

# Genotype-dependent Modification of Sarcoma 37 Growth in Castrated Mice<sup>1</sup>

George L. Wolff

*The Institute for Cancer Research, Philadelphia, Pennsylvania 19111*

## SUMMARY

Sarcoma 37 cells grew more rapidly in castrated male mice than in controls of the same genotype; however, this effect of castration was dependent on the host genotype. Among inbred YS/Wf mice, tumor weight was increased only in castrated yellow  $A^y/a$  males and not in the comparable black  $a/a$  males. In contrast, mean tumor weight was increased in both yellow  $A^y/a$  and black  $a/a$  castrated males of the inbred VY/Wf strain.

## INTRODUCTION

Alteration of the hormonal balance by castration increased spontaneous hepatoma formation in yellow  $A^y/A$  C3H × YBR F<sub>1</sub> hybrid male mice, but in the nonyellow  $A/a$  male siblings a comparable effect was not found (1). The present investigation was undertaken to determine whether castration and host genotype would also affect the growth of transplanted tumor cells. For this purpose, allogeneic Sarcoma 37 cells were implanted in castrated and sham-operated yellow and black male mice of the inbred YS/ChWf and VY/Wf strains. It appears that the response to castration with respect to both allogeneic tumor growth and plasma corticosterone concentration (3) is dependent on the genotype.

Regulatory effects on growth of Sarcoma 37 by the lethal yellow ( $A^y$ ) and viable yellow ( $A^vy$ ) alleles at the agouti locus in the mouse were reported previously (2). Genotype-dependent effects of castration on liver weight and composition have been described (1).

## MATERIALS AND METHODS

All experimental conditions and procedures were identical with those described previously (2). Castrations and sham operations were performed on 4-week-old males under pentobarbital anesthesia. Tumors were excised and weighed on the 8th day after s.c. implantation of  $7.0 \times 10^6$  Sarcoma 37 ascites cells into yellow  $A^y/a$  and black  $a/a$  males of the inbred

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YS/ChWf strain (F<sub>31</sub> to F<sub>33</sub>) and mottled yellow  $A^vy/a$  and black  $a/a$  males of the inbred VY/Wf strain (F<sub>26</sub> to F<sub>28</sub>) at approximately 13 weeks of age. The experiments indicated in Tables 1 and 2 were performed during successive weeks. Analyses of variance were used to determine statistical significance of differences.

## RESULTS AND DISCUSSION

Analysis of the data shown in Tables 1 and 2 indicates that among VY males both yellow  $A^vy/a$  phenotype and castration increased tumor weight independently ( $p < 0.001$ ). Among YS males, on the other hand, castration increased tumor weight only in yellow  $A^y/a$  males ( $p = 0.005 - 0.001$ ). While the difference between the tumor weights in sham-operated yellow and black YS males observed previously (2) was absent, the difference between the 2 genotypes in effect on Sarcoma 37 growth was revealed by castration.

In earlier work (1), it was shown that castration also altered carcass composition of yellow and black YS/ChWf males differently (Table 3). Among black  $a/a$  YS males, fat-free dry weight was decreased significantly as a result of castration, while no change in this parameter was observed among the yellow  $A^y/a$  males. In the same animals, fat-free dry liver weight was increased in yellow  $A^y/a$  males by castration, whereas there was no effect on fat-free dry liver weight in the comparable black  $a/a$  males. While castration-induced fat deposition was higher among yellow than among black mice between 4 and 12 weeks of age, it was considerably lower among yellow than among black mice between 12 and 16 weeks of age (Table 2). These are clear indications that the metabolic matrix of the yellow mice differs from that of black mice in its response to the effects of castration.

In this work, effect of castration on Sarcoma 37 weight in YS males paralleled the effects of castration on the liver rather than those on the carcass. Liver and body weights were not affected by the short period of tumor growth; effects of castration on these parameters resembled those reported earlier (1).

Although plasma corticosterone levels (3) varied with genotype and castration, they did not correlate with tumor weight.

The differential effects of castration on Sarcoma 37 growth in the yellow  $A^y/a$  and black  $a/a$  YS phenotypes may be analogous to the castration-induced doubling of spontaneous hepatoma formation in yellow C3H × YBR F<sub>1</sub> hybrid males

Table 1  
Effect of castration on Sarcoma 37 weight 8 days postimplantation in yellow and black male mice of the inbred YS/ChWf strain

| Mice                                     | Tumor weight (mg)                       |               | Liver weight (g)<br>for | Body weight (g) |              |
|--|---|---------------|-------------------------|-----------------|--------------|
|  | Experiment 1                            | Experiment 2  | Experiment 2            | Experiment 1    | Experiment 2 |
| <b>Yellow (<math>A^y/a</math>) males</b> |   |               |                         |                 |              |
| Castrated                                | 258 ± 14 <sup>a</sup> (12) <sup>b</sup> | 259 ± 27 (11) | 1.29 ± 0.04 (11)        | 34.4 ± 1.2      | 33.7 ± 0.7   |
| Sham operated                            | 176 ± 18 (10)                           | 211 ± 29 (8)  | 1.56 ± 0.09 (8)         | 30.6 ± 1.5      | 33.8 ± 1.3   |
| <b>Black (<math>a/a</math>) males</b>    |   |               |                         |                 |              |
| Castrated                                | 191 ± 17 (14)                           | 153 ± 15 (11) | 0.97 ± 0.04 (11)        | 25.4 ± 0.5      | 24.7 ± 0.4   |
| Sham operated                            | 203 ± 20 (10)                           | 166 ± 19 (10) | 1.14 ± 0.06 (9)         | 26.8 ± 0.8      | 26.2 ± 0.5   |

<sup>a</sup> Mean ± S.E.

<sup>b</sup> No. of animals per group.

Table 2  
Effect of castration on Sarcoma 37 weight 8 days postimplantation in yellow and black male mice of the inbred VY/Wf strain

| Mice  | Tumor weight (mg)                       |               | Liver weight (g) |              | Body weight (g) |              |
|---|---|---------------|------------------|--------------|-----------------|--------------|
|   | Experiment 3                            | Experiment 4  | Experiment 3     | Experiment 4 | Experiment 3    | Experiment 4 |
| <b>Yellow (<math>A^{vy}/a</math>) males</b> |   |               |                  |              |                 |              |
| Castrated                                   | 249 ± 26 <sup>a</sup> (11) <sup>b</sup> | 316 ± 30 (11) | 1.80 ± 0.09      | 2.02 ± 0.09  | 41.0 ± 1.1      | 43.1 ± 0.9   |
| Sham operated                               | 177 ± 26 (11)                           | 239 ± 22 (14) | 2.29 ± 0.13      | 2.27 ± 0.10  | 45.1 ± 1.2      | 44.6 ± 1.0   |
| <b>Black (<math>a/a</math>) males</b>       |   |               |                  |              |                 |              |
| Castrated                                   | 199 ± 20 (12)                           | 227 ± 28 (12) | 1.03 ± 0.02      | 1.04 ± 0.02  | 26.0 ± 0.7      | 25.8 ± 0.6   |
| Sham operated                               | 142 ± 15 (13)                           | 175 ± 15 (13) | 1.42 ± 0.03      | 1.43 ± 0.03  | 30.3 ± 0.4      | 30.4 ± 0.5   |

<sup>a</sup> Mean ± S.E.

<sup>b</sup> No. of animals per group.

Table 3  
Effect of castration on carcass<sup>a</sup> composition in yellow and black YS/ChWf male mice

| Coat color phenotype | Agouti locus genotype | Age (wk)        | Change due to castration <sup>b</sup> |           |                         |
|----------------------|-----------------------|-----------------|---------------------------------------|-----------|-------------------------|
|                      |                       |                 | Fat (%)                               | Water (%) | Fat-free dry weight (%) |
| Yellow               | $A^y/a$               | 12              | +212                                  | -15       | -6                      |
|                      |                       | 16 <sup>c</sup> | +107                                  | -13       | 0                       |
| Black                | $a/a$                 | 12              | +88                                   | -16       | -22                     |
|                      |                       | 16 <sup>c</sup> | +211                                  | -22       | -23                     |

<sup>a</sup> Carcass, body without liver.

<sup>b</sup> Relative to sham-operated control mice; all operations performed at 28 days of age.

<sup>c</sup> Data derived from earlier work (1).

and the apparent absence of an effect on hepatoma formation in their nonyellow male siblings (1). In both phenomena, the  $A^y$  gene was the only common experimental variable.

The present results indicate that alteration of the hormonal

balance by castration affects host metabolism differently in yellow and black mice; the growth response of allogeneic Sarcoma 37 cells in these host environments also differs. In the case of yellow mice, these changes in host and tumor cell

metabolism appear to favor increased growth. Since it is not known whether yellow and black mice differ in their immunological reactivity, the relative roles of immunological and strictly metabolic factors in this phenomenon remain to be elucidated.

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