Angiotensin II receptor blocker pretreatment of rats undergoing sudden renal ablation

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Abstract

Background. Subtotal nephrectomy (N) in rats results in progressive hypertension, proteinuria and renal lesions. Renin–angiotensin system blockade initiated at N prevents these changes; treatments failing to reduce hypertension and proteinuria do not.

Methods. Ten Munich-Wistar rats underwent 1½ surgical N; eight littersmates were pretreated with losartan (L) only for 6 weeks prior to 1½ N (N1L). Pretreated (n=8; C1L) and untreated controls (C; n=8) had sham operations.

Results. Over 6 months, N and N1L rats developed ~80% increase in glomerular filtration rate per nephron over C and C + L, P < 0.001). Hypertension (intra-arterial mean blood pressure 116 ± 6.8 mmHg in N rats versus 102 ± 3.2 in C, 104 ± 8.4 in C + L, and 104 ± 8.4 in N + L rats, P < 0.001 for all) and proteinuria (120 ± 20 mg/day in N versus 39 ± 10 in C, 34 ± 8 in C + L and 35 ± 8 in N + L, P < 0.001 for all) developed only in N. Focal segmental glomerulosclerosis (FSGS) (%) at 6 months was 20 ± 8 in N and 17.5 ± 8 in N + L (ns) and <1 in C and C + L (P < 0.001 versus N and N + L). Interstitial fractional volume (Vv), 4.0 ± 1.7% in C and 4.4 ± 1.6% in C + L (ns), was similarly increased to 7.5 ± 2.5% in N and 9.0 ± 3.9% in N + L (P < 0.04 versus C and C + L). Atrophic tubule Vv was increased by >300% in N and N + L over C and C + L (P < 0.02 for all). Glomerular volume doubled in N and N + L over C and C + L (P < 0.02 for all). Podocyte foot process effacement was greater in N and NL than in C or C + L (P ≤ 0.02 for all). Thus, L given for 6 weeks prior to 1½ N prevented hypertension and proteinuria over the subsequent 6 months without reducing glomerular hypertension, hyperfiltration or interstitial, tubular or FSGS lesions or foot process effacement.

Conclusions. These studies dissociated systemic hypertension and proteinuria from the renal lesions in this model. Durable effects of losartan on blood pressure and proteinuria likely represent epigenetic processes.

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Introduction

The remnant kidney model is characterized by progressive hypertension, proteinuria, focal segmental glomerulosclerosis (FSGS), tubular atrophy, interstitial fibrosis and, ultimately, glomerular filtration rate (GFR) loss in animals subjected to major renal mass reduction [1].

We previously demonstrated that gradual surgical ablation over 6 weeks in rats is associated, over the next 6 months, with higher urinary protein excretion rates and accelerated development of FSGS and tubulointerstitial lesions compared to rats with equivalent sudden renal mass reduction [2]. Reasoning that this slow ablation process (removal of 1½ kidneys by heminephrectomy at baseline, removal of the remainder half kidney 2 weeks later, and heminephrectomy at 6 weeks) adversely conditioned residual nephrons to subsequent injury, we tested the effects of renin-angiotensin system (RAS) blockade with the angiotensin receptor blocker losartan given only during the 6 weeks of slow ablation [3]. Despite discontinuation of losartan at the final surgical procedure, losartan pretreatment completely prevented proteinuria and hypertension and largely prevented the development of FSGS, tubular atrophy and interstitial fibrosis over the subsequent 6 months. This occurred despite equivalent glomerular hypertrophy and hyperfiltration in the losartan-treated and untreated groups [3]. The rationale for the present study was to test, in the absence of residual nephron conditioning by slow renal ablation, whether 6 weeks of losartan pretreatment prior to sudden surgical removal of 1½ kidneys would influence the subsequent course in this renal ablation model.

Methods

Experimental design

Male Munich-Wistar rats (Simonsen laboratory Inc. Gilroy, CA), weighing ≈250 g at the start of the experiments, were randomly allocated into four groups:

1. Nephrectomy (N) group—Sham operations in 10 animals were done at baseline and 3 weeks followed by the removal of 1½ kidneys at 6 weeks [2]. At the initial operation, the left kidney was exposed and renal capsule removed; at the second, the left kidney was again exposed and scar tissues removed from the renal surface [2]. Three weeks later, these rats underwent a final surgical procedure, left nephrectomy and removal of the upper and lower pole of the right kidney. All 10 animals survived.

2. Nephrectomy plus losartan treated (N + L) group—Surgical procedures were exactly as in the N group but with losartan, 30 mg/kg/day in the drinking water, during the 6 weeks prior to the final surgical procedure. Eight of 10 animals survived.

3. Control (C) group—These rats had sham operations during the initial 6 weeks as described for the N group. All eight animals survived.

4. Control-losartan-treated (C + L) group—These rats had the same sham operations as C but received losartan, 30 mg/kg/day in the drinking water, during the 6 weeks prior to the final surgical procedure. All eight animals survived.

Throughout the study, the rats had free access to water and food. Twenty-four-hour water intake was measured weekly during the first 6 weeks of the study and the concentration of losartan in the drinking water adjusted on the basis of water intake ensuring that the correct dose of losartan was ingested by each rat [3]. Rats were followed for 24 weeks after the final surgical procedure as described below.

Separate animals in each of the two groups [sham (n = 7), sham + losartan (n = 7)] had measures of body weight, intra-arterial mean blood pressure (IA-MBP) and GFR at the time of the final surgical procedure (see below). Standards of care of these animals adhered to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. These studies were approved by the Institutional Animal Care and Use Committee at the University of Minnesota.

Renal functional studies

BP, hematocrit and urine protein were measured at baseline (–6 weeks), 3 (–3 weeks) and 6 weeks (time 0 or the time of the final surgical procedure) and +2, +4, +8, +12, +16, +20 and +24 weeks after the final surgical procedure [2]. SBP was measured in awake and lightly restrained rats by a tail-cuff method [2]. The mean of the three to four measurements per rat was used to estimate SBP at each time and on the day of GFR measurement. IA-MBP was measured [2] at the final surgical procedure and 24 weeks later when GFR was also measured. These two BP measurements were highly correlated (r = 0.8, P < 0.001), confirming our earlier studies [2]. Rats were placed individually in metabolic cages for 24-hour urine collections to measure urinary protein, which was measured by the Bradford protein assay method (Bio-Rad Laboratories, Hercules, CA) using a DU Series 600 Spectrophotometer. GFR was determined at 24 weeks after the final surgical procedure in anesthetized rats by 125Iiothalamate clearance [2, 3].

Morphologic and morphometric studies

Renal tissues obtained from surgical removal or at sacrifice were bivalved, cut into slices parallel to the longitudinal renal axis, fixed in 10% formol-aldehyde, embedded in paraffin, sectioned at 5 μm, stained with periodic acid-Schiff (PAS) and imaged using a projection microscope onto a 9 × 9 cm grid for estimation of mean glomerular volume, percentage of glomeruli with FSGS lesions (%FSGS) and FSGS severity score [2, 3] by a masked reader. Mean glomerular volume was measured on at least 60 randomly selected glomerular profiles (see below) at ×150 using the point-counting method of Weibel and Gomez [4, 5]. Percent FSGS and FSGS severity score were both also determined in at least 60 randomly selected glomerular profiles in 30–50 fields at ×300. FSGS was recognized as an increase in tuft PAS-positive extracellular matrix material associated with capillary wall wrinkling and collapse. These lesions were usually associated with adhesions to Bowman’s capsule. Hyalinosis was often seen in these lesions [6]. FSGS score was assessed by assigning a value of 0 to 4 to each glomerulus according to the proportion of the tuft occupied by FSGS lesions: normal glomerulus, 0; up to 25%, 1; 25–50%, 2; 50–75%, 3; >75%, 4. The score was calculated as the product of the sum of FSGS scores and the fraction of glomeruli with FSGS [6]. The volume fraction on interstitium/cortex [Vv (Int/cortex)] was estimated by unbiased morphometric point counting on at least 30, ×200 fields per specimen, acquired by systematic random microscope stage movements [2, 7]. Interstitium was defined as cortical space not occupied by glomeruli, tubules or vessels larger than one tubular diameter [7]. Vv atrophic tubules/cortex [Vv (AT/cortex)] was estimated by point counting on the fields used for Vv (Int/cortex). Atrophic tubules were defined by the presence of thickened or reduplicated tubular basement membranes (TBM) surrounding tubules of reduced diameters, containing shortened or flat tubular epithelial cells; in the absence of thickened TBM, atrophy was defined as a tubular diameter to <50% of normal, as determined by comparison with adjacent tubules [2, 3]. Paraffin-embedded renal tissues were deparaffinized in zylene, rehydrated in an ethanol series, re-embedded in epon and sectioned and stained for electron microscopy using standard methods. Electron microscopic images of rat glomeruli were obtained at 30 000 × according to a systematic uniform random sampling protocol. Images with foot processes prominently affected by artifacts were excluded. The percent of the glomerular basement membrane which was covered by widened (effaced) foot processes was estimated on each image by a masked renal pathologist (B.N.) and the average percent foot process effacement was calculated for each animal.
Statistics
All results for the C and C + L, other than the podocyte foot process effacement data, have been previously reported [3]. Data are provided as $X \pm SD$. After testing for normality, analysis of variance or Kruskal–Wallis tests were chosen for testing for group differences. Post-hoc group differences were determined by the least significant difference test. Statistical significance was accepted when P was <0.05.

Results

Animal data at the time of the final surgical procedure
Body weight and hematocrit values were similar at study baseline (−6 weeks) in all study groups (data not shown). These variables were also similar in sham-operated losartan-treated and untreated rats at the final surgical procedure (Table 1). The GFR and the weights of the right kidneys at the final surgical procedure were similar in the losartan-treated and untreated rats (Table 1). IA-MBP at the final surgical procedure was ≈7 mmHg lower in the losartan-treated group (Table 1).

The course of BP and albumin excretion rate
Blood pressure. There were no statistically significant group differences in baseline awake tail systolic blood pressure (SBP) (−6 weeks from the final surgical procedure; Figure 1). SBP was lower in both losartan-treated animal groups [control + losartan (C + L) and nephrectomy + losartan (N + L)] after 3 (−3) and 6 (0) weeks of losartan administration (P values all <0.001) but there were no differences between these groups (Figure 1). There were no statistically significant differences in tail SBP between any of the four groups at 2 and 4 weeks after losartan cessation (Figure 1). Moreover, at all subsequent times, the control (C), C + L and N + L groups had similar SBP values (Figure 1). The N group, however, had SBP values averaging 10 mmHg or more higher than the C, C + L and N + L groups from the +8th to the +24th week (P < 0.001 for each time point comparison; Figure 1). IA-MBP at 24 weeks were also not significantly different among the C, C + L and N + L groups while the N group IA-MBP was significantly higher than in each of these three groups (P < 0.001 for each comparison, Table 2).

Proteinuria. Increased urinary protein was detectable in the N, compared to the C, C + L and N + L groups by 4 weeks after the final surgical procedure (P < 0.01 for all comparisons) (Figure 2). Urinary protein in the C + L and N + L groups paralleled the age-related increase in urinary protein in the C animals. The N group, however, had higher urinary protein than the C, C + L or N + L groups at 4, 12 and 24 weeks after the final surgical procedure (P < 0.001 for each comparison, Figure 2).

Animal data 24 weeks after the final surgical procedure
There were no statistically significant group differences in body weight at the end of the study (Table 2). Total kidney weights in the control groups (C, C + L) exceeded those in the ablated groups (N and N + L) by −45% (P < 0.001 for each comparison; Table 2) but there were no statistical differences in this parameter between the N and N + L groups (Table 2). Hematocrit values at 24 weeks were slightly but lower in the ablated (N and N + L) than in C groups. GFR at 24 weeks after the final surgical procedure was >50% lower in the ablated (N and N + L) than in the control (C and C + L) groups. The final GFR in the losartan-treated and untreated groups (N + L versus N) were nearly identical (Table 2). GFR in the C and CL groups was also very similar.

Renal structural data at and 24 weeks after the final surgical procedure
Mean glomerular volume at the final surgical procedure was not statistically significantly different in the sham versus sham + losartan animals (Table 3). Mean glomerular volume 24 weeks later was increased by ≥45% in the ablated groups (N and N + L) compared to the control groups (C and C + L, all P values <0.001, Figure 3). There was no statistically significant difference in mean glomerular volume among the two ablated groups or among the two control groups.

There were essentially no FSGS lesions in the sham-operated rats at the final surgical procedure (Table 3). FSGS frequency and severity scores were very low and not statistically different among the C and C + L groups at 24 weeks after the final surgical procedure (Figure 4); the median and range for the FSGS frequency values were C, 0 (0–3.9%) and C + L, 0 (0–3.7%). The N and N + L groups had >30-fold increases in FSGS frequency and >250-fold increases in FSGS severity scores compared to the C and C + L groups at 24 weeks (Figures 4 and 5). There was no statistically significant difference in FSGS frequency (Figure 4) or severity scores (Figure 5) between the N and N + L groups. There were no statistically significant correlations between mean glomerular volume and either FSGS frequency or severity score at 24 weeks (data not shown). Estimates of foot process effacement were greater in N (26 ± 8%; n = 5) and N + L (24 ± 5%; n = 4) than C (14 ± 5%; n = 5) or C + L (10 ± 4%; n = 4), (P = 0.004 and 0.003, respectively, with no statistically significant difference between the N and N + L groups) (Figure 6).

The volume fraction of cortex which was interstitium [Vv (Int/cortex)] was significantly increased to about 7–9% in N and N + L compared to −4% C and C–L animals at 24 weeks, while the latter two groups were not

Table 1. Clinical and renal functional parameters at final surgical procedure

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Weight of right kidney (g)</th>
<th>Hematocrit (%)</th>
<th>GFR (mg/min)</th>
<th>IA-MBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n = 7)</td>
<td>281 ± 18</td>
<td>1.07 ± 0.04</td>
<td>52 ± 1.4</td>
<td>2.3 ± 0.2</td>
<td>101 ± 2.4*</td>
</tr>
<tr>
<td>Sham + losartan (n = 7)</td>
<td>272 ± 10</td>
<td>1.04 ± 0.08</td>
<td>52 ± 1.0</td>
<td>2.2 ± 0.3</td>
<td>94 ± 7.6</td>
</tr>
</tbody>
</table>

*P < 0.001; all other comparisons not significant.
significantly different (Figure 6). The volume fraction of atrophic tubules \( V_v (AT/cortex) \) was \(<0.5\% \) and not statistically different in the C and C L animals at 24 weeks (Figure 7). \( V_v (AT/cortex) \) was \(~4-5\times\) higher in the N and N L animals with no statistical differences between the groups (Figure 8).

### Discussion

Surgical subtotal nephrectomy was used here and in our previous studies [2] in order to avoid the rapid development of severe hypertension [8, 9], which accelerates the renal injury following renal ablation procedures that include partial renal infarction. Also, 1½ nephrectomy was used instead of a unilateral nephrectomy plus infarction of 5/6 of the contralateral kidney in order to slow the process of injury and thus, have a model that was more therapeutically manipulable. Nonetheless, the cardinal features of the renal ablation model in rats, including hypertension, proteinuria and the characteristic renal lesions, all developed in the untreated 1½ nephrectomy animals.
Six weeks of RAS blockade with the angiotensin receptor blocker losartan completely prevented the development of hypertension and albuminuria for the next 6 months in the 1½ nephrectomy animals. This was very similar to the protection from hypertension and proteinuria that we found in a rat model where losartan was administered during the 6 weeks that the animals underwent gradual renal mass reduction. However, in this previous study, losartan pretreatment resulted in a marked protection from renal lesions [3]. In marked contrast, in the present study, losartan, given for the 6 weeks prior to sudden 1½ nephrectomy, did not prevent FSGS or tubulointerstitial lesions.

Multiple studies have documented an association between renal mass reduction-induced FSGS and altered glomerular hemodynamics [9–12]. Renal mass reduction in rats causes increased single nephron glomerular capillary pressures and blood flows. Maneuvers, such as RAS blockade that lower both systemic and glomerular capillary blood pressure (BP), reduce proteinuria and FSGS lesions, while other classes of antihypertensive drugs which lower systemic BP but not glomerular capillary hypertension do not prevent proteinuria or lesions [9, 12]. These earlier studies fit with the hypothesis that glomerular capillary hypertension is important in the pathogenesis of the proteinuria, renal lesions and renal functional loss in these models. All previous rat remnant kidney studies have shown that experimental conditions that are unaccompanied by or that prevent systemic hypertension and proteinuria are...
associated with marked reductions in FSGS and tubulointerstitial lesions. Thus, Wistar-Kyoto rats that did not become hypertensive after 5/6 nephrectomy had less proteinuria and FSGS lesions than animals becoming hypertensive [13]. Importantly, despite the development of hyperfiltration, these non-hypertensive rats did not have glomerular capillary hypertension [13].

The N + L rats in the present studies remained normotensive and had no increase in urinary protein excretion throughout the 6 months following 1½ nephrectomy despite a ~100% relative increase in GFR per nephron. These rats, however, were not protected from the development of the lesions of FSGS, interstitial expansion or tubular atrophy. If it is hypothesized that the N + L animals had glomerular capillary hypertension, there would be a discordance between the present findings and previous studies which regularly found associations between glomerular capillary hypertension and proteinuria, even in animals whose systemic BP was normalized with other classes of antihypertensive agents. Thus, the calcium channel blocker, verapamil, administered intravenously to proteinuric remnant kidney rats, lowered systemic and glomerular capillary hypertension and albuminuria despite sustained increases in single nephron GFR [14].

In the absence of glomerular hypertension, glomerular capillary hypertension may not be associated with FSGS [15–17]. For example, in a model of 2/3 infarction of one kidney with intraperitoneal drainage of the contralateral kidney, there was a reduction in glomerular hypertension, proteinuria and FSGS lesions in the remnant nephrons, despite the increased glomerular capillary blood flow and pressure [18]. These authors concluded that glomerular hypertension was a necessary precondition for the adverse influences of glomerular hyperfiltration and hypertension. However, glomerular volume in the present study was equally increased at 24 weeks after 1½ nephrectomy in losartan pretreated and untreated animals. Thus, prevention of glomerular hypertension cannot explain the absence of proteinuria in the N + L rats.

Assuming, on the other hand, that the N + L animals had normal glomerular capillary pressures, their equivalent development of FSGS lesions as compared to the untreated N rats, in the absence of any proteinuria and hypertension, is even more difficult to explain. Uninephrectomized rats with puromycin aminonucleoside induced proteinuria developed FSGS without glomerular capillary hypertension or hyperfiltration [19]; both FSGS lesions and proteinuria could be lessened with RAS blockade in this model [19]. Long-term exercise prevents glomerular capillary hypertension but not proteinuria or glomerular sclerosis in remnant kidney rats [20]. Thus, although other studies have disassociated FSGS lesions from glomerular capillary hypertension in rat remnant models, the association of these lesions with proteinuria has remained intact until the present study. Undoubtedly, studies of glomerular hemodynamics would add to the understanding of the present model. Interestingly, estimates of podocyte foot process effacement were similarly increased in N and N + L over C and C + L rats. Despite the marked increase in urinary protein excretion in the N compared to the N + L rats, these groups had equivalent increases in podocyte foot processes effacement. As reviewed by D’Agati [21], podocyte injury is critical to the development of FSGS lesions in a wide variety of animal models, including models of renal mass reduction. Thus, the equivalent podocyte injury in our N and N + L animals could possibly explain their equivalent development of FSGS lesions. However, to the best of our knowledge, there has been no previous demonstration of increased podocyte foot process effacement in the absence of proteinuria in any animal model of renal mass reduction, and this finding is unexplained.

Much has been written about the association of proteinuria and tubulointerstitial injury in animal models [22–26]. It has been posited that proteinuria causes tubules...

![Fig. 7. Volume fraction of interstitium per cortex [Vv (Int/cortex)] 24 weeks after the final surgical procedure. The lines indicate the P-values for the group comparisons.](https://academic.oup.com/ndt/article-abstract/27/1/107/1928360)

![Fig. 8. Volume fraction of atrophic tubules per cortex [Vv (AT/cortex)] 24 weeks after the final surgical procedure. The lines indicate the P-values for the group comparisons.](https://academic.oup.com/ndt/article-abstract/27/1/107/1928360)
engaged in increased protein reabsorption to over-express osteopontin and inflammatory mediators that attract macrophages and T-lymphocytes to the renal interstitium which, in turn, release pro-fibrotic cytokines initiating tubular damage and interstitial scarring [22–25]. These effects could be inhibited by RAS blockade [26]. However, some studies have suggested at least a partial dissociation of proteinuria and nephron injury. In the remnant kidney model, nephrons with tubulointerstitial injury are typically associated with glomeruli with FSGS or global glomerulosclerosis. However, Ichikawa’s group performed serial section histologic analyses of previously micropunctured glomeruli and found that the proteinuria after subtotal nephrectomy largely originated from glomeruli with minimal structural abnormalities, i.e. not those undergoing structural injury [14]. The present studies go much further, demonstrating that FSGS lesions, tubular atrophy, interstitial expansion and podocyte foot process effacement can be independent of any measurable increases in urinary protein.

Current understanding of the direct action of losartan cannot explain why 6 weeks of administration prior to 1½ nephrectomy completely prevented proteinuria and hypertension over the next 6 months. Losartan had no influence on the age-related increases in systemic BP and proteinuria in the sham-operated but otherwise normal animals. Thus, losartan’s long-term effects were specific to the 1½ nephrectomy animals and these effects were seen far beyond any possible persistence of losartan in body tissues or fluids [27]. As previously discussed [3], other studies have also shown that influences of prior RAS blocking drugs remain long after their discontinuation. Thus, spontaneously hypertensive rats treated with losartan only during early life, while still normotensive, had much less hypertension over the subsequent 4 months [28]. Also, 6 weeks of RAS blockade prior to diabetes onset in a strain of obese rats markedly ameliorated proteinuria and diabetic renal lesions over the next 39 weeks following discontinuation of RAS blockade [29]. Diabetes was not prevented, but the diabetes induced increases in the expression of genes for collagen IV and growth factors were prevented over the next 39 weeks [29]. Finally, we have previously shown that losartan pretreatment for 6 weeks during gradual reduction in renal mass had long-lasting effects [3].

These studies are consistent with epigenetic effects of these antihypertensive drugs. It is known that epigenetic influences can powerfully program the RAS. A maternal low-protein diet in pregnant rats results in offspring that develop hypertension in later life; this can be prevented by treatment in early life with RAS blockers but not with calcium channel blockers [30]. Adrenal AT1b receptor gene and protein upregulation antedates the hypertension in these rats and is associated with hypomethylation of the AT1b promoter gene [31], supporting a link between epigenetic gene modifications and the later development of hypertension. However, important epigenetic renal phenomena are not restricted to RAS blockade. Lee and Azar [32] showed that transfer of embryos of rats destined to develop genetic hypertension to the wombs of normotensive rats has an ameliorative effect on BP for months after birth. Thus, studies of other antihypertensive agents and of other possible preventative strategies would be of interest in the present model. Studies of gene expression and epigenetic phenomena could also be useful in understanding the prolonged effect of losartan in the N + L animals. Such studies might help explain the markedly different outcomes in the current model compared to our previous findings where losartan treatment for 6 weeks during gradual renal mass reduction not only prevented hypertension and proteinuria but also markedly reduced renal lesions [3].

In summary, these studies show that 6 weeks of losartan pretreatment in rats then undergoing sudden surgical reduction in renal mass prevented the development of hypertension and proteinuria but not the development of renal lesions over the subsequent 6 months. However, these studies raise more questions than they answer. Thus, this may be a very useful model to study the hemodynamic and molecular epigenetic renal effects of antihypertensive treatment, in general, and RAS blockade specifically, as well as the mechanisms of ablation-induced renal injury in the absence of proteinuria and hypertension.

Conclusions

Pretreatment of rats with losartan for 6 weeks prior to sudden 1½ surgical nephrectomy completely prevented the development of hypertension and proteinuria over the subsequent 6 months without affecting hyperfiltration, glomerular enlargement, FSGS frequency, the severity of tubulointerstitial lesions or podocyte foot process effacement. These studies completely dissociate systemic hypertension and proteinuria from the pathogenesis of these lesions in this model. Currently, there is no convenient conceptual framework with which to explain these results. The testing of other classes of antihypertensive agents and glomerular micropuncture hemodynamic studies as well as broadly targeted studies of gene expression and of epigenetic processes may provide help in the understanding these unexpected findings.

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