Effects of $N^G$-Nitro-L-Arginine on Isolated Rabbit Afferent Arterioles

Toshiaki Tamaki, Kouichi Hasui, Yasuharu Aki, Shoji Kimura and Youichi Abe

Department of Pharmacology, Kagawa Medical School, Ikenobe, Miki-cho, Kita-gun, Kagawa 761-07, Japan

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ABSTRACT—We examined the effects of $N^G$-nitro-L-arginine (L-NNA) on isolated rabbit afferent arterioles to confirm that nitric oxide is released at the resistance vessel level in the kidney. We microdissected the superficial afferent arterioles from the kidneys of New Zealand White rabbits. Each afferent arteriole was cannulated with a micropipette system, and the intraluminal pressure was set at 80 mmHg. By our methods, we found that norepinephrine (NE) decreased the lumen diameter of the afferent arterioles in a dose-dependent manner, and acetylcholine increased the lumen diameter of NE-constricted afferent arterioles. L-NNA ($10^{-4}$ M) gradually decreased the lumen diameter of afferent arterioles from 21.5±0.9 to 18.6±0.9 μm in 20 min, but $N^G$-nitro-D-arginine ($10^{-4}$ M) did not affect them (from 21.8±1.3 to 21.8±1.5 μm). L-Arginine ($10^{-2}$ M) restored the lumen diameter of L-NNA-contracted afferent arterioles to the control levels. These findings indicate that the isolated afferent arteriole has the ability to release or to synthesize and release nitric oxide under basal conditions and that this basal release of nitric oxide plays an important role in the basal tone of the afferent arteriole.

Keywords: Afferent arteriole (isolated), $N^G$-Nitro-L-arginine, L-Arginine, Endothelium-derived relaxing factor, Nitric oxide

In 1980, Furchgott and Zawadzki (1) reported the existence of endothelium-derived relaxing factor (EDRF). Subsequent studies (2–4) have shown that EDRF activity is due to the release of nitric oxide (NO), which originates from the terminal guanidino nitrogen atom of the amino acid L-arginine. Moreover, NO synthase (NOS) inhibitors have been developed (5–7). These inhibitors make it possible for us to evaluate the physiological role of EDRF/NO in regulating systemic hemodynamics and organ hemodynamics.

Recently, we reported that NO plays an important role in renal hemodynamics and function in pentobarbital anesthetized dogs (8). Other researchers have also reported that NO is an important factor in the regulation of renal hemodynamics and urine formation (9–15). However, there are few reports evaluating the importance of NO in the regulation of renal hemodynamics at the resistance vessel level. Moreover, NO seems to be generated not only in the vascular endothelium but also in other cells such as vascular smooth muscle (16), peripheral nerve (17), mesangium (18) and macula densa cell (19). Thus, the renal effects of NOS inhibitors may not be solely due to a decrease in the release and/or production of endothelial NO. We are also interested in knowing whether or not NO is produced at the resistance vessel level in the kidney as well as in the large arteries, because arterioles and capillaries were reported to display very little NOS by the use of immunohistochemical techniques (20). Kon et al. (21) suggested that EDRF may be mainly produced by the main renal artery and may then be distributed to the resistance vessels in the rat kidney.

The present study was designed to examine the ability of the afferent arteriole to release NO and evaluate the importance of NO in regulating vascular tone at the afferent arteriole. We examined the effects of $N^G$-nitro-L-arginine (L-NNA), a NO synthesis inhibitor, and L-arginine on isolated rabbit afferent arterioles without glomeruli.

MATERIALS AND METHODS

Adult male New Zealand White rabbits (2.0–2.5 kg) maintained on standard rabbit chow, were anesthetized with intravenous sodium pentobarbital (25 mg/kg), followed by a maintenance dose when necessary. The kidney was exposed through a retroperitoneal flank incision, and the renal pedicle was clamped and cut. The kidney was quickly removed and placed in iced modified Krebs-Ringer solution. The renal artery was catheterized with PE 50
tubing, and the kidney was flushed with chilled modified Krebs-Ringer solution to remove the cell components from the blood. The kidney was then perfused with an isosmotic Krebs-Ringer solution containing human albumin (Green Cross, Osaka), dextran blue 2,000 (Pharmacia Fine Chemical, Uppsala, Sweden), and indocyanine green (Daiichi Seiyaku, Tokyo) (22). This dye solution enabled us to easily distinguish the afferent arteriole. Thin slices were cut and transferred to a dish containing chilled modified Krebs-Ringer solution. The dissection solution was a modified Krebs-Ringer (pH 7.4) consisting of 105 mM NaCl, 5 mM KCl, 25 mM NaHCO3, 2.3 mM Na2HPO4, 10 mM Na acetate, 1 mM MgSO4, 2 mM CaCl2, 8.3 mM glucose, 5 mM alanine, 0.01 mM EDTA, and 10 mM HEPES. The superficial afferent arteriole was dissected free from the surrounding tissue and all tubular fragments were removed under a stereoscopic microscope (SZH, Olympus, Tokyo) using thin steel needles and sharpened forceps (No. 5, Dumont, Basel, Switzerland); all procedures were performed at 4°C (23). Great care was taken to avoid touching the vessels and to avoid exerting longitudinal or transverse tension on them. The intraluminal pressure was controlled with a screw driven syringe and set at 80 mmHg (Fig. 2). The intraluminal pressure was continuously monitored with a pressure transducer and monitor (Digic VPC, Valcom, Tokyo). Major leaks of fluid could be seen because of the different refractile properties of the perfusate and bath solution. If the intraluminal pressure could not be maintained at a constant level, the experiment was discarded. After the pressure was set, the pipettes were adjusted so that all bends in the vessel were removed. Microdissection and cannulation of the afferent arteriole were completed within 90 min at 4°C. The temperature of the bath was gradually raised to 37°C and monitored during the experiment (ESCS, Omron, Kyoto). A 30-min equilibration period was allowed before each experiment. The image of the afferent arteriole was recorded with a video system, consisting of a CCD camera with a control unit and camera adaptor (CCD-10, Olympus),

Fig. 1. Schematic illustration of a cannulated afferent arteriole.
monitor (NV-0930Z, Mitsubishi, Tokyo) and video recorder (TIMELAPSE BR-9000, JVC, Tokyo). The lumen diameter of the afferent arteriole was measured directly on the video monitor screen at 3 to 5 points. Repeat measurements were made at these same points. Data represented are mean values of the lumen diameter of 3 to 5 points. At the end of the experiment, the viability of the vessel was assessed by the response to 10^{-6} M norepinephrine (NE).

**Experimental protocols**

*Responses to NE:* Following a 30-min equilibration, control measurements of lumen diameter were made at 1-min intervals for 3 min. The control value is the mean value of three measurements. During the control measurements, we confirmed that the lumen diameter was stable. If the lumen diameter was not stable during the control observation, the experiment was discarded. After the control measurements, continuous bath exchange was stopped, and NE was applied cumulatively at 2-min intervals. A 100-pl aliquot of oxygenated bath medium containing NE was gently applied from the right side of the chamber, and drainage of bath medium was continued from the left side of the chamber. The lumen diameter was measured 1 min after application of each concentration of the drug.

*Responses to acetylcholine (ACh):* After the control measurements, vessel tone of the afferent arteriole was induced by NE (mean concentration of NE was 2.7 \times 10^{-7} M). The concentration of NE used to induce vessel tone varied, but the concentration decreased the lumen diameter by about 30%. After we confirmed the stable lumen diameter, ACh was applied to the bath cumulatively at 2-min intervals, and lumen diameter was measured 1 min after the application.

*Effects of L-NNA on isolated afferent arterioles:* After the control measurements, the infusion of bath medium containing L-NNA (10^{-4} M) was initiated at 0.5 ml/min, and the arteriole was observed for 60 min. These experiments showed that L-NNA decreased the lumen diameter of the afferent arterioles, and the effect of L-NNA reached maximum at 20 min after the start of L-NNA. Thus, we evaluated the effects of L-NNA after 20 min. The effect of \text{N}^{\text{G}}\text{-nitro-}\text{d}-\text{arginine} (\text{D-NNA}) on the afferent arterioles was also evaluated by the same method.

*Effect of \text{l-arginine} on the lumen diameter of the afferent arterioles pretreated with L-NNA:* \text{l-arginine} is reported to be a substrate of EDRF (7), and L-NNA is believed to be an inhibitor of NO synthase (5, 27). We examined the effects of \text{l-arginine} on the L-NNA-constricted afferent arterioles. After a 20-min application of L-NNA (10^{-4} M), the bath medium was changed to a medium containing L-NNA (10^{-4} M) and \text{l-arginine} (10^{-2} M).

**Chemicals**

\text{N}^{\text{G}}\text{-nitro-}\text{l-arginine}, \text{N}^{\text{G}}\text{-nitro-}\text{d}-\text{arginine}, \text{l-arginine} and \text{d-arginine} were purchased from the Peptide Institute (Osaka). Bovine albumin fraction V was purchased from Seikagaku Kogyo Co., Ltd. (Tokyo).

**Statistics**

Values are expressed as the mean±S.E.M. The data were analyzed with a two-way analysis of variance with completed randomized block. The significance of differences were determined by the least significance test (28).

**RESULTS**

*Responses to NE*

Figure 3 shows an example of the afferent arteriolar response to NE. Because NE at 10^{-6} M constricted the entire afferent arteriole, we could not observe the lumen diameter. The dose-response curves of NE on the lumen diameter of afferent arterioles are shown in Fig. 4 (upper panel). The lumen diameter of the afferent arterioles under control conditions was 21.8±1.0 \mu m (n=9). NE decreased the lumen diameter of afferent arterioles in a dose-dependent manner.
Responses to ACh

The dose-response curves of ACh on the lumen diameter of afferent arterioles are shown in Fig. 4 (lower panel). Before we applied ACh, the afferent arteriole was partially constricted with NE (mean concentration of NE was $2.7 \times 10^{-7}$ M). The lumen diameter of the afferent arteriole decreased from 21.8±1.0 to 15.4±1.0 μm with NE (n=9). ACh increased the lumen diameter of NE-constricted afferent arterioles.

Effects of L-NNA on isolated afferent arterioles

Figure 5 shows the time course of the effects of L-NNA ($10^{-4}$ M) on the lumen diameter of afferent arterioles (n=5). The lumen diameter of afferent arterioles were stable for at least 3 hr under the control condition. L-NNA gradually decreased the lumen diameter of isolated afferent arterioles, and the effect of L-NNA reached maximum at 20 min. L-NNA decreased the basal lumen diameter of afferent arterioles by 16% in 20 min. ACh ($10^{-5}$ M) did not increase the lumen diameter of afferent arterioles pretreated with L-NNA for 20 min (data not shown).

L-NNA ($10^{-4}$ M) decreased the lumen diameter of afferent arterioles from $21.5 \pm 0.9$ to $18.7 \pm 0.9$ μm (n=11), but D-NNA ($10^{-4}$ M) did not change the lumen diameter (from $21.8 \pm 1.3$ to $21.8 \pm 1.5$ μm) (n=6) (Fig. 6).

Effect of L-arginine on the lumen diameter of the afferent arterioles pretreated with L-NNA

A 20-min application of L-NNA ($10^{-4}$ M) also decreased the lumen diameter of afferent arterioles from $21.9 \pm 1.3$ to $16.9 \pm 0.9$ μm (n=6). A 20-min application of L-arginine ($10^{-2}$ M) restored the lumen diameter of L-NNA-contracted afferent arterioles to the control value (from $16.9 \pm 0.9$ to $20.5 \pm 1.5$ μm, n=6) (Fig. 7). D-Arginine ($10^{-2}$ M) did not increase the lumen diameter of L-NNA-constricted afferent arterioles (data not shown).

Responses to ACh

The dose-response curves of ACh on the lumen diameter of afferent arterioles are shown in Fig. 4 (lower panel). Before we applied ACh, the afferent arteriole was partially constricted with NE (mean concentration of NE was $2.7 \times 10^{-7}$ M). The lumen diameter of the afferent arteriole decreased from 21.8±1.0 to 15.4±1.0 μm with NE (n=9). ACh increased the lumen diameter of NE-constricted afferent arterioles.

Effects of L-NNA on isolated afferent arterioles

Figure 5 shows the time course of the effects of L-NNA ($10^{-4}$ M) on the lumen diameter of afferent arterioles (n=5). The lumen diameter of afferent arterioles were stable for at least 3 hr under the control condition. L-NNA gradually decreased the lumen diameter of isolated afferent arterioles, and the effect of L-NNA reached maximum at 20 min. L-NNA decreased the basal lumen diameter of afferent arterioles by 16% in 20 min. ACh ($10^{-5}$ M) did not increase the lumen diameter of afferent arterioles pretreated with L-NNA for 20 min (data not shown).

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DISCUSSION

Many experiments using large vessels have provided substantial information about the mechanisms of vasoactive substances. However, organ circulation is mainly regulated at the resistance vessel level, not at the large vessel level. Recent technological developments have enabled us to directly assess renal microcirculation (29, 30). Our method is modified from Edwards' method (25) and enables us to evaluate the direct actions of vasoactive substances on the arterioles. With our methods, we found that NE decreased the lumen diameter of afferent arterioles in a dose-dependent manner, and ACh increased the lumen diameter of NE-constricted afferent arterioles. These results indicate that our method can be used to evaluate the effects of vasoactive substances at the resistance vessel level.

Since Furchgott and Zawadzki (1) proposed the function of EDRF in 1980, evidence that EDRF plays a role in the regulation of renal circulation has been accumulated. We have previously reported that an intrarenal infusion of L-NNA decreased renal blood flow (RBF) and L-arginine increased RBF in pentobarbital anesthetized dogs (8). The blockade of NOS with several inhibitors has been reported to decrease RBF under several experimental conditions (9, 11–14, 31). These results suggest that NO plays an important role in regulating renal hemodynamics. However, there are few reports that evaluate the role of EDRF in the renal resistance vessels (23, 32), and it is still a question whether NO is produced and released in the resistance vessels. Immunohistochemical studies have indicated that the NOS of the endothelial layers is localized mainly in large vessels, not in arterioles and capillaries (20). Kon et al. (21) reported that EDRF, which is primarily produced by the main renal artery, acts as a vasodilator at resistance arterioles in Munich-Wistar rats.

In this study, we determined whether EDRF/NO is produced and released at the resistance vessel level of the kidney with isolated rabbit afferent arterioles. L-NNA decreased the lumen diameter of afferent arterioles, but D-NNA did not affect them. Moreover, L-arginine reversed the lumen diameter of L-NNA-contracted afferent arterioles to control values. Ito et al. (23, 32) have already reported that L-NNA decreased the basal diameter of the isolated microperfused rabbit afferent arterioles by 15% or 18%. In preliminary experiments, Hoffend et al. (33) reported that \( \text{N}^2 \)-nitro-L-arginine methyl ester decreased the diameter of efferent arterioles but did not affect that of afferent arterioles in the split hydropnephrotic kidney of rats. Our results are consistent with Ito's reports. However, Mundel et al. (19) recently reported that macula densa cells may produce considerable amounts of NO. The microdissected afferent arteri-
ole with the glomerulus may contain a portion of macula densa cells (34). Thus, we cannot rule out the influence of NO produced in the macula densa cells when evaluating the results of experiments using microdissected afferent arteriole with the glomerulus. To avoid this difficulty, we microdissected only the afferent arteriole without the glomerulus and tubule from the kidney of New Zealand White rabbit. Our findings indicate that the isolated afferent arteriole has the ability to release or to synthesize and release NO under basal conditions and this basal release of NO plays a significant role in the basal tone of the afferent arteriole.

At least three types of NOS, endothelial NOS, neuronal NOS and macrophage NOS, have been identified (20). In endothelial cells and neuronal tissue, NOS is calcium/calmodulin-dependent, and its enzymatic activity is constitutively expressed. However, macrophage NOS is independent of calcium/calmodulin, and its enzymatic activity is induced by lipopolysaccharide and γ-interferon over a period of many hours (20, 35). In the kidney, NO may be synthesized not only in the vascular endothelium but also in other cells such as macrophages (36), vascular smooth muscle (16), peripheral nerve (17), mesangium (18) and macula densa cells (19). In this experiment, we used only isolated afferent arteriole without the glomerulus. Thus, we can rule out the NO that originates from mesangium and macula densa cell. Our acute experiment suggests that the basal release of NO from isolated afferent arterioles may be derived from the cells having constitutive NOS. In our preparation, the endothelium and nerve fibers may be the candidates for the NO-releasing cells. The origin of NO remains unclear in our experiment because endothelial denudation is difficult in microvascular studies.

In summary, the microdissected afferent arteriole of New Zealand White rabbit has the ability to release or to synthesize and release NO, and the basal release of NO plays a significant role in the basal tone of the afferent arteriole.

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REFERENCES

1 Furchgott, R.F. and Zawadzki, J.V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288, 373–376 (1980)
2 Palmer, R.M.J., Ferrige, A.G. and Moncada, S.: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327, 524–526 (1987)
3 Palmer, R.M.J., Ashton, D.S. and Moncada, S.: Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 333, 664–666 (1988)
4 Ignarro, L.J., Buga, G.M., Wood, K.S., Byrns, R.E. and Chaudhuri, G.: Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc. Natl. Acad. Sci. U.S.A. 84, 9265–9269 (1987)
5 Moore, P., al-Swayeh, O., Chong, N., Evans, R. and Gibson, A.: L-N^6-nitroarginine (L-NOARG), a novel, L-arginine-reversible inhibitor of endothelium-dependent vasodilator in vitro. Br. J. Pharmacol. 99, 408–412 (1990)
6 Rees, D.D., Palmer, R.M.J., Schulz, R., Hudson, H.F. and Moncada, S.: Characterization of three inhibitors of endothelial nitric oxide synthase in vitro and in vivo. Br. J. Pharmacol. 101, 746–752 (1990)
7 Palmer, R.M.J., Rees, D.D., Ashton, D.S. and Moncada, S.: L-Arginine is the physiological precursor for the formation of nitric oxide in endothelium-dependent relaxation. Biochem. Biophys. Res. Commun. 153, 1251–1256 (1988)
8 Kiyomoto, H., Matsuo, H., Tamaki, T., Aki, Y., He, H., Iwao, H. and Abe, Y.: Effect of L-N^6-nitroarginine, inhibitor of nitric oxide synthesis, on autoregulation of renal blood flow in dogs. Japan. J. Pharmacol. 58, 147–155 (1992)
9 Murakami, M., Suzuki, H., Ichihara, A., Naitoh, M., Nakamoto, H. and Saruta, T.: Effects of L-arginine on systemic and renal hemodynamics in conscious dogs. Clin. Science 81, 727–732 (1991)
10 Tölns, J.P., Palmer, R.M.J., Moncada, S. and Raji, L.: Role of endothelium-derived relaxing factor in regulation of renal hemodynamic responses. Am. J. Physiol. 258, H655–H662 (1990)
11 Tölns, J.P. and Raji, L.: Effects of amino acid infusion on renal hemodynamics. Hypertension 17, 1045–1051 (1991)
12 Beierwaltes, W., Sigmon, D. and Carretero, O.: Endothelium modulates renal blood flow but not autoregulation. Am. J. Physiol. 262, F943–F949 (1992)
13 Majid, D.S. and Navar, I.G.: Suppression of blood flow autoregulation plateau during nitric oxide blockade in canine kidney. Am. J. Physiol. 262, F40–F46 (1992)
14 Naess, P., Kirkeboen, K.A., Christensen, G. and Kii, F.: Inhibition of renal nitric oxide synthesis with \( \mathrm{N}^6 \)-monomethyl-L-arginine and \( \mathrm{N}^6 \)-nitro-arginine. Am. J. Physiol. 262, F939–F942 (1992)
15 Salom, M.G., Lahera, V., Miranda-Guardiola, F. and Romero, C.: Blockade of pressure natriuresis induced by inhibition of renal synthesis of nitric oxide in dogs. Am. J. Physiol. 262, F718–F722 (1992)
16 Wood, K.S., Buga, G.M., Byrns, R.E. and Ignarro, L.J.: Vascular smooth muscle-derived relaxing factor (MDRF) and its close similarity to nitric oxide. Biochem. Biophys. Res. Commun. 170, 80–88 (1990)
17 Bredt, D.S., Hwang, P.M. and Snyder, S.H.: Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 347, 768–770 (1990)
18 Marsden, P.A. and Ballermann, B.J.: Tumor necrosis factor \( \alpha \) activates soluble guanylate cyclase in bovine glomerular mesangial cells via an \( L \)-arginine. J. Exp. Med. 172, 1843–1852 (1990)
19 Mundel, P., Bachmann, M.B., Fischer, A., Kummer, W., Mayer, B. and Kriz, W.: Expression of nitric oxide synthase in kidney macula densa cells. Kidney Int. 42, 1017–1019 (1992)
20 Lowenstein, C.J. and Snyder, S.H.: Nitric oxide, a novel biologic messenger. Cell 70, 705–707 (1992)
21 Kon, V., Harris, R.C. and Ichikawa, I.: A regulatory role for large vessels in organ circulation. J. Clin. Invest. 85, 1728–1733 (1990)
22 Osgood, R.W., Patton, M., Hanley, M.J., Venkatachalam, M., Reineck, H.J. and Stein, J.H.: In vitro perfusion of the isolated dog glomerulus. Am. J. Physiol. 244, F349–F354 (1983)
23 Ito, S., Johnson, C.S. and Carretero, O.A.: Modulation of angiotensin II-induced vasoconstriction by endothelium-derived relaxing factor in the isolated microperfused rabbit afferent arteriole. J. Clin. Invest. 87, 1656–1663 (1991)
24 Duling, B.R., Gore, R.W., Dacey, R.G. and Damon, D.N.: Methods for isolation, cannulation, and in vitro study of single microvessels. Am. J. Physiol. 241, H108–H116 (1981)
25 Edwards, R.M.: Segmental effects of norepinephrine and angiotensin II on isolated renal microvessels. Am. J. Physiol. 244, F526–F534 (1983)
26 Ito, S. and Carretero, O.A.: An in vitro approach to the study of macula densa-mediated glomerular hemodynamics. Kidney Int. 38, 1206–1210 (1990)
27 Kobayashi, Y. and Hattori, K.: Nitroarginine inhibits endothelium-derived relaxation. Japan. J. Pharmacol. 52, 167–169 (1990)
28 Sokal, R.S. and Rohlf, F.J.: Biometry. W.H. Freeman, New York (1966)
29 Navar, L.G., Gilmore, J.P., Joyner, W.L., Steinhausen, M., Edwards, R.M., Casellas, D., Carmines, P.K., Zimmerhackl, L.B. and Yokota, S.D.: Direct assessment of renal microcirculatory dynamics. Fed. Proc. 45, 2851–2861 (1986)
30 Roman, R.J., Carmines, P.K., Loutzenhiser, R. and Conger, J.D.: Direct studies on the control of the renal microcirculation. J. Am. Soc. Nephrol. 2, 136–149 (1991)
31 Gardiner, S.M., Compton, A.M., Bennett, T., Palmer, R.M.J. and Moncada, S.: Control of regional blood flow by endothelium-derived nitric oxide. Hypertension 15, 486–492 (1990)
32 Ito, S., Juncos, L.A., Nushiro, N., Johnson, C.S. and Carretero, O.A.: Endothelium-derived relaxing factor modulates endothelin action in afferent arterioles. Hypertension 17, 1052–1056 (1991)
33 Hoffend, J., Cavarape, A. and Steinhausen, M.: Effects of N^G-nitro-arginine methyl ester (L-NAME) in the split hydronephrotic kidney of rats (Abstract). J. Microcirc. Clin. Exp. 11, 222 (1992)
34 Bock, H.A., Hermle, M., Brunner, F.P. and Thiel, G.: Pressure dependent modulation of renin release in isolated perfused glomeruli. Kidney Int. 41, 275–280 (1992)
35 Moncada, S., Palmer, R.M.J. and Higgs, E.A.: Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol. Rev. 43, 109–142 (1991)
36 Stehr, D.J. and Nathan, C.F.: Nitric oxide: A macrophage product responsible for cytostasis and respiratory inhibition in tumor target cells. J. Exp. Med. 169, 1543–1555 (1989)