Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders

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Age-related sarcopenia; muscle biopsy; resistance training; muscle damage

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extremity resistance training or nutritional supplementation, both active interventions, or a placebo-controlled condition. Resistance training consisted of three sets of eight repetitions at 80% of the most recently determined one-repetition maximum (1-RM) for the hip and knee extensor muscles, 3 days/wk for 10 wk, using pneumatic resistance training equipment (Keiser Sports Health, Fresno, CA). The nutritional supplement (Exceed; Ross Laboratories, Columbus, OH) was a 240-ml liquid administered daily supplying 360 kcal in a 60% carbohydrate, 23% fat, 17% soy-based protein formula including one-third of the recommended daily allowance of essential vitamins and minerals. A nonnutritive placebo liquid (Crystal Light; Kraft General Foods, White Plains, NY) and nonresistive recreational activities were offered to the exercise and nutrition control subjects.

Clinical Characteristics

Methods for assessment of health status, functional level, cognition, depressive symptoms, physical activity levels, and nutritional intake have been published previously (17). Three-day food weighing was used to analyze nutrient intakes. The average of 72-h counts of movement of three degrees or more per 72-h period were analyzed to determine the appropriateness of subsequent ANOVAs and regression models. Lower extremity power was estimated from maximal chair-rise time (1).

Body Composition

Regional thigh muscle area was measured using blinded digital analysis of computerized tomography images using a Sytec 4000 (Somatom-Siemens, Erlangen, Germany) or Sytec 4000 (General Electric, Milwaukee, WI) scanner in the supine position at the nondominant midthigh. Total body water (liters) was estimated from bioelectric impedance (RJL Systems, Clinton, MI) measurements of resistance and reactance. Whole body potassium was measured as an index of body cell mass (7) in a K⁺ counter calibrated daily. The coefficient of variation (CV) of weekly anthropomorphic phantom measurements was 5%.

Muscle Biopsy Procedure

A needle biopsy of the nondominant vastus lateralis was obtained at baseline and 4–6 days after the last exercise session under local anesthesia (1% xylocaine hydrochloride) using a 5-mm ducenne needle with applied suction (15). The sample obtained from each biopsy was divided into three pieces. The first piece was quick-frozen in liquid nitrogen. The second piece was oriented longitudinally, mounted in embedding medium [optimum cutting temperature compound (OCT); Miles Laboratories, Naperville, IL], and frozen in isopentane cooled to the temperature of liquid nitrogen. Within 5 min after the biopsy material was obtained, the third piece was finely minced and fixed in 0.1 M cacodylate-buffered glutaraldehyde and paraformaldehyde for 3 h at 4°C, rinsed with 0.1 M sodium cacodylate buffer at least 3 × 5 min at room temperature (RT), and postfixed with 1% osmium tetroxide in 0.1 M sodium cacodylate buffer for 1 h at 4°C.

Light and Electron Microscopy

After postfixation, the samples were rinsed with cacodylate buffer, dehydrated sequentially with methanol (30, 50, 70, 80, 90, and 100%), and infiltrated with propylene oxide. The samples were then embedded in LR white (medium). Semi-thin sections (1 µm) were cut using an Ultratome (LKB, Bromma, Sweden) and stained with toluidine blue. Samples were dehydrated sequentially in graded methanol alcohol (30, 50, 70, 80, 90, and 100%) 15 min for each concentration at RT. Thin sections were cut and stained with uranyl acetate and lead citrate and examined with a Zeiss EM-10CA electron microscope (Carl Zeiss, Thornwood, NY). Stereological measurements of volume densities of sarcoplasmic space, Z bands, damaged Z bands, and myofibril damage were made with a 100-point isotropic semicircular test system, as described previously (18). Intersection counts were obtained with the test lines oriented at an angle of 19° to the direction of the longitudinal axis of the myofibrils. The ratio of damaged to total Z bands was determined for each time point along with the analysis of focal damage. Myofibril damage was defined as an area showing absent or disorganized myofilaments not associated with the Z band.

Muscle Histochemistry

The OCT-mounted samples were sectioned (8 µm) in a cryostat and stained for myofibrillar ATPase activity at a preincubation pH of 4.3 and 4.6 (31). Fiber type distribution and fiber areas were determined using a computer-operated image analysis system (image 1.39 from W. Rasband, National Institutes of Health [NIH]), as modified for our applications (Muscle Fiber Image from G. Solares), to threshold the image, trace the fiber boundaries, identify and count the light and dark fibers, and measure the cross-sectional areas of all the fibers. An average of 437 fibers per subject were measured for each time point. The mean CV for fiber measurements using this technique in our laboratory is 0.57% for type I fibers and 0.68% for type II fibers in elderly subjects.

Immunohistochemistry

Embryonic (eMHC) and neonatal (nMHC) myosin heavy chain antibodies (Vector Laboratories, Burlingame, CA) were used to identify the presence of developmental myosin in myoblasts and mature muscle fibers. IGF-I antibodies (Chemicon International, Temecula, CA) were used to examine changes in the presence of this growth factor in response to the interventions. For immunohistochemistry, transverse sections (8 µm) were mounted on glass slides (Superfrost Plus) and incubated for 1 h at 37°C in primary antibody (IGF-I diluted 1:50 in PBS; eMHC diluted 1:20 in PBS; nMHC diluted 1:20 in PBS). Sections were subsequently rinsed in PBS (3 × 10 min) and incubated in secondary antibody. Sections were rinsed in PBS (3 × 10 min) and mounted on coverslips. The area positively stained by the above immunofluorescent technique for eMHC, nMHC, or IGF-I was quantified from digitized images of micrographs using NIH Image version 1.39 and was expressed as a percentage of the total cross-sectional fiber area examined.

Statistical Analysis

Data were analyzed using the SuperANOVA or Statview software packages (Abacus Concepts, Berkeley, CA). All values are reported as means ± SE. Baseline differences between groups were assessed by unpaired t-tests or chi square analysis as appropriate. Linear regression was used to determine the appropriateness of subsequent ANOVAs and analy-
Table 1. Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise</th>
<th>Supplement</th>
<th>Exercise and Supplement</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>83.5 ± 2.7</td>
<td>87.7 ± 1.8</td>
<td>84.0 ± 1.2</td>
<td>91.0 ± 1.8*</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>2/4</td>
<td>2/5</td>
<td>5/2</td>
<td>4/5</td>
<td>0.19</td>
</tr>
<tr>
<td>Functional status score (0–6)</td>
<td>1.3 ± 0.5</td>
<td>1.1 ± 0.3</td>
<td>2.4 ± 0.6</td>
<td>1.3 ± 0.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Medical diagnoses</td>
<td>5.2 ± 0.9</td>
<td>5.0 ± 1.0</td>
<td>5.0 ± 0.6</td>
<td>3.3 ± 0.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Depression score (0–30)</td>
<td>6.5 ± 2.3</td>
<td>12.1 ± 2.8</td>
<td>7.4 ± 2.4</td>
<td>9.8 ± 2.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Habitual activity level, counts/day</td>
<td>23,988 ± 3,511</td>
<td>10,666 ± 2,686</td>
<td>17,424 ± 8,666</td>
<td>18,460 ± 2,701</td>
<td>0.33</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9 ± 1.5</td>
<td>24.4 ± 1.2</td>
<td>26.4 ± 1.1</td>
<td>25.2 ± 1.5</td>
<td>0.74</td>
</tr>
<tr>
<td>Dietary energy intake, kcal/day</td>
<td>1,479 ± 2,701</td>
<td>1,646 ± 97</td>
<td>1,634 ± 102</td>
<td>1,449 ± 24</td>
<td>0.24</td>
</tr>
<tr>
<td>Dietary protein intake, g·kg⁻¹·day⁻¹</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Lower body strength, kg</td>
<td>34.4 ± 4.5</td>
<td>30.5 ± 6.2</td>
<td>23.1 ± 3.4</td>
<td>30.5 ± 3.6</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. M, males; F, females. Functional status score determined using the Katz activities of daily living (ADL) index where 0 = independent in all ADLs and 6 = dependent in all ADLs (23). Depression score determined using the geriatric depression scale where 0 = no depressive symptoms and >9 is consistent with clinical diagnosis of depression (38). P value refers to baseline differences between groups in an ANOVA model in all cases. *Control group significantly different from the other 3 groups (P < 0.01).

Muscle Function

As shown in Fig. 1, there was a significant effect of the weight-lifting exercise intervention on muscle strength (P = 0.0332) and an exercise-supplement interaction (P = 0.0563), with the exercise-supplement group gaining significantly more strength than the exercise group (P = 0.0091), the supplement group (P = 0.0001), and the control group (P = 0.0002). The exercise group gained more strength than the supplement group (P = 0.05) and showed a similar trend compared with the control group (P = 0.0981).

Table 2. Correlates of muscle fiber areas at baseline

<table>
<thead>
<tr>
<th>Clinical Correlate</th>
<th>Type I fibers</th>
<th>P Value</th>
<th>Type II fibers</th>
<th>r or t Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical diagnoses</td>
<td>-0.449</td>
<td>0.054</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.552</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>2.67</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT muscle area, cm²</td>
<td>0.540</td>
<td>0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body potassium, g</td>
<td>0.625</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body water, liters</td>
<td>0.813</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity level, counts/day</td>
<td>0.484</td>
<td>0.094</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg power, W</td>
<td>0.585</td>
<td>0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography.
The observed changes in strength were greatest in those with the fewest depressive symptoms at baseline ($r = 0.511, P = 0.015$) and the greatest increases in energy intake ($r = 0.602, P = 0.003$) during the trial. The level of depression was unrelated to compliance with the exercise or placebo sessions. In a stepwise multiple-regression model including age, depression score, and changes in energy intake, 45% of the variance in strength gain was predicted by independent contributions of baseline depression and change in energy intake alone ($r = 0.671, P = 0.0034$).

Muscle Fiber Type Distribution and Areas

Baseline. There were no significant differences between groups in fiber type ratio or areas. Type II (fast-twitch) fibers comprised 57.0 ± 3.7% of the fibers counted in these subjects, and abnormal fiber type grouping (areas predominated by one fiber type rather than the normal variegated pattern) and small, angular fibers were often observed in specimens. The type II-to-type I ratio was greater with higher baseline energy intake ($r = 0.519, P = 0.0189$).

Mean type I fiber cross-sectional area was 3,603 ± 244 µm², comparable to five young controls (mean age 27.0 ± 2.1 yr) whose mean type I fiber area was 3,379 ± 462 ($P = 0.61$). Type II fibers were often small and irregular in appearance under light microscopy, with a mean fiber area of 2,229 ± 146 µm², which is ~60% of the area of young controls (3,857 ± 565, $P = 0.0003$). Clinical features related to baseline fiber areas are shown in Table 2. In a model including gender, age, leg power, and activity level, age was the only independent predictor of type II fiber area ($P = 0.0189$).

Regional and whole body measures of lean tissue [midthigh muscle area by computed tomography (CT) scan, whole body potassium, and total body water] were all highly correlated with type II fiber area but unrelated to type I fiber area, as seen in Fig. 2, A and B, and Table 2.

Intervention effects. In response to the intervention, type II fiber area increased significantly in the combined exercise-supplement group (10.1 ± 9.0%), with no change or decreases in the other treatment groups, as shown in Table 3 ($P = 0.033$). This increase in type II fiber area was associated with higher baseline energy intake ($r = 0.642, P = 0.0055$). No significant effect of the intervention was seen on type I fiber area, although similar trends as with type II fibers were seen, and the changes in type I and II fiber area were directly correlated ($r = 0.555, P = 0.0208$).

Muscle Damage

Baseline. At baseline, there was extensive evidence of Z band and myofibril disruption (see Table 4). Approximate values are means ± SE. Pre, preintervention; Post, postintervention. Analysis of covariance (ANCOVA) models were adjusted for age, gender, baseline value, and %change in kcal intake during the study and were analyzed for exercise treatment, supplement treatment, and interactions. *There was a significant effect of group assignment on the change in type II area ($P = 0.033$), with the Exercise and supplement group different from the Exercise ($P = 0.04$) and the Control groups ($P = 0.09$).
IGF-I and Developmental Myosin in Skeletal Muscle

Table 4. Ultrastructural and Immunohistochemical Evidence of Muscle Damage and Regenerative Proteins

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise Group</th>
<th>Percent Change</th>
<th>No Exercise Group</th>
<th>Percent Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>For Exercise</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Z band damage, %volume density</td>
<td>21 ± 5</td>
<td>41 ± 5</td>
<td>141 ± 58</td>
<td>20 ± 2</td>
<td>19 ± 1</td>
</tr>
<tr>
<td>Myofibril damage, %volume density</td>
<td>5 ± 3</td>
<td>15 ± 4</td>
<td>589 ± 349</td>
<td>3 ± 1</td>
<td>2 ± 0</td>
</tr>
<tr>
<td>Sarcoplasmic space, %volume density</td>
<td>18 ± 4</td>
<td>18 ± 5</td>
<td>−1 ± 13</td>
<td>16 ± 1</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Embryonic myosin staining, %</td>
<td>6 ± 1</td>
<td>17 ± 3</td>
<td>241 ± 82</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Neonatal myosin staining, %</td>
<td>7 ± 2</td>
<td>19 ± 3</td>
<td>253 ± 120</td>
<td>4 ± 1</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>IGF-I staining, %</td>
<td>6 ± 2</td>
<td>22 ± 4</td>
<td>491 ± 137</td>
<td>8 ± 2</td>
<td>7 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. IGF-I, insulin-like growth factor I. For presentation, the data were collapsed into exercise or no exercise conditions for clarity of data presentation and effect size, as the nutritional supplement use had no independent or interactive effect on any of the above variables. All analyses were done as ANCOVA models of exercise and supplement main effects and interaction terms, adjusted for age, gender, and the baseline value of the relevant variable. P value refers to the main effect of exercise on the adjusted percent change scores in all cases.

Findings:

- Approximately 20% of the Z band volume density was damaged, as evidenced by Z band streaming, zigzagging, or spreading, sometimes accompanied by a complete disarray of the myofibril architecture. As shown in Fig. 3A, narrow bundles of myofibrils were separated by large intracellular (sarcoplasmic) spaces. The volume densities of sarcoplasmic space (r = 0.583, P = 0.047) and myofibril damage (r = 0.825, P = 0.001) were highly correlated with Z band damage.

- Intervention effects. There was a large increase in Z band (141.3 ± 58.9%) and myofibril damage (589.2 ± 349.1%) with exercise as shown in Table 4 and Fig. 3B, with no changes in the nonexercising subjects. These changes in Z band and myofibril damage paralleled each other (r = 0.907, P < 0.0001). The nutritional supplement had no independent or interactive effect on muscle damage. The increase in muscle damage was highly predictive of the increase in strength of the biopsied quadriceps muscle group (r = 0.857, P = 0.0007) and overall lower extremity strength gains (r = 0.670, P = 0.0341).

Muscle Regeneration

- eMHC and nMHC staining, baseline. A small percentage of muscle fiber area (6–7%) was positively stained with either eMHC or nMHC in subjects at baseline, as shown in Table 4. eMHC and nMHC staining was directly related (r = 0.846, P < 0.0001) and was highest in those with the least evidence of ultrastructural damage before the intervention (r = −0.716, P = 0.020).

- Intervention effects. Positive staining for eMHC and nMHC increased by ~250% in the strength-training group, with no significant changes in the nonexercising subjects, as shown in Table 4 and Fig. 4, A-D. The increased staining for these two isoforms was linked (r = 0.817, P = 0.0022), was in general distributed diffusely throughout the cell cytoplasm, and appeared in both small and large cells. The increases in nMHC were associated with fewer depressive symptoms at baseline (r = −0.616, P = 0.0435). Subjects with the greatest adaptation in terms of developmental myosin also had the greatest increases in ultrastructural damage after training (r = 0.802, P = 0.030) and the greatest strength increases (r = 0.667, P = 0.0353).

IGF-I, baseline. At baseline, 1–17% of the analyzed muscle fiber area was positively stained for IGF-I, averaging 6.7 ± 1.3%, as shown in Table 4. Higher baseline presence of IGF-I was predictive of increases...
INTERVENTION EFFECTS. Exercise training resulted in a 500% increase in IGF-I staining, as shown in Table 4 and Fig. 5, with no significant effects of the nutritional supplement. Positive IGF-I staining was observed in mature muscle fibers and smaller fibers consistent with myogenic precursor cells. IGF-I staining after strength training was localized to both pericellular and intracellular regions of transverse sections (see Fig. 6, A and B). The increase in IGF-I was greatest in subjects with fewer depressive symptoms at baseline (r = -0.708, P = 0.0217). IGF-I increases closely paralleled increases in both damage (r = 0.855, P = 0.0301) and developmental myosin (r = 0.901, P = 0.0009).

DISCUSSION

This study provides the first immunohistochemical and ultrastructural evidence of skeletal muscle remodeling in response to resistance training in frail individuals of extreme old age. We have demonstrated that, in individuals with a high burden of chronic disease, skeletal muscle is characterized by a preservation of type I fiber area, severe selective type II fiber atrophy, widened sarcoplasmic spaces, and Z band and myofibrillar disruption. In addition, we find that female gender, low physical activity level, undernutrition, and depression are linked to sarcopenia, extending findings that have been seen in other studies (16). This would suggest that interventions aimed specifically at stimulating type II fibers (e.g., contractions demanding high force output) may be most effective in the prevention and treatment of sarcopenia. Although hypertrophy of similar magnitude was seen in type I fibers in the combined exercise and supplement group, the response was more variable and not statistically significant in this sample.

The fact that muscle hypertrophy was linked to higher caloric intake at baseline and was only significant in those who received nutritional supplementation and exercise suggests that adequate energy balance is critical to treatment of sarcopenia with exercise in frail elders. It is notable in this regard that, in results previously published from this trial (17), we showed...
that subjects who received supplementation without exercise suppressed their habitual dietary intake so that, despite compliance with the study supplement, they had no significant net gain in calorie intake. Thus nutritional status appears to be important for muscle hypertrophy, but altering it in frail elders may require attention to physical activity levels, not simply access to additional food.

Adaptation at both the physiological and functional levels was blunted in individuals with lower calorie intakes before and during the trial, as well as in those with more depressive symptoms at baseline. These effects were independent of each other and require further investigation. These clinical factors, in addition to age, may contribute to the heterogeneous hypertrophic response to resistance training seen in previous trials in elderly populations. Most of the previous studies of resistance training in the elderly (3, 5, 19, 25, 33) demonstrate muscle fiber hypertrophy in response to exercise, although the responses are variable (27), and two report no significant hypertrophy (1, 4). When these studies are examined in relation to subject age, there is a significant inverse relationship between type II fiber hypertrophy within the vastus lateralis and mean age of the study group, as shown in Fig. 7, suggesting age and/or age-related disease may moderate the degree of cellular adaptation to loading.

The baseline atrophy of type II fibers in our study was accompanied by levels of ultrastructural damage that have not been seen in healthy subjects at younger ages (12). The etiology of this damage is unknown, but alterations such as the age-related impairment in the ATP-dependent ubiquitin pathway regulating protein degradation in muscle may contribute (8). Our resistance training regimen, which included eccentric contractions as the weight was lowered, markedly increased the baseline damage. Whereas acute experimental damage is accompanied by edema, neutrophil and cytokine localization in muscle tissue (18), and has been shown to be associated with delayed-onset muscle soreness and reduced force-generating capacity (29, 30), the long-term adaptation to the milder eccentric component during resistance training in this study was, by contrast, characterized by damage associated with large gains in strength. This suggests that not all damage is alike and, when accompanied by regenerative processes, such as shown here, may in fact be a positive adaptation to stress. Whether such damage is essential to strength gains or whether it occurs in concentric only weight lifting is unknown at this time.

Our biopsy results suggest that the early adaptation to progressive resistance training includes such muscle damage as a step in a remodeling process that ultimately leads to muscle regeneration. We have demon-

![Fig. 6. Immunofluorescent micrograph of transverse sections of the vastus lateralis stained for IGF-I. A: exercise subject, baseline (magnification, ×1700). A small amount of IGF-I staining is seen in pericellular areas but not within fibers. B: same exercise subject as in A, after 10 wk of training (magnification, ×1700). Positive staining for IGF-I is seen diffusely increased, both at the borders of cells and within the cytoplasm of large and small fibers.](http://ajpendo.physiology.org/entire/10.220.32.246)
Regeneration after injury (22). Growth factors, including IGF-I, have been shown to increase during recovery from overload injury induced by ablation of synergistic muscles in rats (9). Our novel finding that IGF-I appearance in mature human skeletal muscle accompanies standard resistance training suggests that it may be a mechanism of increased protein synthesis required for new or hypertrophied myofibril formation during recovery from mechanical load-induced damage. Neither endurance training (36) nor resistance training (33, 34) in healthy elders has been shown to augment circulating levels of growth hormone or IGF-I, in contrast to findings in young adults (37). Additionally, exogenous administration of growth hormone or IGF-I has not been shown to augment muscle function in older subjects (32, 35). Such findings have led to speculation that blunted responsiveness to growth hormone may limit muscle adaptation in the elderly. However, in our study, increases in strength were proportional to the large increases in IGF-I immunoreactivity in the muscle after training, which was linked to damage and developmental myosin appearance, suggesting that endogenous, local modulation of IGF-I is possible with appropriate physical stimuli and is of continuing importance to muscle regeneration in the very elderly.

In conclusion, we have shown for the first time in human skeletal muscle simultaneous appearance of ultrastructural damage and developmental myosin and IGF-I immunoreactivity in response to resistance training. Compared with some previous training studies, the extent of hypertrophy induced may have been attenuated by the presence of factors that we have now identified to be linked to muscle fiber atrophy in this population (very advanced age, inactivity, depressive symptoms, and nutritional status), but functional gains were nonetheless substantial. Age-related sarcopenia clearly has modifiable contributants, and skeletal muscle retains remarkable plasticity in individuals as old as 98 yr of age. Future preventive and rehabilitative strategies for age-related sarcopenia should be designed to maximally exploit this potential.

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References


