Normal somatomedin-C/insulin-like growth factor I binding and action in cultured human fibroblasts from Turner syndrome

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Abstract. Growth retardation is a major manifestation of Turner syndrome (TS). Since plasma growth hormone and somatomedin-C/insulin-like growth factor I (SM-C/IGF-I) levels are generally normal, growth failure has been ascribed to peripheral defects in SM-C/IGF-I receptors or action. We have measured the binding of $^{125}$I-SM-C/IGF-I to cultured fibroblast monolayers derived from patients with Turner syndrome, and have evaluated SM-C/IGF-I stimulation of both $^3$H$\text{thymidine}$ incorporation and cell replication. When compared to fibroblasts from normal adults, newborns, and age-matched children, no significant differences were observed in specific binding of $^{125}$I-SM-C/IGF-I to fibroblast monolayers, and displacement curves demonstrated similar receptor affinities for all groups. Similarly, equivalent SM-C/IGF-I stimulation of $^3$H$\text{thymidine}$ incorporation was seen in both Turner and control fibroblasts. In the absence of serum, SM-C/IGF-I, at a concentration of 10–25 ng/ml, stimulated thymidine incorporation 3.7–11.8-fold in Turner fibroblasts and 1.9–9.8-fold in control cells. In combination with 1.0% human hypopituitary serum (HHS), SM-C/IGF-I stimulated thymidine incorporation 20–70-fold in all cell lines. Cell replication in both TS and control cells was increased 90% by the combination of SM-C/IGF-I + 0.5% HHS, and 140% by SM-C/IGF-I + 0.5% HHS + dexamethasone. We conclude that TS fibroblasts have normal SM-C/IGF-I receptors and sensitivity, and are capable of enhanced DNA synthesis and replication following SM-C/IGF-I stimulation.

Growth retardation is a cardinal feature of Turner syndrome, affecting virtually 100% of children with 45,XO karyotypes, and 75–100% of children with structural abnormalities of the X chromosome or mosaicism (Simpson 1974; Palmer & Reichmann 1976). Previous studies have demonstrated normal basal and stimulated growth hormone levels in subjects with Turner syndrome, as well as normal plasma levels of somatomedin-C/insulin-like growth factor I (SM-C/IGF-I) (Almquist et al. 1963; Daughaday et al. 1969; Morabito et al. 1978; Rudman et al. 1981). Accordingly, it has been suggested that a primary defect in Turner syndrome might be peripheral resistance to SM, secondary to an abnormality in SM binding or SM stimulation of cell replication (Almquist et al. 1963; Daughaday et al. 1969; Morabito et al. 1978; Rudman et al. 1981).

The cultured human fibroblast offers an excellent model for the evaluation of SM binding and action, since these non-transformed cells are easily obtained, can be cultured in defined medium, and lend themselves readily to experimental manipulation. High affinity receptors for SM-C/IGF-I have been previously characterized in both fibroblast suspensions (Rechler et al. 1977) and monolayers (Rosenfeld & Dollar 1982), and the mitogenic action of SM in this cell system has been defined, at least in a preliminary manner (Rechler et al. 1974; Clemmons & Van Wyk 1981; Conover et al. 1983).

In the studies to be presented in this report, we have employed cultured human fibroblast monolayers to investigate SM-C/IGF-I binding and stimulation of $^3$H$\text{thymidine}$ incorporation and cell replication in cells from subjects with Turner syndrome.

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Materials and Methods

Cell culture
Human fibroblasts of dermal origin were obtained by punch biopsy of the forearm or subscapular region, or were purchased form the Human Mutant Genetic Cell Repository (Camden, NJ). Human newborn fibroblasts were derived from foreskin resection. Table 1 lists the 10 separate fibroblast lines employed in these studies.

Cells were cultured in Dulbecco’s minimum essential medium (DMEM), obtained from Grand Island Biological Co. (Gibco; Grand Island, NY), supplemented with 20% foetal bovine serum (Tissue Culture Biological; Tulare, CA), glutamine (4 mM; Gibco), penicillin (100 U/ml) and streptomycin (100 µg/ml). Cells were grown in 250-ml Falcon flasks (Falcon Plastics; Los Angeles, CA) at 37°C in a humidified atmosphere containing 5% CO2.

Table 1.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Karyotype</th>
<th>Donor age (years)</th>
<th>Sex</th>
<th>PDL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T993</td>
<td>45,XO</td>
<td>9</td>
<td>F</td>
<td>9-15</td>
</tr>
<tr>
<td>T1176</td>
<td>45,XO</td>
<td>8</td>
<td>F</td>
<td>9-15</td>
</tr>
<tr>
<td>T225</td>
<td>91% 45,XO</td>
<td>5</td>
<td>F</td>
<td>8-15</td>
</tr>
<tr>
<td>9% 46,XX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1723</td>
<td>45,XO</td>
<td>23</td>
<td>F</td>
<td>9-13</td>
</tr>
</tbody>
</table>

| Normals   |           |                   |     |      |
| NRG5      | 46,XY     | 33                | M   | 13-18|
| N238      | 46,XY     | 35                | M   | 7-12 |
| N239      | 46,XY     | 35                | F   | 7-12 |
| N337      | 46,XY     | 25                | M   | 9-11 |
| N964      | 46,XY     | 33                | M   | 16-18|
| N498      | 46,XY     | 3                 | M   | 13-17|
| N3348     | 46,XY     | 10                | M   | 9-12 |
| N9302     | 46,XY     | newborn           | M   | 8-14 |
| NHFF3     | 46,XY     | newborn           | M   | 8-16 |

* Population doubling.

Materials

Thymidine, dexamethasone and bovine serum albumin were purchased from Sigma Chemical Co. (St. Louis, MO). Thymidine-([3H]methyl) (20 Ci/mmol) and protocol were obtained from New England Nuclear Co. (Boston, MA) and Scintiverse was purchased from Fisher Scientific Corp. (Fairlawn, NJ). [125I]sodium iodide was obtained from Amersham Corp. (Arlington Heights, IL).

SM-C/IGF-I was purified by our previously published methods (Rosenfeld & Dollar 1982). After acid-ethanol extraction, gel filtration chromatography, thin-layer isoelectric focusing and Sephadex G-50 chromatography, fractions were collected and assayed by SM-C/IGF-I RIA, using the National Pituitary Agency antisem (Furlanetto et al. 1977), and by a RIA develop against the eight-amino acid C-peptide segment of IGF-II (Hintz & Liu 1982). The isolated active peptide had a pi of 8.0, and was found to have a SM-C/IGF-I concentration of 6615 ng/ml, with no detectable IGF-II. This preparation was employed to prepare [125I]SM-C/IGF-I, to a specific activity of 250-300 µCi/µg, using the method of Hunter & Greenwood (1962).

Because of the scarcity of purified SM-C/IGF-I, a partially purified SM-C/IGF-I preparation was employed for the standard binding curves and for some of the in vitro stimulation experiments. This preparation was an acid-ethanol extract of Cohn fraction IV-I, purified short of isoelectric focusing. The SM-C/IGF-I content was 25 µg/mg weight, and the IGF-II content was 12 µg/mg weight. This preparation will be subsequently designated SM in the text, and the SM-C/IGF-I concentration stated.

Human hypopituitary serum was obtained from 4 donors with growth hormone deficiency, documented by failure to raise serum GH levels above 7 ng/ml following arginine-insulin stimulation. SM-C/IGF-I concentrations in these sera ranged from 29–80 ng/ml (normal adult 150–250 ng/ml)

SM-C/IGF-I binding assay

Fibroblasts were subcultured into 60 × 15 mm tissue culture dishes and grown to confluence. All binding experiments were performed 3–5 days after the last feeding with complete medium. Cell counts at the time of assay were always between 1–2 million cells/dish, and there were no significant differences in cell number among the experimental groups. Binding assays were performed directly on the cell monolayers, as previously described (Rosenfeld & Dollar 1982).

[3H]Thymidine incorporation

Three–5 days after plating in 4 ml of DMEM with 20% FCS, cells were incubated in DMEM + 0.1% bovine serum albumin for 48 h. At that point, the medium was changed to 1) fresh DMEM + 0.1% BSA (serum-free medium), or 2) DMEM + 0.1% BSA + SM-C/IGF-I, or 3) DMEM + 0.1% BSA + human hypopituitary serum (0.5 or 1.0%), or 4) DMEM + 0.1% BSA + SM-C/IGF-I + human hypopituitary serum. At 21 h, 50 µl of [3H]thymidine was added, to yield a final concentration of 0.2 µCi/ml. Cells were harvested at 23 h by washing monolayers twice with 4 ml of ice cold phosphate buffered saline, followed by
the addition of 1 ml of cold 5% trichloroacetic acid (TCA). Cells were scraped off the dish with a rubber policeman and transferred to a 12 × 75 mm disposable borosite tube (American Scientific Products; McGaw Park, IL). The dish was rinsed with an additional ml of 5% TCA, which was then transferred to the tube. The combined supernatants were centrifuged at 3000 r.p.m., and the resulting pellet was drained, and then solubilized overnight in 0.5 ml of protosol. Duplicate 0.1 ml aliquots of the solubilized pellet were then counted in 5 ml of Scintiverse acidified with 25 µl of 2 N HCl.

**Cell replication**

Fibroblast monolayers were plated in DMEM supplemented with 20% FCS. Cells were allowed to attach for 24 h, and the medium was then changed to the experimental medium (see Results and figure legends). Addition of the experimental medium was designated day 0. The medium was changed on day 2, and cell number determined by Coulter Counter on day 4.

**Results**

**SM-C/IGF-I binding**

The binding of [125I]SM-C/IGF-I to fibroblast monolayers from subjects with Turner syndrome and controls is shown in Table 2. At the time of

<table>
<thead>
<tr>
<th>Table 2. [125I]SM-C/IGF-I binding to fibroblasts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Line</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td><strong>Turner</strong></td>
</tr>
<tr>
<td>T993</td>
</tr>
<tr>
<td>T1176</td>
</tr>
<tr>
<td>T225</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td><strong>Normal adult</strong></td>
</tr>
<tr>
<td>NRGR</td>
</tr>
<tr>
<td>N238</td>
</tr>
<tr>
<td>N239</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td><strong>Normal newborns</strong></td>
</tr>
<tr>
<td>N9302</td>
</tr>
<tr>
<td>NHFF3</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td><strong>Normal children</strong></td>
</tr>
<tr>
<td>N498</td>
</tr>
<tr>
<td>N3348</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

* Binding is expressed as per cent specifically bound per million cells, ± the standard deviation. Data represent the means of triplicate or sextuplicate determinations on each cell line.
Table 3.
Stimulation of [3H]thymidine incorporation.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>SFM*</th>
<th>SM-C 10 ng/ml</th>
<th>HHS 1%</th>
<th>SM-C + HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1176</td>
<td>0.077**</td>
<td>0.405 (5.2)***</td>
<td>0.219</td>
<td>1.90 (24.5)</td>
</tr>
<tr>
<td>T1723</td>
<td>0.028</td>
<td>0.154 (5.5)***</td>
<td>0.350</td>
<td>1.35 (48.2)</td>
</tr>
<tr>
<td>T993</td>
<td>0.042</td>
<td>0.220 (5.2)***</td>
<td>0.122</td>
<td>0.70 (16.7)</td>
</tr>
<tr>
<td>N964</td>
<td>0.040</td>
<td>0.053 (2.8)</td>
<td>0.134</td>
<td>0.38 (8.1)</td>
</tr>
<tr>
<td>NRGR</td>
<td>0.050</td>
<td>0.139 (2.8)</td>
<td>0.193</td>
<td>0.63 (12.5)</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1176</td>
<td>0.046</td>
<td>0.301 (6.5)</td>
<td>0.269</td>
<td>1.04 (22.3)</td>
</tr>
<tr>
<td>T1723</td>
<td>0.116</td>
<td>0.429 (3.7)</td>
<td>0.946</td>
<td>1.82 (15.6)</td>
</tr>
<tr>
<td>T993</td>
<td>0.044</td>
<td>0.302 (6.9)</td>
<td>0.506</td>
<td>3.08 (69.9)</td>
</tr>
<tr>
<td>NRGR</td>
<td>0.076</td>
<td>0.187 (2.5)</td>
<td>0.458</td>
<td>0.95 (12.5)</td>
</tr>
<tr>
<td><strong>Experiment 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1176</td>
<td>0.34</td>
<td>3.23 (9.5)</td>
<td>0.84</td>
<td>11.24 (33.1)</td>
</tr>
<tr>
<td>T993</td>
<td>0.12</td>
<td>1.42 (11.8)</td>
<td>0.58</td>
<td>4.19 (34.9)</td>
</tr>
<tr>
<td>N238</td>
<td>0.10</td>
<td>0.98 (9.8)</td>
<td>0.81</td>
<td>7.19 (71.9)</td>
</tr>
<tr>
<td>NRGR</td>
<td>0.14</td>
<td>1.27 (9.1)</td>
<td>0.97</td>
<td>8.28 (59.1)</td>
</tr>
<tr>
<td>N239</td>
<td>0.22</td>
<td>0.59 (2.7)</td>
<td>0.92</td>
<td>4.30 (19.5)</td>
</tr>
<tr>
<td>N337</td>
<td>0.13</td>
<td>1.28 (9.8)</td>
<td>1.19</td>
<td>8.48 (65.2)</td>
</tr>
<tr>
<td>N498</td>
<td>0.29</td>
<td>1.95 (6.7)</td>
<td>1.32</td>
<td>14.67 (50.6)</td>
</tr>
</tbody>
</table>

Three—5 days after plating in 4 ml of DMEM with 20% FCS, cells were incubated in DMEM + 0.1% BSA for 48 h. At that point, the medium was changed to fresh DMEM + 0.1% BSA plus 1) SFM: serum-free medium, or 2) SM-C: somatomedin-C (10 ng/ml in experiment 1 and 2; 25 ng/ml in experiment 3), or 3) HHS: human hypopituitary serum (1% in experiments 1 and 2; 0.5% in experiment 3), or 4) SM-C + HHS. At 21 h, 50 µl of [3H]thymidine was added, to yield a final concentration of 0.2 µCi/ml. Cells were harvested at 23 h, as described in Materials and Methods.

* Serum free medium.
** Per cent incorporation of [3H]thymidine. Each entry represents the mean of triplicate determinations.
*** Numbers in parentheses indicate % incorporation in SFM

In vivo, all cultures were visually confluent, with cell counts ranging from 1.22—1.99 million cells/dish; there were no significant differences among study groups in cell number at the time of assay. Mean specific binding of [125I]SM-C/IGF-I to monolayers from 3 subjects with Turner syndrome ranged from 4.86—6.61% per million cells, with a mean of 5.68%. These values were virtually identical to those seen in control subjects (mean specific binding 5.25% in newborns, 6.35% in age-matched children, and 5.85% in adults).

The displacement of [125I]SM-C/IGF-I from fibroblast monolayers by unlabelled SM is depicted in Fig. 1. Fifty per cent receptor occupancy in fibroblasts from subjects with Turner syndrome was observed at SM-C/IGF-I concentrations of 6, 7, and 3 ng/ml, compared to adult control values of 6, 6, and 5 ng/ml.

**Stimulation of [3H]thymidine incorporation**

The stimulation of [3H]thymidine incorporation in fibroblasts from subjects with Turner syndrome...
and from normal controls is shown in Table 3. The data presented in this table summarize three representative experiments. In experiments 1 and 2, fibroblasts were incubated in the presence or absence of 10 ng/ml SM-C/IGF-I and/or 1% human hypopituitary serum. In experiment 3, SM-C/IGF-I and HHS concentrations were 25 ng/ml and 0.5%, respectively. In the absence of serum, SM-C/IGF-I stimulated $[^3]H$thymidine incorporation into Turner fibroblasts 3.7–11.8-fold. Under identical conditions, stimulation of control fibroblasts ranged from 1.3–9.8-fold.

Table 3 also shows that the mitogenic action of SM is synergistic with hypopituitary serum, even at low concentrations of both. When fibroblasts were simultaneously incubated with SM-C/IGF-I (10–25 ng/ml) and human hypopituitary serum (0.5–0.1%), $[^3]H$thymidine incorporation was increased 15–70-fold in cells from Turner syndrome, and 8–72-fold in control cells. No significant differences were observed among the groups in the magnitude of stimulation by either SM-C/IGF-I or by the combination of SM-C/IGF-I plus hypopituitary serum.

**Stimulation of cell replication**

Although incorporation of $[^3]H$thymidine is a commonly employed marker of mitogenic activity, incorporation may be influenced by other factors, such as alterations in pool size and membrane transport. Fig. 2 shows the effect of SM-C/IGF-I upon cell replication, as reflected by increases in cell number. SM-C/IGF-I, by itself, only weakly stimulated cell replication. However, as was shown in the thymidine incorporation experiments, the combination of SM-C/IGF-I plus low concentra-

![Cell Replication Graph](image)

**Fig. 2.**

Stimulation of fibroblast replication. Fibroblast monolayers from lines N498 and T1176 were plated in DMEM supplemented with 20% foetal calf serum. Cells were allowed to attach for 24 h, and the medium was changed to the experimental medium (noted on the abscissa) on day 0. The medium was replaced by fresh medium on day 2, and cell number determined on day 4. Data are expressed as the per cent of the cell count of fibroblasts grown in DMEM alone. Each bar represents the mean ± SD of triplicate determinations. DEX: dexamethasone (0.1 µM); SM-C (25 ng/ml); HHS: human hypopituitary serum (0.5%).
tions of human hypopituitary serum proved to be synergistic. In the presence of 0.5% hypopituitary serum, SM-C/IGF-I (25 ng/ml) increased cell number by 95% in fibroblasts from Turner syndrome, and by 90% in the control.

We have previously demonstrated that while dexamethasone, alone, has little mitogenic activity in human fibroblasts, and may actually blunt the stimulatory effects of serum, there exists a striking synergism between SM-C/IGF-I, serum and dexamethasone (Conover et al. 1983). In the experiment shown in Fig. 2, the combination of SM-C/IGF-I (25 ng/ml), human hypopituitary serum (0.5%) and dexamethasone (0.1 µM) resulted in 140–150% increases in cell number in fibroblasts from both the subject with Turner syndrome and the control. In similar experiments, this combination consistently approached the mitogenic activity of 20% FCS.

Discussion

Although short stature is an almost universal characteristic of Turner syndrome, the etiology of growth retardation in this condition is still uncertain. Almqvist et al. (1963) measured sulphation factor activity in 22 subjects with Turner syndrome; 9 had normal sulphation factor activity, while 12 demonstrated increased activity, occasionally in the acromegalic range. Similarly, Daughaday et al. (1969) found normal or elevated sulphation factor activity in 12 girls with Turner syndrome, and Morabito et al. (1978) reported normal SM-A levels in 10 adolescents with Turner syndrome. On the basis of these studies, it was proposed that the growth failure of Turner syndrome might be secondary to peripheral unresponsiveness to SM. This hypothesis was seemingly supported by the recent report of normal radioimmunoassayable SM-C levels in 5 children with Turner syndrome (Rudman et al. 1981). Furthermore, while GH treatment of these subjects resulted in a 100% increase in plasma SM-C levels, the regression slope of height vs SM-C level was significantly lower than that observed in normal and growth hormone deficient children, further supporting the concept of peripheral unresponsiveness in Turner syndrome.

In previous studies in achondroplastic dwarfism, employing mononuclear cells, we observed quantitatively and qualitatively normal SM-C receptors (Rosenfeld & Hintz 1980). In the present study, we have compared cultured human fibroblast monolayers from subjects with Turner syndrome and normal controls, thus allowing us to both characterize SM-C/IGF-I receptors and to evaluate cellular responsiveness to SM stimulation of thymidine incorporation and cell replication. The cultured fibroblast has proven to be a valuable tool for the evaluation of intrinsic receptor and/or post-receptor disorders, since the cell is cultured in defined medium, removed from the metabolic milieu of the patient (Griffin 1979; Podskalny & Kahn 1982). Previous studies have employed the cultured fibroblast to identify inborn defects in SM-C/IGF-I binding and/or action in leprochaunism (Van Obberghen-Schilling et al. 1981; Kaplowitz & D’Ercole 1982). Furthermore, recent investigations from our laboratory have shown that the fibroblast monolayer provides a convenient system for the simultaneous evaluation of SM-C/IGF-I receptors and sensitivity (Conover et al. 1983).

The experiments presented here demonstrate that the binding of [125I]SM-C/IGF-I to fibroblast monolayers from Turner syndrome is indistinguishable from that seen in a variety of controls. Competition studies show that receptors from Turner an control cells have equivalent affinities for SM-C/IGF-I, with 50% displacement of [125I]SM-C/IGF-I occurring at concentrations of unlabelled SM-C/IGF-I similar to those previously reported for human foreskin fibroblasts (Rosenfeld & Dollar 1982).

Two different measures of cellular responsiveness to mitogenic stimulation were employed in these studies: 1) [3H]thymidine incorporation and 2) cell replication, assessed by increase in cell number. The time course of SM-C/IGF-I stimulation of [3H]thymidine incorporation was identical in Turner and control cells, and SM-C/IGF-I, alone, induced similar increases in incorporation. Low concentrations of human hypopituitary serum, containing less than 1 ng/ml of radioimmunoassayable SM-C/IGF-I, also stimulated [3H]thymidine incorporation equally in both experimental groups. Previous investigations have indicated that the full mitogenic activity of whole serum can be attributed to a combination of 'competence factors' (such as platelet-derived growth factor) and 'progression factors' (such as SM-C/IGF-I), which promotes recruitment of cells from Go and traverse of G1, to
reach S phase (Stiles et al. 1979). When we simultaneously exposed fibroblast monolayers to 0.5–1.0% human hypopituitary serum (which is SM-C/IGF-I poor, but contains competence factors) and SM-C/IGF-I, a striking synergistic stimulation of thymidine incorporation was observed in both Turner and control cells. The most stringent test of cellular responsiveness to mitogenic stimulation is increased cell replication. When serum-deprived cells were exposed to SM-C/IGF-I, alone, little enhancement of cell number was observed. As was the case with thymidine incorporation, the combination of SM-C/IGF-I and hypopituitary serum synergistically stimulated an increase in cell number, and equivalent responses were observed in Turner and control cells. We have recently reported that glucocorticoids, which by themselves or in combination with hypopituitary serum have virtually no stimulatory effect in human fibroblasts, show an impressive synergism with SM-C/IGF-I and hypopituitary serum in the stimulation of fibroblast replication (Conover et al. 1983). Thus, both Turner and control cells had a 140% increase in cell number following 4 days' exposure to SM-C/IGF-I (25 ng/ml) + hypopituitary serum (0.5%) + dexamethasone (0.1 μM). This represents a striking stimulation of cell replication, approaching that observed with 20% foetal calf serum.

The data presented indicate that cultured fibroblasts from Turner syndrome have normal SM-C/IGF-I receptors, and respond appropriately to SM-stimulation of DNA synthesis and cell replication. These conclusions must, at this point, be restricted to the fibroblast cell line, and should not a priori be extrapolated to other actively dividing cells, such as chondrocytes at the epiphysial growth plates. Nevertheless, it is clear that Turner syndrome is not characterized by a generalized intrinsic defect in either SM-C/IGF-I binding or action. Whether the growth failure of Turner syndrome is attributable to localized defects in responsiveness to SM-C/IGF-I, or represents a cellular abnormality which is independent of the growth hormone-somatedin axis remains to be determined.

References


Rosenfeld R G & Dollar L A (1982): Characterization of the somatomedin-C/insulin-like growth factor I (SM-C/IGF-I) receptor on cultured human fibroblast mono-

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