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>10.5 ± 1.5</td>
<td>2.3 ± 0.49</td>
<td>1.1 ± 0.20</td>
<td>1.6 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>12.8 ± 2.7</td>
<td>2.5 ± 0.77</td>
<td>2.8 ± 0.09</td>
<td>1.1 ± 0.21</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significantly higher than S/H, B/H, and K/H ratios for all groups (P < 0.05). Mean ± SEM.
non-tumor-specific nonimmunoreactive MoAb could be observed visually by comparing gamma camera images (Fig. 2). As seen in Fig. 2A, preadministration of 19 mg NIR-MoAb to a patient 1 h prior to administration of $^{111}$In-96.5 demonstrated a significant amount of radioactivity in liver (compared to blood pool) at 72 h. In contrast, less radioactivity in liver along with an increase in blood pool was observed at 72 h in a patient receiving 19 mg 96.5 prior to $^{111}$In-96.5 (Fig. 2B).

**Pharmacokinetics of $^{111}$In-96.5.** The changes in plasma half-life as well as other pharmacokinetic parameters in general paralleled differences in $^{111}$In-labeled MoAb biodistribution. There were no significant differences in plasma half-life ($t_\text{\scriptsize{1/2}}$), volume of distribution ($V_d$), concentration of MoAb $\times$ time ($C \times t$), clearance from plasma ($C_{\text{\scriptsize{pl}}}$), or urinary excretion of $^{111}$In observed among patients receiving 9, 19, or 39 mg NIR-MoAb at either 1 or 24 h prior to $^{111}$In-96.5 (data not shown). Fig. 3 shows the plasma disappearance curves for $^{111}$In-96.5 following either 1- or 24-h infusions of either 19 mg NIR-MoAb or 19 mg 96.5. Patients who received NIR-MoAb either 1 or 24 h prior to $^{111}$In-96.5 demonstrated a rapid $\alpha$ phase clearance followed by a prolonged $\beta$ phase; four of six patients who received immunoreactive 96.5 prior to $^{111}$In-96.5 lacked an $\alpha$ phase clearance. Table 2 compares the pharmacokinetic parameters of $^{111}$In-96.5 for patients receiving 19 mg of NIR-MoAb versus 19 mg of 96.5. There was a significant decrease in the $V_d$ of $^{111}$In-96.5 in patients receiving preinfusions of 96.5 compared

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**Fig. 2.** A, anterior (left) and posterior (right) 72-h scans of the abdomen in a patient receiving 19 mg of NIR-MoAb 1 h prior to 1 mg of $^{111}$In-96.5. Note large amount of radioactivity in liver compared to heart (arrow). B, similar views of a patient receiving 19 mg of unlabeled 96.5 1 h prior to 1 mg of $^{111}$In-96.5. Note significantly less radioactivity in liver and greater radioactivity in heart at 72 h (arrow) compared to A.
to patients receiving preinfusions of NIR-MoAb (P < 0.05).
Significant changes in $C \times t$ ($P < 0.005$) and $C_{ip}$ ($P < 0.05$)
were also noted between groups. No significant changes in
mean urinary excretion of $^{111}$In were noted. There were also no
significant differences in mean plasma half-lives ($\beta$ phase)
between groups.

Comparison of Tumor Imaging between Groups. The sensitivity
of tumor detection was compared in patients who received
preinfusions of NIR-MoAb versus 96.5. A greater number of
metastases were detected in patients receiving 19 mg 96.5 prior to
$^{111}$In-96.5 (23 of 28 = 82%) versus patients receiving 19 mg
NIR-MoAb prior to $^{111}$In-96.5 (10 of 18 = 56%; $P < 0.05$, $x^2$).
Although there were a greater number of skin lesions in the
group receiving tumor-specific MoAb (17) compared to patients
receiving nonimmunoreactive MoAb (3), 100% of lesions were
imaged in each group. Patients receiving tumor-specific MoAb
prior to $^{111}$In-96.5 had a greater percentage of tumors imaged
in liver compared to those receiving NIR-MoAb (96.5: 4 of 4
= 100%; NIR-MoAb, 1 of 2 = 50%) as well as a greater percent-
gease of metastases imaged in lymph nodes (96.5, 1 of 1 =
100%; NIR-MoAb, 3 of 6 = 50%), lung (96.5, 2 of 4 = 50%;
NIR-MoAb, 0 of 1 = 0%), and brain (96.5, 1 of 1 = 100%;
NIR-MoAb, 2 of 3 = 66%).

DISCUSSION

Uptake of $^{111}$In-labeled MoAb in liver has been a major
problem in the majority of clinical trials to date. This study is
the first to systematically analyze in humans whether prein-
fluences of 10- to 40-fold greater quantities of an irrelevant,
nonimmunoreactive MoAb of the same subclass as an immu-
noreactive MoAb were capable of partially saturating receptor
sites in non-target organs such as liver and spleen. Although
blocking of normal tissue uptake of $^{111}$In-96.5 did not occur
following NIR-MoAb irrespective of dose and schedule, signif-
ificant saturation of liver, spleen, and bone with respect to blood
pool occurred following preinfusions of a 20-fold excess of
tumor-specific MoAb. Although the number of patients studied
per group was small, the data strongly suggest that saturation
of receptor sites in liver might be due to cross-reactivity with
specific antigen in liver, rather than saturation of nonspecific
clearance mechanisms by the reticuloendothelial system.

Preliminary studies in animals suggested that hepatic clearance
mechanisms for $^{111}$In-labeled antibodies could be blocked
by concomitant administration of unlabeled antibody specific
for target-associated antigen (24-27). Blocking of liver uptake of
radiolabeled antibody appeared to be specific and not related to
reticuloendothelial system function (28) or chelating agents
alone (29).

Trials examining the effect of unlabeled non-tumor-specific
antibodies on MoAb biodistribution in humans are largely
anecdotal. In a study by Carrasquillo et al. (19), preadministra-
tion of 20 mg of unlabeled anti-melanoma MoAb 9.2.27 prior to
administration of $^{111}$In-labeled T101, an anti-T-cell MoAb,
in one patient with cutaneous T cell lymphoma failed to alter
biodistribution of $^{111}$In-T101 in non-tumor tissues. When scans
from eight patients in a previous trial (3) who had received 19
mg unlabeled 96.5 simultaneously with 1 mg $^{111}$In-96.5 were
analyzed retrospectively, a similar $L/H$ ratio was observed (2.81
± 0.20) as that seen in this prospective study with 96.5 given 1
hour (3.14 ± 0.068) or 24 h prior (2.47 ± 0.10). Biodistribution
and pharmacokinetic data in this study suggested that satu-
ration of liver uptake was related to the immunoreactivity and
amount of antibody administered and not the timing of admin-
istration of unlabeled MoAb. These data could also account for
the improvement in imaging noted in other trials as the overall
mass of tumor-specific MoAb was increased (3, 4, 16, 18),
although one should use caution in inferring similar mecha-
nisms for saturation for antibodies of differing affinity and
immunoreactivity.

Eger et al. (30) have suggested that a mathematical model for
9.2.2.7 pharmacokinetics includes the presence of antigen-
saturable compartments for MoAb uptake in various tissues
studied. Although the model developed is extrapolated from
observed data, a clinical study was not performed in order to
test the model prediction using unlabeled nonimmunoreactive
antibody as in the current study. From the data in the current
study, the performance of the antibody as it relates to the
saturable antigen compartment may be estimated. The differ-
ence in the volume of distribution ($V_d$) between the patients
who received NIR-MoAb and those who received 96.5 should
account for the total volume of the saturable antigen compart-
ment (6.9 liters - 3.5 liters = 3.4 liters) extrapolated to $t = 0$.
In addition, the observed differences in the clearance rate be-
tween these two groups must be the result of saturation of

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**Table 2** Pharmacokinetics of $^{111}$In-96.05 (1 mg) following infusions of unlabeled MoAb

<table>
<thead>
<tr>
<th>Unlabeled MoAb (19 mg)</th>
<th>No. of patients studied</th>
<th>$t_{1/2}$ (min)</th>
<th>$V_d$ (liters)</th>
<th>$C \times t \mu Ci/ml \times (\times \min)$</th>
<th>$C_{ip}$ (ml/kg/min)</th>
<th>Urinary excretion (cumulative %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIR-MoAb</td>
<td>6</td>
<td>42 ± 26a</td>
<td>2394 ± 401</td>
<td>6.9 ± 1.5</td>
<td>382 ± 46</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>37a</td>
<td>1988 ± 287</td>
<td>3.5 ± 0.3a</td>
<td>1178 ± 183a</td>
<td>0.02 ± 0.005</td>
</tr>
</tbody>
</table>

a Total number of patients who received NIR-MoAb or 96.5 1 h (3 patients) or 24 h (3 patients) prior to $^{111}$In-96.5.
b Mean ± SEM.
c Significant decrease versus NIR-MoAb, $P < 0.053$.
d Significant increase versus NIR-MoAb, $P < 0.005$.
antigen sites by immunoreactive antibody and not merely the saturation of clearance mechanisms for nonspecific murine immunoglobulin. Therefore, the clearance rate from the plasma (CIP) of 0.06 ml/kg × min likely represents the rate of clearance of antibody from plasma by the saturable antigen pool. Based on the regions of interest measurements, the predominant site for this saturable antigen compartment could be the liver with smaller components present in the spleen, bone, and kidney.

Tumor uptake and detection with $^{111}$In-labeled MoAb is dependent on numerous variables including tumor size, site of disease, and vascularity. In previous studies, we have noted that a greater number of melanoma skin lesions were imaged compared to other sites (3, 4). Hence, it is of interest that the percentage of skin lesions imaged in each group was identical, despite the fact that there were more s.c. lesions in the 96.5 group than in the NIR-MoAb group. The differences in imaging seen were not due to the presence of more lesions larger than 1 cm in the 96.5 group compared to the NIR-MoAb group (3, 4, 9); in fact, the opposite was true. For example, 38% of visceral lesions in the 96.5 group were smaller than 1 cm as opposed to only 17% in the NIR-MoAb group. Of the number of visceral lesions larger than 1 cm, 3 of 5 (60%) were imaged in the 96.5 group whereas only 1 of 8 (13%) were imaged in the NIR-MoAb group. Nevertheless, one must use caution in inferring that enhanced imaging was related to the differences in biodistribution. In view of the small number of lesions and the lack of biopsy data to directly quantify the amount of antibody in tumors, these data are merely suggestive and do not confirm that enhanced tumor uptake of $^{111}$In-96.5 has occurred.

Although the exact mechanisms underlying saturation of liver uptake of radiolabeled MoAb have not been addressed in this study, the type of antibody and the antigen to which it reacts may be of significant importance. P97, the antigen recognized by 96.5, has been shown to be similar in structure to transferrin (31). Therefore, it is conceivable that $^{111}$In-96.5 could be binding to transferrin receptors in liver (32) with subsequent deconjugation and uptake of $^{111}$In by hepatocytes (33). Halpern et al. (34) have shown that 10% of $^{111}$In is coupled with circulating transferrin daily. However, it is unlikely that the decreasing uptake of radiolabeled antibody by liver was due to the formation of immune complexes and blocking of receptor sites since P97 is not shed into the circulation in the majority of patients (3, 35). Additional preclinical as well as clinical studies are needed to clarify the specific mechanisms involved.

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