Local Injection of Hepatocyte Growth Factor/Scatter Factor (HGF/SF) Alters Cyclic Growth of Murine Hair Follicles

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Hepatocyte growth factor/scatter factor (HGF/SF) has recently been shown to stimulate the hair follicle growth of mouse vibrissae *in vitro*. In this study, we analyzed the effect of cutaneous injections of recombinant human HGF/SF on hair follicle growth using mice in different hair cycle stages. Five male newborn mice, five male mice in second anagen, and five male mice in second telogen were administered a dorsal intradermal injection of 1 μg HGF/SF dissolved in 0.1% albumin-phosphate-buffered saline once daily for five or seven consecutive days, and then sacrificed on days 7 or 10. Hair follicle growth was evaluated photometrically and histologically using three parameters: the skin color of the reverse side of the resected skin, the skin thickness, and the area occupied by hair follicle tissue. The HGF/SF injected skin of newborn mice had hair follicles that were histologically longer and larger than those of the 0.1% albumin-phosphate-buffered saline injected skin. Mice that had received HGF/SF injection in second anagen, retained anagen hair follicles after 10 d only at the injection site, suggesting that HGF/SF delayed the transition from anagen to telogen. The HGF/SF injected skin of telogen mice had a significant increase in hair follicle tissue in the dermis, suggesting a mild anagen inducible activity by HGF/SF. Furthermore, precise measurements of the 20 hairs plucked from the HGF/SF injection sites revealed mild hair elongation in all the aforementioned experiments. These results imply that HGF/SF acts as a paracrine factor that alters cyclic hair growth of mice. *Key words: hair cycle/hair growth/mouse. J Invest Dermatol 110:338–342, 1998*

Hepatocyte growth factor/scatter factor (HGF/SF) is a multifunctional heterodimeric polypeptide originally identified as a mitogen for hepatocytes (for review see Rubin *et al*, 1993; Matsumoto and Nakamura, 1994; Zarnegar and Michalopoulos, 1995). HGF/SF has been thought to be secreted by mesenchymally derived cells and to function as a paracrine factor on neighboring epithelial or endothelial cells. Mitogenic, motogenic, and morphogenic activities of HGF/SF vary with the target cells and experimental conditions.

We recently reported that HGF/SF stimulated the hair follicle growth of mouse vibrissae (Jindo *et al*, 1994) and human scalp hairs (Jindo *et al*, 1995) in an organ culture system. We subsequently reported that HGF/SF stimulated DNA synthesis of hair bulb derived keratinocytes with the strongest response at 30 ng HGF/SF per ml (Shimaoka *et al*, 1995). Furthermore, HGF/SF expressed in cultured follicular papilla cells was upregulated in response to interleukin (IL)-1α and tumor necrosis factor (TNF)-α (Shimaoka *et al*, 1995).

For a series of experiments clarifying the stimulatory effect of HGF/SF on hair growth, we designed an *in vivo* experiment using mice having well-known hair cycles. Because the molecular size of HGF/SF is too large to be absorbed from the skin surface, dissolved HGF/SF was injected intradermally to the dorsal skin on consecutive days. Hair follicle growth was evaluated photometrically and histologically. To examine the anagen-preservable and anagen-inducible activities of HGF/SF, mice in second anagen and second telogen, as well as newborn mice, were used for the experiments. Basic fibroblast growth factor (bFGF), which is known to retard hair development in neonatal mice (du Cros, 1993), was also examined for comparison.

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Abbreviations: bFGF, basic fibroblast growth factor; BSA-PBS, bovine serum albumin-phosphate-buffered saline; HGF/SF, hepatocyte growth factor/scatter factor.

MATERIALS AND METHODS

Reagents Recombinant human HGF/SF (five amino acids-deleted form) was donated by Snow Brand Milk Products (Tokyo, Japan) (Shima *et al*, 1991). Recombinant human bFGF was purchased from R&D Systems (Minneapolis, MN). These reagents were dissolved in sterile and toxin-free phosphate-buffered saline containing 0.1% bovine serum albumin (0.1% BSA-PBS) (Sigma, St. Louis, MO).

Animals and treatment Animals used in this study were obtained from Japan SLC (Hamamatsu, Japan), and maintained on a standard laboratory diet and water *ad libitum*. The experimental design of this study was approved by the appropriate ethical committee on animal study in Juntendo University. The mice hairs were neither clipped nor shaved except for the experiment that measured hair elongation in clipped second telogen mice. Male B6C3F1 mice (F1: C57BL6 × C3H, 1 d old; body weight, 1.4–1.5 g) were administered a dorsal intradermal injection of 1 μg HGF/SF or bFGF dissolved in 50 μl of 0.1% BSA-PBS once daily for 5 d (total 5 μg). All mice were sacrificed on day 7, and one skin sample per mouse was prepared. In other experiments, 29 d old male C3H mice (second anagen phase; body weight, 16.6–21.2 g) and 45 d old male C3H mice (second telogen phase; body weight, 22.2–25.4 g) were administered a dorsal intradermal injection of 1 μg HGF/SF or bFGF in 50 μl of 0.1% BSA-PBS once daily for 7 d (total 7 μg), and then sacrificed on day 10. Control mice of the same age were injected with 50 μl of 0.1% BSA-PBS once daily for 5 or 7 d. Each mouse received one treatment only, and each treated group consisted of five mice from different litters.

Evaluation The effect of the local injection of HGF/SF on hair follicle growth was analyzed photometrically and histologically. The skin color of the

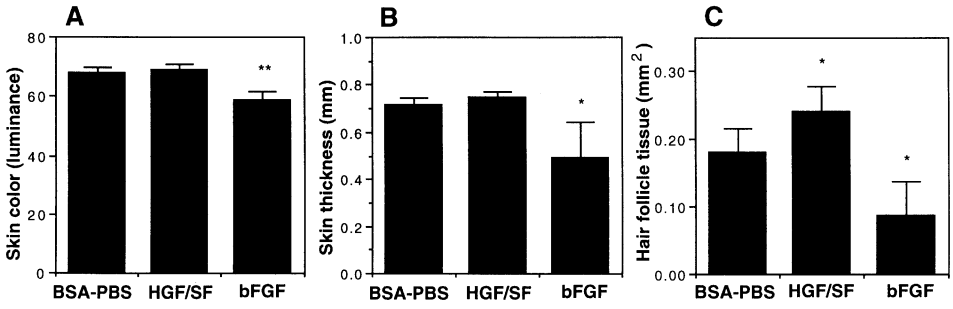

Figure 1. Local injection of HGF/SF promoted hair follicle growth in newborn mice. HGF/SF, bFGF, or vehicle solution (0.1% BSA-PBS) was injected intradermally into 1 d old B6C3F1 mice for 5 d (total 5 μg). The mice were sacrificed on day 7, and the effect of the reagents on hair follicle growth assessed as described in *Materials and Methods* using three parameters: (*A*) skin color, (*B*) skin thickness, and (*C*) hair follicle tissue. Data are expressed as mean ± SD of five mice. * $p < 0.05$, ** $p < 0.01$.

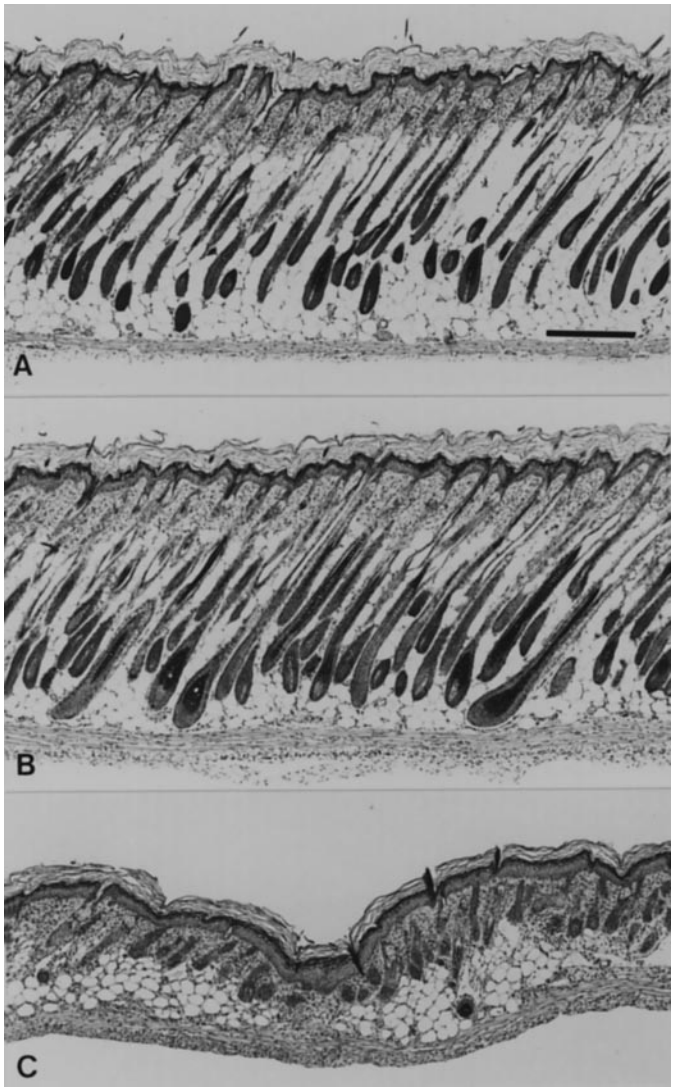

Figure 2. The HGF/SF injected newborn mouse had histologically longer and larger hair follicles. Histologic sections typical from the data summarized in **Fig 1** are shown: (*A*) 0.1% BSA-PBS; (*B*) HGF/SF (1 μg × 5 d); (*C*) bFGF (1 μg × 5 d). *Scale bar*, 0.5 mm.

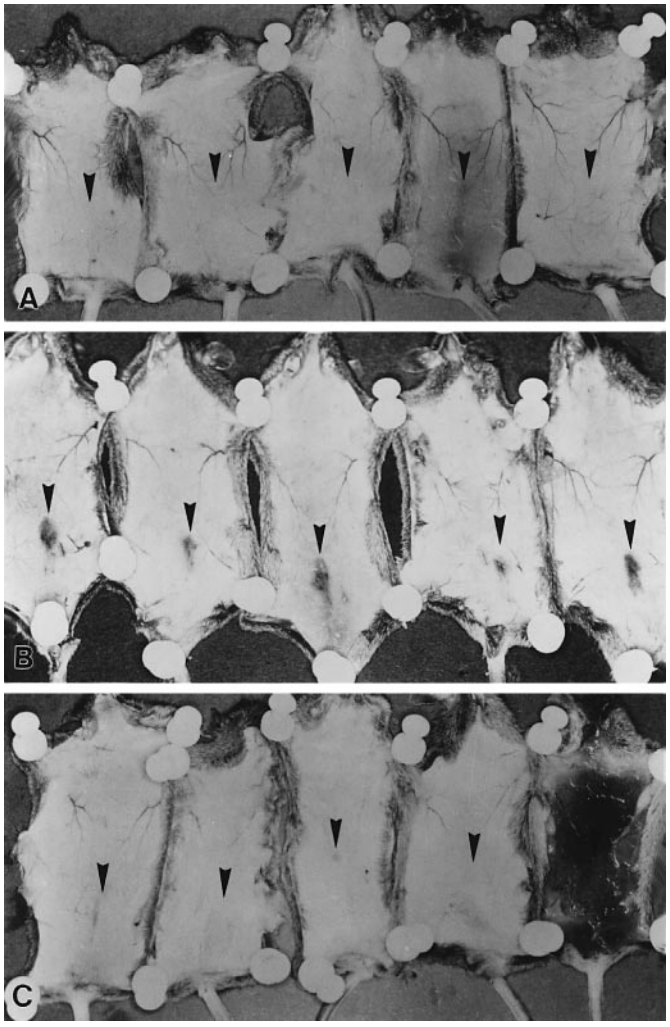

Figure 3. Local injection of HGF/SF prolonged the second anagen. HGF/SF, bFGF, or vehicle solution (0.1% BSA-PBS) was injected intradermally into 29 d old male C3H mice (the second anagen) for 7 d (total 7 μg), and then the mice were sacrificed on day 10. The photographs shown are the reverse side of the resected murine skin: (*A*) 0.1% BSA-PBS; (*B*) HGF/SF (1 μg × 7 d); (*C*) bFGF (1 μg × 7 d). The *arrowheads* indicate the injection sites.

reverse side of the resected murine skin was measured three times in the proximity of the injection site within a 8 mm diameter field by a Minolta Chroma Meter (CR-300, Minolta, Tokyo, Japan) (Queille-Roussel *et al*, 1991). The luminance measured reflects the relative darkness ranging from white (0) to black (100). The darkness of the reverse side of murine skin varied due to the increase in the melanization of the hair follicle. The skin sample resected from the injection site was then fixed in 10% buffered formalin solution and paraffin embedded. A 4 μm thick section was stained with hematoxylin and eosin, and then analyzed histologically by an image analyzer (Mac scope, Mitani, Fukui, Japan). Skin thickness, which has been shown to correspond to hair follicle length (Andreasen, 1953), was defined as the distance from the epidermal granular layer to the top edge of the panniculus carnosus. Measurements were carried out in three fields, and their average value per mouse was expressed in millimeters. The size of the hair follicle was estimated by considering the histologic area occupied by the hair follicles per 1 mm^2 field of the dermis and subcutaneous tissue. Measurements were carried out in three fields, and their

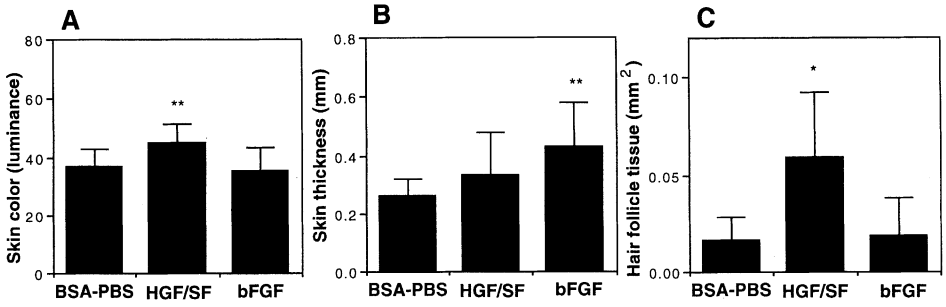

Figure 4. Local injection of HGF/SF delayed the transition from anagen to telogen. The results shown in **Fig 3** were quantitatively analyzed using the same methods as described in **Fig 1**: (*A*) skin color, (*B*) skin thickness, and (*C*) hair follicle tissue. Data are expressed as mean ± SD of five mice. *$p < 0.05$, **$p < 0.01$.

average values expressed in millimeters squared. In order to examine the effect of HGF/SF on hair length, hairs in the proximity of the injection site were plucked by forceps under a stereoscopic microscope, and their length measured by a micrometer. To confirm that the hairs had been plucked in their entirety, the morphology of every hair tip was checked under a stereoscopic microscope. The average length of the 20 plucked hairs was expressed in millimeters.

Statistical analysis The data from the tested groups were compared with those of the 0.1% BSA-PBS injected group, and analyzed by Student's unpaired t test. Results were expressed as mean ± SD.

RESULTS

Local injection of HGF/SF promoted hair follicle growth in newborn mice Male B6C3F1 mice generally produced black hairs and dark skin at the age of 5 d. Intradermal injection of HGF/SF or 0.1% BSA-PBS for five consecutive days did not produce any macroscopic change; however, injection of bFGF produced a pale and sclerotic skin appearance and fewer hairs (data not shown). Histologic sections at the injection sites were prepared, and hair follicle growth evaluated quantitatively using the three parameters illustrated in **Fig 1**. As defined in *Materials and Methods*, the relative darkness of the reverse side of the resected skin corresponds to the increase in melanization of the hair follicle, the skin thickness corresponds to hair follicle length, and hair follicle tissue corresponds to the area occupied by the hair follicles. As shown in **Fig 1(*A*)**, skin darkness (white, 0; black, 100) was significantly suppressed in bFGF injected mice ($p < 0.01$), whereas that of HGF/SF injected mice was not affected. When compared with BSA-PBS injected mice, the skin of HGF/SF injected mice showed a slight increase in skin thickness and a significant increase in hair follicle tissue ($p < 0.05$) (**Fig 1*B*, *C***). In contrast, the skin of bFGF injected mice showed a significant decrease both in skin thickness ($p < 0.05$) and in hair follicle tissue ($p < 0.05$) (**Fig 1*B*, *C***). **Figure 2** shows histologic sections typical of those summarized in **Fig 1**. HGF/SF treated skin (**Fig 2*B***) had longer and larger hair follicles than 0.1% BSA-PBS treated skin. bFGF treated skin had many immature hair follicles and an increase in connective tissue under the panniculus carnosus. The thickness of the dermal and subcutaneous tissues varied with hair follicle length (**Fig 2*A*–*C***). The data shown in **Figs 1** and **2** were found to be reproducible in two other smaller sized experiments. Moreover, significantly increased skin thickness and hair follicle tissue ($p < 0.05$) were observed when five newborn rats were treated with 1 μg HGF/SF daily for five consecutive days (data not shown).

Local injection of HGF/SF into anagen mice delayed the transition from anagen to telogen Positive results in newborn mice led us to examine further the effect of HGF/SF on cyclic hair growth in adult mice. A preliminary experiment confirmed that 29 d old male C3H mice are generally in the second anagen, and 10 d later they are in the second telogen. Accordingly, HGF/SF, bFGF, or vehicle solution (0.1% BSA-PBS) was injected intradermally into 29 d old mice for seven consecutive days (total 7 μg), and the mice were then sacrificed on day 10. The results were analyzed using the same methods as described for newborn mice, and are illustrated in **Figs 3–5**. When HGF/SF was injected intradermally, a striking result was observed on day 10 (**Fig 3*B***). The areas in close proximity to the injection site of

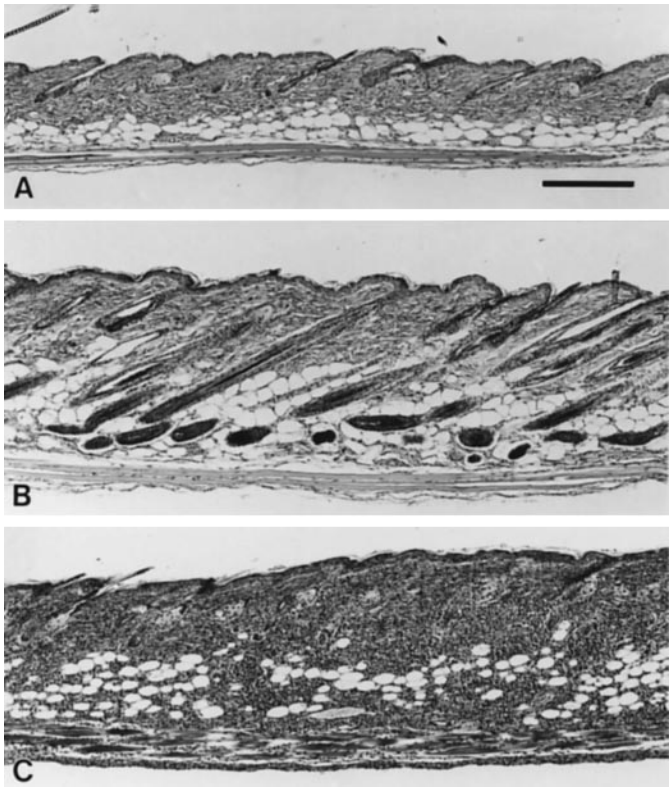

Figure 5. The HGF/SF injected anagen mouse retained histologically anagen hair follicles. Histologic sections typical from the data summarized in **Fig 4** are shown: (*A*) 0.1% BSA-PBS; (*B*) HGF/SF (1 μg × 7 d); (*C*) bFGF (1 μg × 7 d). *Scale bar*, 0.5 mm.

all five mice were still dark in color, and therefore in anagen, whereas the remaining areas of the HGF/SF treated mice and the injection sites of the 0.1% BSA-PBS treated mice were pale in color, suggesting that they were in telogen. These data are supported by the quantitative analyses shown in **Fig 4**. The skin of HGF/SF injected mice was dark in color ($p < 0.01$), and was thicker and had a larger amount of hair follicle tissue ($p < 0.05$). A typical histologic section (**Fig 5*B***) clearly demonstrates that the HGF/SF treated skin had anagen hair follicles, though the number of hair follicles was less than that of regular skin in anagen. In contrast, the areas around the bFGF injected site had teleangiectasia, probably due to the angiogenetic activity of bFGF (**Fig 3*C***). One mouse in the bFGF treated group was found to be in anagen phase rather than second telogen, due to the variation in hair cycle of individual animals (**Fig 3*C***). Quantitative analyses revealed that the skin thickness of four bFGF treated mice had significantly increased ($p < 0.01$) (**Fig 4*B***) due to the increased connective tissue with many mononucleated cells in the dermis and subcutaneous tissue (**Fig 5*C***). The control site injected with 0.1% BSA-PBS was

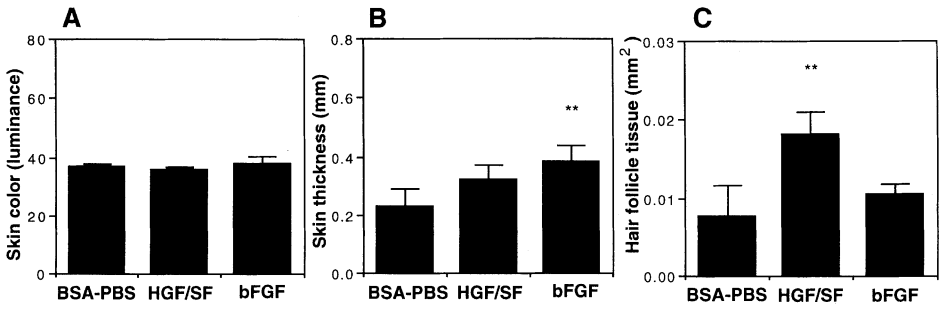

Figure 6. Local injection of HGF/SF into telogen mice increased the size of hair follicles. HGF/SF, bFGF, or vehicle solution (0.1% BSA-PBS) was injected intradermally into 45 d old male C3H mice (the second telogen) for 7 d (total 7 μg), and the mice were then sacrificed on day 10. The results were quantitatively analyzed using the same methods as described in **Fig 1**: (*A*) skin color, (*B*) skin thickness, and (*C*) hair follicle tissue. Data are expressed as mean ± SD of five mice. *$p < 0.05$, **$p < 0.01$.

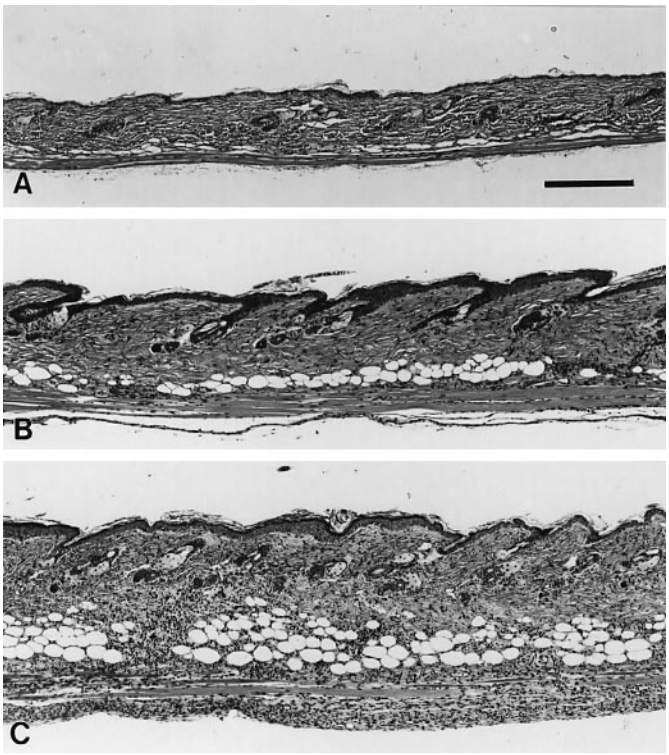

Figure 7. The HGF/SF injected telogen mouse had histologically larger hair follicles. Typical histologic sections from the data summarized in **Fig 6** are shown: (*A*) 0.1% BSA-PBS; (*B*) HGF/SF (1 μg × 7 d); (*C*) bFGF (1 μg × 7 d). *Scale bar*, 0.5 mm.

indistinguishable from the surrounding skin for all parameters (data not shown).

Local injection of HGF/SF into telogen mice exhibited a mild anagen inducible activity Subsequently, induction of anagen hairs by HGF/SF injection was examined using mice in telogen. HGF/SF, bFGF, or vehicle solution (0.1% BSA-PBS) was injected intradermally into 45 d old male C3H mice (second telogen) for seven consecutive days (total 7 μg), and the mice were then sacrificed on day 10. Macroscopic and photometric observation did not reveal any anagen-inducible activity by HGF/SF; however, microscopic analysis pointed out a significant increase in hair follicle tissue ($p < 0.01$) (**Fig 6*C***). HGF/SF injected mice (**Fig 7*B***) had histologically larger hair follicles in the dermis than those of 0.1% BSA-PBS injected mice, although they were not complete anagen hair follicles. The same study using male C3H mice in late second telogen (86 d old) was then carried out, and the results obtained were almost identical with the data described above (data not shown). The effect of a local administration of bFGF on murine skin in telogen was the same as that observed in anagen skin. bFGF treatment increased the skin thickness (**Fig 6*B***), which was caused by an increase in cell infiltration and connective tissue in the dermis and subcutaneous tissue (**Fig 7*C***).

Local injection of HGF/SF slightly elongated the hair length Because no macroscopic increase in hair number or length was observed upon HGF/SF injection, precise measurements of the hair shaft at the HGF/SF injection sites were carried out by measuring the plucked hair length. The HGF/SF was injected for 7 d into newborn mice (1 d old), second anagen mice (29 d old), second telogen mice (45 d old), and clipped second telogen mice (45 d old), and, 10 d later, 20 hairs were collected from each of the five mice of each group. As shown in **Fig 8**, hairs collected from the HGF/SF injected mice were slightly longer for all four different conditions than those collected from the 0.1% BSA-PBS injected mice or from the noninjected sites of the treated mice; however, no statistical significance was observed due to the variation in individual hair length.

DISCUSSION

Recently, particular families of cytokines and growth factors have been reported to be involved in the regulation of hair morphogenesis and cyclic hair growth (for review see Messenger, 1993; Stenn *et al*, 1994). Such factors include epidermal growth factor, transforming growth factor-α, transforming growth factor-β, FGF-1 (acidic FGF), FGF-2 (bFGF), FGF-5, FGF-7 (keratinocyte growth factor, KGF), insulin-like growth factor-I, IL-1α, and HGF/SF. The influence of these molecules on hair growth has been demonstrated by immunohistochemical studies, external administration of the proteins, and phenotypic observation of the mice with a targeted gene deletion or overexpression. The external administration of such growth factors was initially expected to stimulate hair growth *in vivo*; however, epidermal growth factor (Moore *et al*, 1983) and bFGF (du Cros, 1993) were reported as retarding hair growth in animal models. A recent study has reported that subcutaneous injections of KGF at a daily dose of 5 μg per gram of body weight for 13 or 17 consecutive days stimulated hair growth in athymic nude mice, and when administered by intraperitoneal injection protected cytosine arabinoside-induced alopecia in neonatal rat (Danilenko *et al*, 1995). In this study, we demonstrated that a growth factor named HGF/SF alters the hair cycle and slightly increases the hair length in normal mice when 1 μg of the protein was administered intradermally for five or seven consecutive days. Although the amount of hair elongation was not to the level of that stimulated by chemical reagents such as FK506 and cyclosporin A, it is worth noting that a direct growth regulatory ligand influenced hair growth.

Unlike human hairs, murine hair coat has a synchronized hair cycle. Anagen in mice can easily be distinguished from telogen by skin color, skin thickness, and the amount of melanogenesis-related proteins (Andreasen, 1953; Slominski *et al*, 1991). We previously reported that the skin color of C3H mice in telogen (milky pink) became zonally dark (gray to black) when a hair growth stimulatory reagent was locally applied (Hattori and Ogawa, 1983). To test the effect of HGF/SF *in vivo*, we initially used this method; however, macroscopic observation

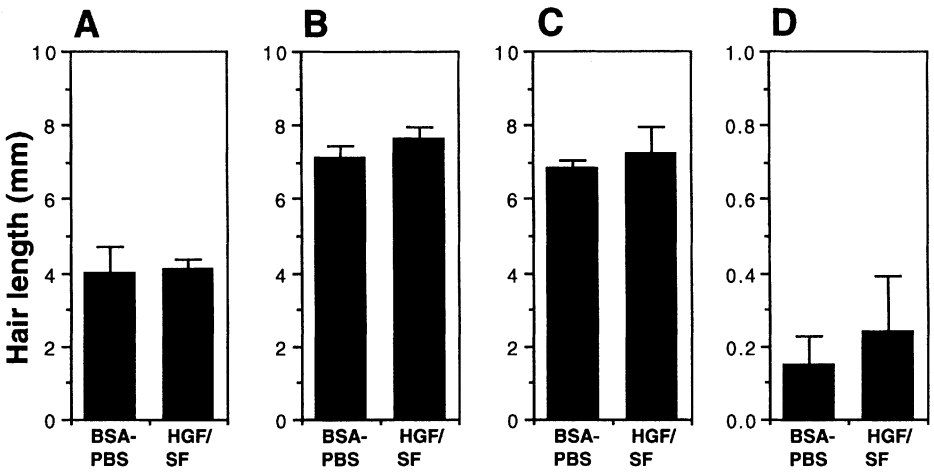

Figure 8. Local injection of HGF/SF slightly elongated the hair length. HGF/SF (1 μg) was injected intradermally into four different groups of mice for 7 d (total 7 μg), and all mice were sacrificed on day 10. Twenty hairs in the proximity of the injection site were plucked, and their length measured by a micrometer. (*A*) newborn mice (1 d old); (*B*) second anagen mice (29 d old); (*C*) second telogen mice (45 d old); (*D*) clipped second telogen mice (45 d old). Data are expressed as mean ± SD of five mice.

after the intradermal injection did not reveal any significant increase in skin pigmentation or hair length. We therefore performed accurate evaluations by measuring the color of the reverse side of the resected murine skin, the histologic skin thickness and hair follicle tissue, and the exact length of the plucked hairs. The color of the reverse side of the skin reflects the increase in melanization in anagen, and the two histologic parameters reflect the size of each hair follicle. We were not able to monitor the hair length of the living mice due to the thinness of the hair shafts and their high density.

We clearly demonstrated that HGF/SF has anagen-preservable and mild anagen-inducible activities, which resulted in mild hair elongation. Although we could not test the effect of higher doses of HGF/SF due to its limited supply, 1 μg HGF/SF per ml appeared to be sufficient to produce effects on hair follicle growth, with our *in vitro* study showing that the effect of HGF/SF in cultured cells and organ culture plateaued at a dose of 10–30 ng per ml. The reliability of the findings in this study was ensured by repeating the experiments and by the negative effects induced by the administration of bFGF in a simultaneously performed experiment (du Cros, 1993). Our previous data indicated that HGF/SF mRNA is expressed in single human anagen hair follicles (Mitsui *et al*, 1997) and in cultured follicular papilla cells (Shimaoka *et al*, 1995); however, the level of immunoreactive HGF/SF protein secreted from cultured follicular papilla cells was not high (Shimaoka *et al*, 1995). A circulating inactive form of HGF/SF and papilla cells-secreted HGF/SF may bind to heparin in the extracellular matrix, and further to the HGF/SF receptor (c-Met) on the hair matrix cells after processing by the proteinases. HGF/SF stimulated keratinocyte growth (Sato *et al*, 1995) and DNA synthesis of hair bulb derived keratinocytes (Shimaoka *et al*, 1995); however, the mitogenic activity of HGF/SF on keratinocytes appeared to be significantly milder than that of KGF (Sato *et al*, 1995), and only HGF/SF revealed hair follicle growth stimulatory activity in organ culture among numerous growth factors, including KGF, insulin-like growth factor-I, and transforming growth factor-α (Jindo *et al*, 1994). These results imply that the effect of HGF/SF on hair follicle growth is mainly due to its morphogenic activity for epithelial cells (Rubin *et al*, 1993; Matsumoto and Nakamura, 1994; Zarnegar and Michalopoulos, 1995). Further *in vivo* studies to examine the effect of HGF/SF, reconstituted in liposome or transfersome to cross skin barriers, are now in progress in order to evaluate the clinical utility of HGF/SF as a hair growth stimulant.

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