Mini Review

Roles of Prostaglandin E_2 and Histamine in Angiogenesis in Inflammatory Granulation Tissue

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In an air pouch-type carrageenin-induced inflammation model in rats, the selective cyclooxygenase (COX)-2 inhibitor NS-398 dose dependently inhibited the granulation tissue formation, angiogenesis and the level of vascular endothelial growth factor (VEGF) in the granulation tissue. In culture of the minced granulation tissue, PGE_2 induced VEGF production in a concentration-dependent manner. Histamine also induced VEGF production in the granulation tissue ***in vitro***. The H2 receptor antagonist cimetidine, the cAMP antagonist Rp-cAMP and the protein kinase A inhibitor H-89 suppressed the histamine-induced VEGF production in the granulation tissue. However, the H1 receptor antagonist pyrilamine maleate, the H3 receptor antagonist thioperamide, the protein kinase C inhibitors Ro31-8425 and calphostin C or the tyrosine kinase inhibitor genistein showed no effect. Subcutaneous implantation of a cotton thread in the dorsum of histidine decarboxylase-deficient ($HDC^{-/-}$) mice, but not in mast cell-deficient ($WBB6F_1$-***W/W^v***) mice, induced less angiogenesis with lower levels of VEGF in the granulation tissue than in their corresponding wild-type ($HDC^{+/+}$ and $WBB6F_1$-$^{+/+}$) mice. In $HDC^{-/-}$ mice, the topical injection of histamine or the H2 receptor agonist dimaprit rescued the defective angiogenesis and granulation tissue formation. In addition, cimetidine but not pyrilamine maleate and thioperamide inhibited the histamine-induced angiogenesis in the granulation tissue in $HDC^{-/-}$ mice. These findings suggest that PGE_2 and histamine play a significant roles in angiogenesis in the inflammatory granulation tissue via induction of VEGF production, and histamine augments VEGF production possibly through the H2 receptor-cAMP-protein kinase A pathway.

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The progress of chronic and proliferative inflammation depends on angiogenesis[1]. Angiogenesis in a chronic inflammatory state facilitates migration of inflammatory cells to the inflammatory site and supplies nutrients and oxygen to the granulation tissue[1]. Therefore, the suppression of angiogenesis is important to suppress chronic inflammatory diseases[2-6] and tumor growth[7].

Cyclooxygenase (COX) which converts arachidonic acid to prostaglandin (PG) H_2 has two isoforms, COX-1 and COX-2[8]. COX-2 is induced at the inflammatory site in an experimental inflammation model[9] and in patients with rheumatoid arthritis[10]. The injection of carrageenin into a subcutaneous air pouch of rats increased the protein levels of COX-2 in the cells lining the inner layer of the pouch and in macrophages infiltrating the pouch fluid[11]. In the recurrence of allergic inflammation model in rats, we reported that COX-2 protein is induced in the granulation tissue by antigen challenge and COX-2-derived PGE_2 participates in the vascular formation and the development of the granulation tissue[12]. It is also reported that E-type PGs, such as PGE_1 and PGE_2, enhance the angiogenesis in rabbit corneas[13] and chorioallantoic membrane of 8-day-old chicken embryos[14]. In addition, COX-2 modulates production of angiogenic factors by colon cancer cells[15] and basic fibroblast growth factor (bFGF)-induced angiogenesis[16].

Histamine plays a variety of roles as an autacoid which regulates allergic inflammatory reactions[17, 18], differentiation of leu-

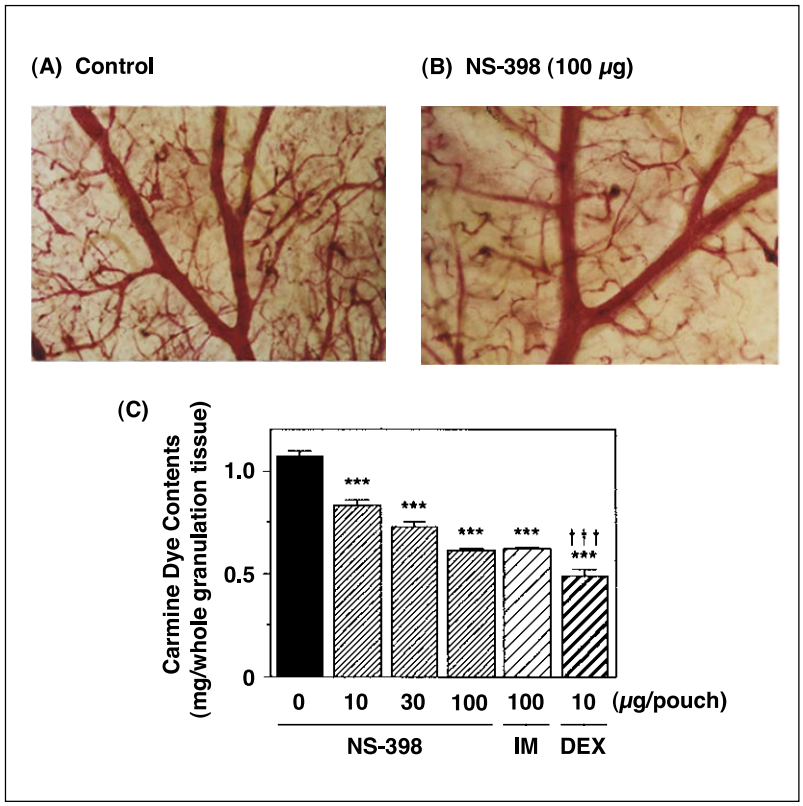

Fig. 1
Effects of NS-398, indomethacin and dexamethasone on angiogenesis in the granulation tissue 6 days after carrageenin injection[27]. Four milliliters of a 2% (w/v) carrageenin solution in saline was injected into the air pouch. NS-398 (10, 30, and 100μg), indomethacin (IM, 100μg) or dexamethasone (DEX, 10μg) dissolved in 500μl of saline was injected into the pouch 0, 2 and 4 days after carrageenin injection. Six days after carrageenin injection, 3ml of a 5% (w/v) carmine dye solution in 5% (w/v) gelatin in saline was injected intravenously into each anesthetized rat. The granulation tissue was dissected and cleared in cedarwood oil (A and B). The angiogenesis in the granulation tissue was observed by a light microscope (40 × magnification). The total carmine dye contents in the granulation tissue was determined (C). Values are the means with s.e. mean shown by vertical bars from 9 rats. Statistical significance: $^{***}p<0.001$ versus control and $^{†††}p<0.001$ versus NS-398 (100) or IM.

kocytes precursors[19] and gastric acid secretion[20], and as a neurotransmitter in the central nervous system[21]. In addition, histamine is produced in rapidly growing tissues, and suggested to promote neoplastic growth and angiogenesis[17, 22-24]. Zauberman et al.[25] first reported that histamine is angiogenic in rabbit cornea. However, the roles of PGE_2 and histamine in angiogenesis in chronic inflammation has not been fully clarified. Therefore, in this review, by employing an air pouch-type carrageenin-induced inflammation model in rats, and cotton thread-induced inflammation model in histidine decarboxylase-deficient mice ($HDC^{-/-}$) , mast cell-deficient mice ($WBB6F_1$-W/W^v) , and their corresponding wild-type mice ($HDC^{+/+}$ and WBB6F1-$^{+/+}$), we describe the roles of PGE_2 and histamine in angiogenesis in the inflammatory granulation tissue focusing in the production of VEGF.

A role of COX-2-derived PGE_2 in angiogenesis in carrageenin-induced granulation tissue in rats

Using an air pouch-type carrageenin-induced inflammation model in rats[26], we demonstrated that COX-2-derived PGE_2 plays a role in angiogenesis in the developing chronic granulation tissue[27]. From the determination of dye content in the granulation tissue and histological analysis, it was concluded that the selective COX-2 inhibitor NS-398 as well as the COX-1/COX-2 nonspecific inhibitor indomethacin inhibit the angiogenesis in the granulation tissue (Fig. 1) and inflammatory responses[27].

In the granulation tissue in the air pouch-type carrageenin-induced inflammation model in rats, COX-2-derived PGE_2 was suggested to be involved in VEGF production, because NS-398 as well as indomethacin significantly reduced VEGF contents in the granulation tissue and in the pouch fluid (Fig. 2). To clarify whether PGE_2 is involved in VEGF production, the granulation tissue from the indomethacin-treated rats in which the effect of endogenous PGE_2 on the VEGF production might be minimized, was excised, minced into 1 to 2-mm pieces with a pair of small scissors and incubated in the presence and absence of PGE_2. It was demonstrated that PGE_2 increased both the VEGF mRNA and its protein levels[27]. These findings suggested that NS-398 reduced angiogenesis by inhibiting COX-2-dependent PGE_2 production resulting in the reduction of VEGF production. NS-398 and indomethacin at l00μg inhibited PGE_2 production almost completely[27] but VEGF production and angiogenesis were inhibited only about 50% (Fig.1, 2). Thus, in the carrageenin-induced inflammation model in rats, COX-2-derived PGE_2 partially participates in the angiogenesis in the granulation tissue possibly by stimulating VEGF production.

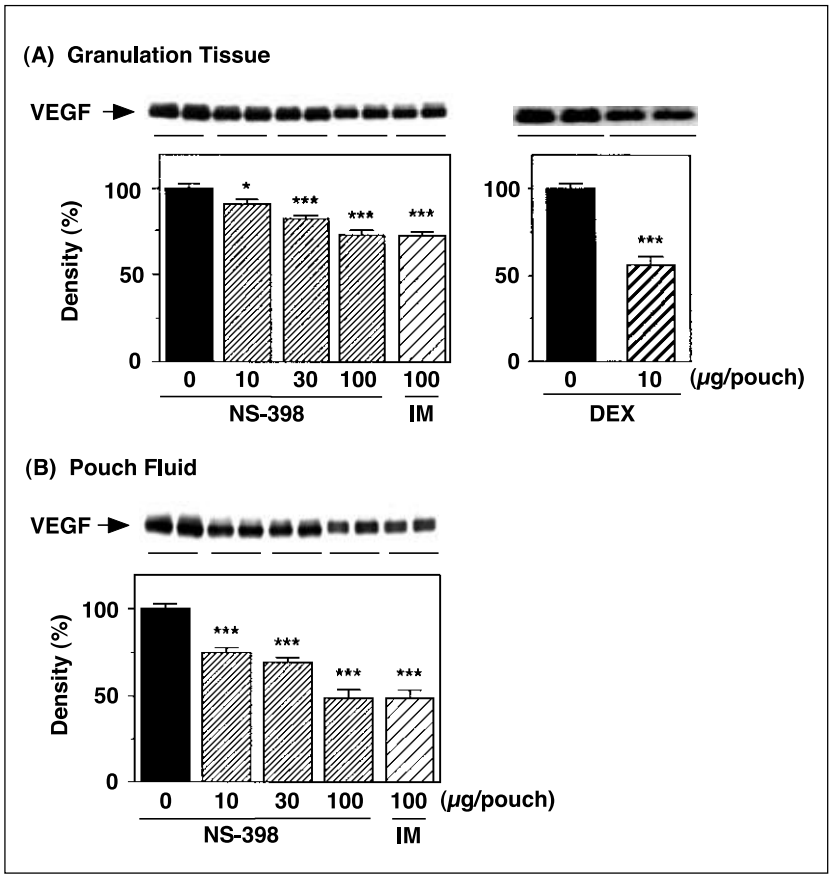

Fig. 2
Effects of NS-398, indomethacin and dexamethasone on VEGF protein levels in the granulation tissue and the pouch fluid 6 days after carrageenin injection[27]. Four milliliters of a 2% (w/v) carrageenin solution in saline was injected into the air pouch. NS-398 (10, 30, and 100μg), indomethacin (IM, 100μg) or dexamethasone (DEX, 10μg) dissolved in 500μl of saline was injected into the pouch 0, 2 and 4 days after carrageenin injection. The granulation tissue 6 days after carrageenin injection was dissected, homogenized and centrifuged. VEGF protein levels in the supernatant fraction of the homogenate of the granulation tissue (A) and the pouch fluid (B) were immunoblotted and analyzed densitometrically. The immunoblots of VEGF proteins in the granulation tissue and the pouch fluid from 2 rats in each group are shown on the top. Values are the means with s.e. mean shown by vertical bars from 6 rats. The mean density in the control group is set to 100%. Statistical significance: $^{*}p < 0.05$, $^{***}p < 0.001$ versus control.

Enhancement by histamine of VEGF expression in carrageenin-induced granulation tissue via H2 receptors

VEGF is a secreted protein[28] with several isoforms translated from alternatively spliced mRNAs[29]. In rats, there are three isoforms of VEGF protein, VEGF188, VEGF164 and VEGF120, of which mRNA are 711, 636 and 504 bp, respectively[30]. In culture of carrageenin-induced granulation tissue, histamine (1 and 10μM) increased the levels of VEGF protein and three isoforms of VEGF mRNA (Fig. 3A, B). In the ovarian epithelial carcinoma tissue in humans, Sowter et al.[31] reported that VEGF164 and VEGF120 play a significant role in the angiogenesis. However, in rats, we could not clarify each role of the three isoforms of VEGF in the angiogenesis in the carrageenin-induced granulation tissue. The VEGF-producing cells in the granulation tissue stimulated by histamine were macrophages, endothelial cells and fibroblasts[32], as reported in bFGF-induced granulation tissue in rats[33]. In isolated macrophages and fibroblasts in rats, histamine at 1 and 10μM increased the levels of VEGF mRNA [32].

In the carrageenin-induced granulation tissue, histamine induced expression of VEGF protein through the H2 receptor, because the H2 receptor antagonist cimetidine but not the H1 receptor antagonist pyrilamine or the H3 receptor antagonist thioperamide, inhibited the histamine-induced VEGF production (Fig. 4A). The possibility that histamine induces the production of VEGF by increasing PGE_2 production by the minced granulation tissue (1 to 2-mm) was excluded because indomethacin at 1μM, high enough to inhibit PGE_2 production by macrophages almost completely[34], did not inhibit the histamine-induced VEGF production[32]. In addition, although histamine induces PGE_2 production in various cells, the action is not mediated by H2 receptors[35]. Therefore, it is likely that histamine directly induces VEGF production via H2 receptors. In general, it is accepted that the stimulation of H2 receptor increases cAMP levels[36]. We found that the induction of VEGF protein by histamine in the granulation tissue is cAMP-mediated, because the histamine induced VEGF production was markedly inhibited by the cAMP antagonist Rp-cAMP and the PKA inhibitor H-89 (Fig. 4B). In contrast, PKC and the protein tyrosine kinase do not play critical roles in the VEGF induction by histamine because the PKC inhibitors Ro31-8425 (10μM) and calphostin C (l0μM), and the protein tyrosine kinase inhibitor genistein (30μM) did not inhibit the histamine-induced VEGF production (Fig. 4B). These findings suggest that the histamine-induced production of VEGF

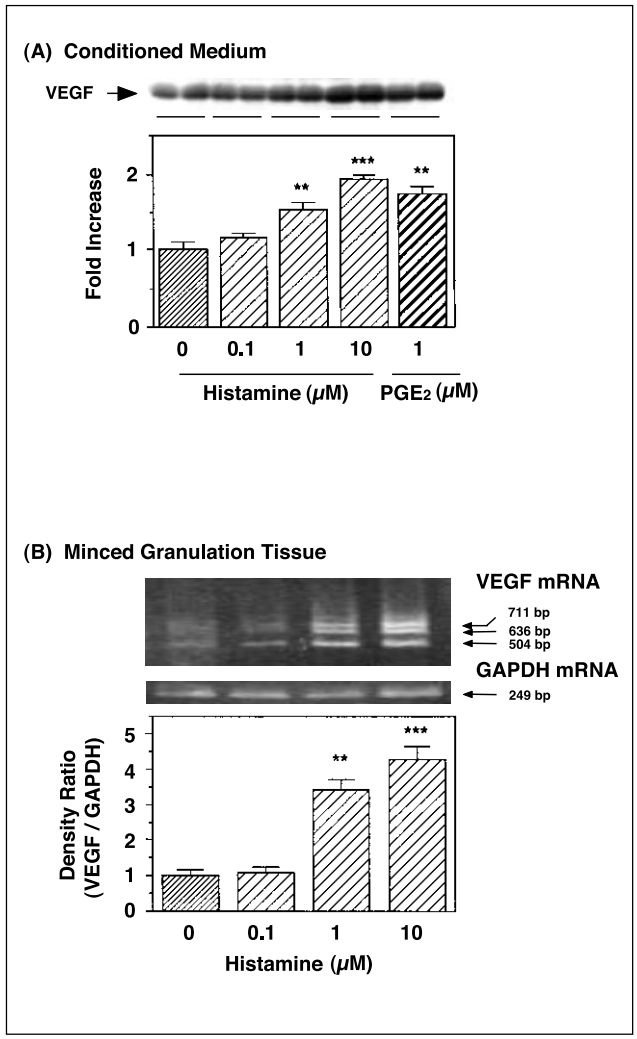

Fig. 3

Effects of various concentrations of histamine on VEGF production in the minced granulation tissue (1 to 2-mm)[32]. The minced granulation tissue (0.4g) was incubated in 4ml of EMEM containing 10% (v/v) calf serum at 37°C for 3h. After three washes, the tissue was further incubated at 37°C for 6h (A) and 1h (B) in medium containing the indicated concentrations of histamine and PGE_2. (A) VEGF protein in the conditioned medium was detected by immunoblotting and analyzed densitometrically. Representative immunoblots from two samples of each group are shown at the top. The mean VEGF protein level in the conditioned medium in the control group is set to 1.0. (B) VEGF mRNA levels in the minced granulation tissue were determined by RT-PCR and analyzed densitometrically. Representative VEGF mRNA bands are shown at the top. The mean density ratio of mRNA for VEGF to that for GAPDH in the control group is set to 1.0. Values are the means from four samples with s.e. mean shown by vertical bars.

Statistical significance: $^{**}p < 0.01$, $^{***}p < 0.001$ versus the corresponding control.

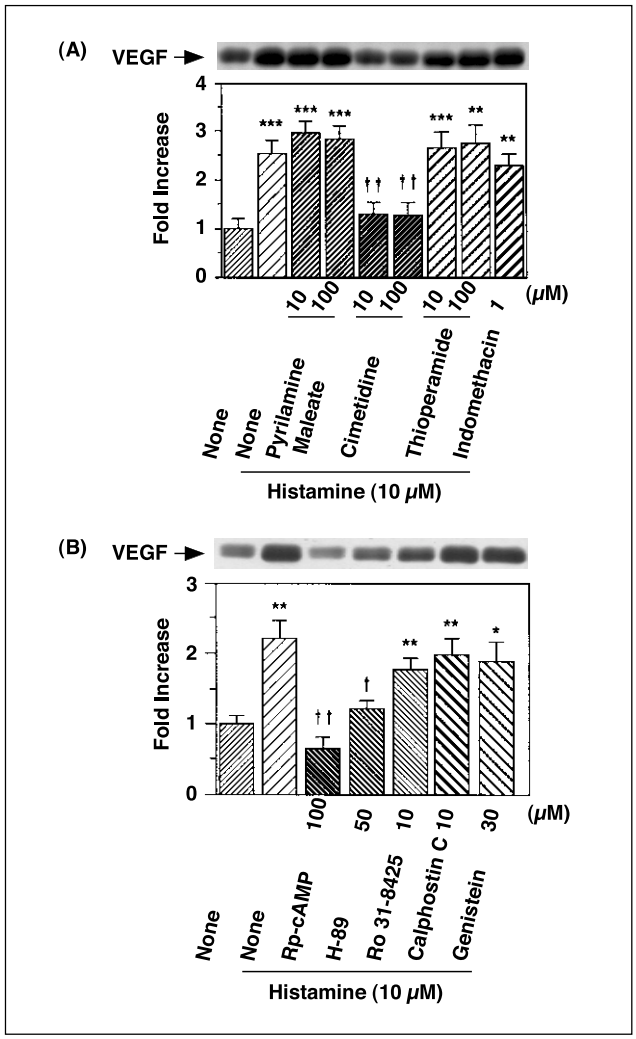

Fig. 4

Effects of histamine receptor antagonists, indomethacin, and inhibitors of PKA and PKC on VEGF protein expression induced by histamine[32]. The minced granulation tissue (1 to 2-mm, 0.4g) was incubated in 4ml of EMEM containing 10% (v/v) calf serum at 37°C for 3h. After three washes, the tissue was further incubated at 37°C for 6h in medium containing histamine (10μM) in the presence or absence of each histamine receptor antagonist or indomethacin (A), and Rp-cAMP, H-89, Ro31-8415, calphostin C or genistein (B) at the concentrations indicated. VEGF protein in the conditioned medium was detected by immunoblotting and analyzed densitometrically. Representative immunoblots are shown at the top. The mean VEGF protein level in the conditioned medium in the control group is set to 1.0. Values are the means from four samples with s.e.mean shown by vertical bars.

Statistical significance: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus control and $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$ versus histamine (10μM) alone.

in the granulation tissue is dominantly mediated by the cAMP - PKA pathway. This hypothesis is supported by the observation that histamine modulates the expression of *c-fos* through the production of cAMP via H2 receptors in a human promonocytic cell line U937[36] and *c-fos* participates in the induction of VEGF[37]. PGE_2 also induces VEGF production in a human monocytic cell line and lung tissues through the cAMP - PKA pathway[38]. Therefore, histamine and PGE_2 might activate a common signal pathway for VEGF production.

We also indicated that endogenous histamine plays a significant role in the angiogenesis in the carrageenin-induced granulation tissue in rats. The intra-pouch injection of indomethacin and cimetidine resulted in the decrease in the granulation tissue weight, VEGF protein levels both in the granulation tissue and in the pouch fluid, and the angiogenesis in the granulation tissue[32]. Consistent with our previous findings that treatment with cimetidine, 6 and 12h after the injection of carrageenin solution, increased the number of infiltrating neutrophils in the pouch fluid at 24h[39], the intra-pouch injection of cimetidine once a day for 6 consecutive days also increased the number of infiltrating neutrophils at day 6[32]. Although cimetidine increased neutrophil infiltration, it decreased infiltration of macrophages and lymphocytes, pouch fluid accumulation and angiogenesis[32]. Since indomethacin inhibits neutrophil infiltration and vascular permeability increase at the acute phase of this model[40], the inhibition of angiogenesis by indomethacin might be caused both by inhibition of VEGF production and by inhibition of acute inflammatory responses. Cimetidine also inhibited pouch fluid accumulation, infiltration of macrophages and granulation tissue formation[32]. Therefore, the possibility remains that the inhibition of angiogenesis by cimetidine was also caused both by inhibition of histamine-induced VEGF production and by inhibition of the infiltration of macrophages in which VEGF mRNA levels were increased by histamine[32]. Because cimetidine and indomethacin showed additive inhibitory effects on VEGF production and angiogenesis[32], it is suggested that histamine in addition to PGE_2 participates in VEGF production and angiogenesis in the granulation tissue in carrageenin-induced inflammation in rats.

Although there are several reports describing that cimetidine delays wound healing[41, 42], the mechanism of action has not been clarified. However, it is possible that cimetidine inhibits the histamine-mediated upregulation of angiogenesis, thus delays wound healing.

A role of non-mast cell-derived histamine in angiogenesis in cotton thread-induced granulation tissue in mice

Subcutaneous implantation of a cotton thread in mouse dorsum induced the rapid formation of granulation tissue with an apparent angiogenesis (Fig. 5A, B, C). The angiogenesis was highly dependent on VEGF production, as it was strongly inhibited by goat anti-VEGF IgG[43].

Using $HDC^{-/-}$ mice, we found that the development of angiogenesis especially in the early phase (3 to 5 days after cotton thread implantation) depends on endogenous histamine (Fig. 5A, C). The possibility that the functioning of hemangioblasts and endothelial cells is defective due to the destruction of the HDC gene was ruled out because the injection of histamine or dimaprit rescued the defective angiogenesis in $HDC^{-/-}$ mice[43]. The production of VEGF in $HDC^{-/-}$ mice was significantly less than that in $HDC^{+/+}$ mice (Fig. 5D), and the injection of dimaprit or histamine increased the VEGF levels in the granulation tissue[43]. In addition, topical injection of cimetidine inhibited the histamine-induced angiogenesis in $HDC^{-/-}$ mice[43]. Therefore, we concluded that endogenous histamine enhances VEGF production via H2 receptors.

Although it is known that histamine production is increased in rapidly growing tissues[39, 44], the histamine-producing cells have not yet been identified. It has been reported that the number of mast cells in the rapidly growing tissues increases[45] and mast cell-derived histamine is angiogenic[46]. However, we found that HDC activity in the tissue surrounding the implanted cotton thread including the skin, cutaneous muscle layer, subcutaneous tissues and the granulation tissue increased even in mast cell-deficient ($WBB6F_1$-W/W^v) mice[43]. In addition, histochemical analysis of the granulation tissue dissected 5 days after the cotton thread implantation indicated the absence of mast cells in the granulation tissue. In contrast, HDC-producing cells in the granulation tissue were identified as infiltrating macrophages[43]. Histamine production by non-mast cells was observed in mouse skin treated with PMA[47], in various tissues such as liver and lung in IL-1-treated mice[48], and in the infiltrating leukocytes in allergic inflammation in rats[49]. Our findings did not exclude the possibility that mast cells in the granulation tissue and the surrounding tissues release histamine. Because the cotton thread implantation induced an apparent angiogenesis in $WBB6F_1$-W/W^v mice as well as in $WBB6F_1$-$^{+/+}$ mice (Fig. 6A, B), we concluded that histamine from infiltrating macrophages play a significant role in angiogenesis of the granulation tissue.

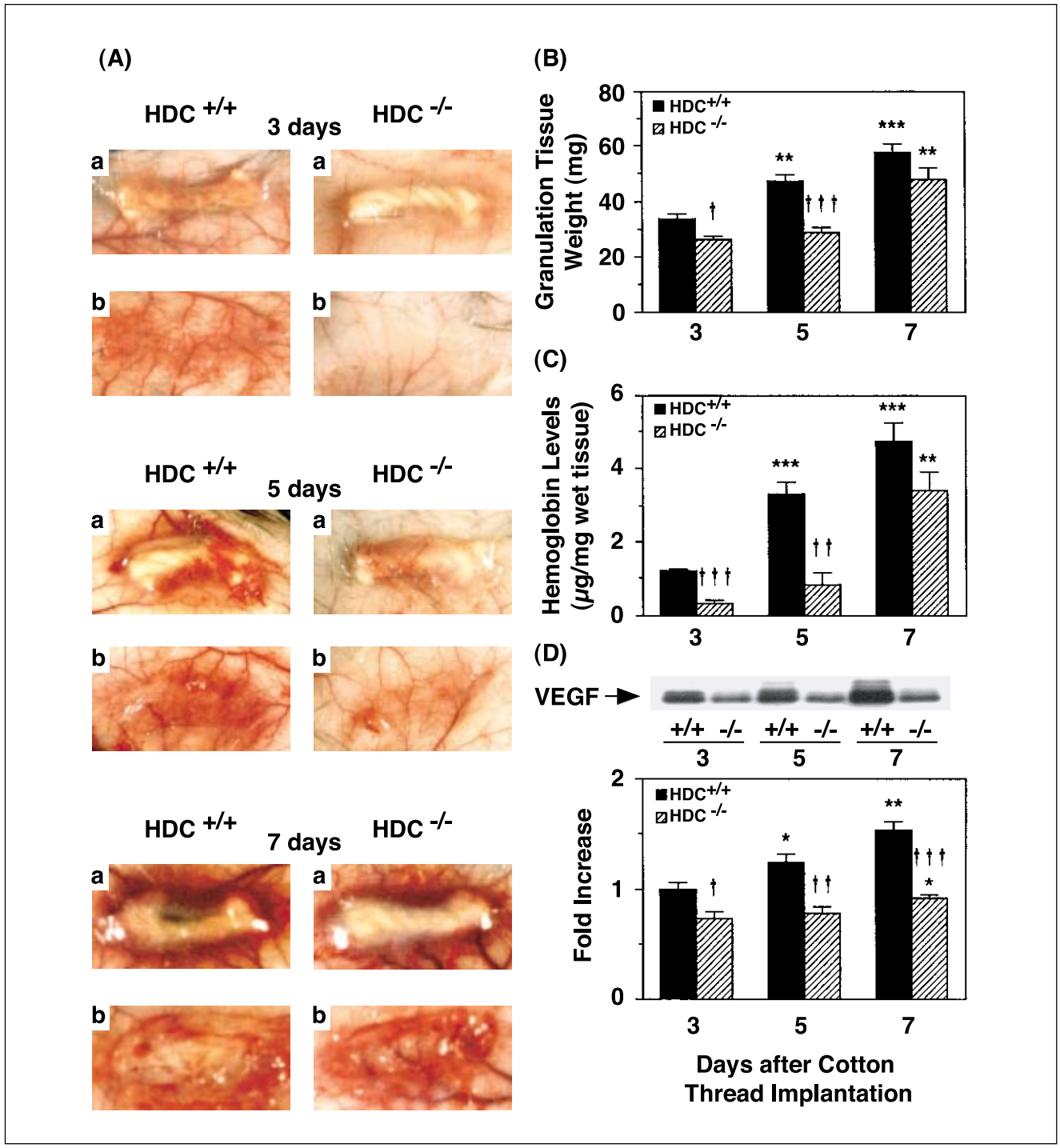

Fig. 5

The defective angiogenesis in HDC$^{-/-}$ mice. A cotton thread (1cm, 7mg) was implanted subcutaneously in the dorsum of each mouse[43]. The mice were sacrificed 3, 5 and 7 days after cotton thread implantation. (A) The vascular network formation around the cotton thread (a) and the subcutaneous tissue beneath the cotton thread (b). (B) The granulation tissue weight. (C) Hemoglobin levels in the granulation tissue. (D) VEGF protein levels in the granulation tissue. VEGF protein levels in the granulation tissue were determined by immunoblotting and analyzed densitometrically. Representative immunoblots from one mouse in each group are shown at the top of (D). The mean VEGF protein level in the granulation tissue 3 days after cotton thread implantation in HDC$^{+/+}$ mice is set to 1.0. Values are the means from five mice with s.e. mean shown by vertical bars.

Statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with values at 3 days in HDC$^{+/+}$ mice and $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ compared with values in HDC$^{+/+}$ mice at corresponding days.

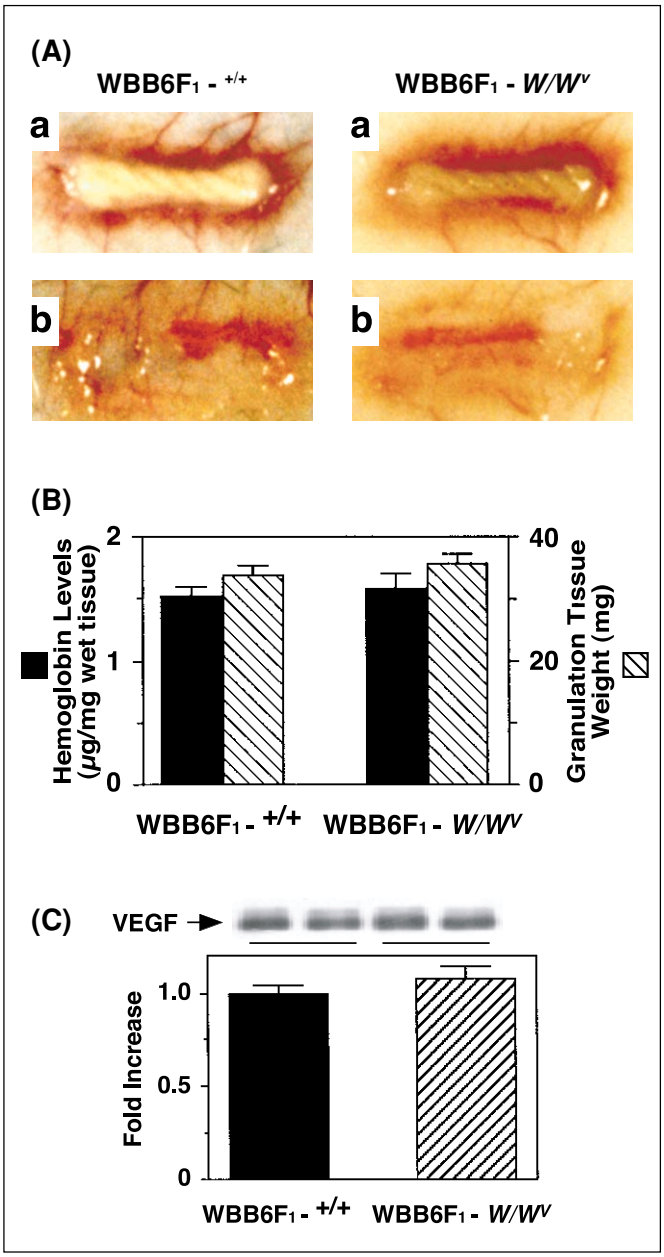

Fig. 6

Comparison of granulation tissue formation between WBB6F$_1$-$^{+/+}$ and WBB6F$_1$-***W/W^v*** mice[43]. A cotton thread (1cm, 7mg) was implanted subcutaneously in the dorsum of each mouse. The mice were sacrificed 5 days after the cotton thread implantation. (A) The vascular network formation around the cotton thread (a) and the subcutaneous tissue beneath the cotton thread (b) . (B) The granulation tissue weight and hemoglobin levels in the granulation tissue. (C) VEGF protein levels in the granulation tissue. VEGF protein levels in the granulation tissue were determined by immunoblotting and analyzed densitometrically. Representative immunoblots from 2 mice in each group are shown at the top of (C). The mean VEGF protein level in the granulation tissue of WBB6F$_1$-$^{+/+}$ mice is set to 1.0. Values are the means from five mice with s.e. mean shown by vertical bars.

It is reported that cimetidine, an H2 antagonist, delays wound healing especially in peptic ulcer[42], but its mechanism of action has not been clarified. We found that cimetidine reduces VEGF production in the carrageenin-induced inflammation model in rats[32]. In the cotton thread-induced inflammation model in mice[43], treatment with cimetidine showed partial but significant inhibition of angiogenesis and VEGF production. Therefore, we hypothesized that cimetidine delays wound healing by inhibiting histamine-mediated VEGF production and angiogenesis. In addition, because cimetidine inhibits tumor growth *in vivo*[41], there is a possibility that the growth of some tumors may also be regulated by histamine-mediated angiogenesis.

Our findings that the defective angiogenesis in the inflammatory granulation tissue in histidine decarboxylase-deficient mice but not in mast cell-deficient mice, suggest that histamine derived from non-mast cells plays a significant role in the angiogenesis in the inflammatory granulation tissue.

Regulation of angiogenesis is a new approach to treat chronic inflammation as well as solid tumor growth because anti-angiogenic therapy is demonstrated as much safer and better tolerated compared to conventional chemotherapy. Therefore, the approach to investigate the roles of chemical mediators of inflammation in regulation of angiogenesis in inflammatory granulation tissue might be hold a great promise to treat angiogenesis-dependent inflammatory diseases.

Conclusion

The chemical mediators of inflammation, PGE_2 and histamine, directly induce VEGF production and play significant roles in angiogenesis in inflammation. In addition, it was suggested that H2 receptor antagonists as well as COX-2 inhibitors, are useful for the suppression of angiogenesis-dependent formation of inflammatory granulation tissue, and conversely, H2 receptor agonists enhance angiogenesis in wound healing and several ischemic diseases.

References

1) Jackson JR, Seed MP, Kircher CH, Willoughby DA, Winkler JD: The codependence of angiogenesis and chronic inflammation. FASEB J, 11: 457-465, 1997.
2) Colville-Nash PR, Scott DL: Angiogenesis and rheumatoid arthritis: pathogenic and therapeutic implications. Ann Rheum Dis, 51: 919-925, 1992.
3) Sueishi K, Yonemitsu Y, Nakagawa K, Kaneda Y, Kumamoto M, Nakashima Y: Atherosclerosis and angiogenesis. Its

pathophysiological significance in humans as well as in an animal model induced by the gene transfer of vascular endothelial growth factor. Ann New York Acad Sci, 811: 311-322, 1997.

4) Ishibashi T, Murata T, Kohno T, Ohnishi Y, Inomata H: Peripheral choriovitreal neovascularization in proliferative diabetic retinopathy: histopathologic and ultrastructural study. Ophthalmol, 213: 154-158, 1999.
5) Li VW, Li WW: Cyclosporine and angiogenesis in psoriasis. J Am Acad Dermatol, 35: 1019-1021, 1996.
6) Thurston G, Murphy TJ, Baluk P, Lindsey JR, McDonald DM: Angiogenesis in mice with chronic airway inflammation: strain-dependent differences. Am J Pathol, 153: 1099-1112, 1998.
7) Folkman J: Angiogenesis in cancer, vascular, rheumatoid and other disease. Nature Med, 1: 27-31, 1995.
8) Herschman HR: Regulation of prostaglandin synthase-1 and prostaglandin synthase-2. Cancer Metastasis Rev, 13: 241-256, 1994.
9) Appleton I, Tomlinson A, Mitchell JA, Willoughby DA: Distribution of cyclooxygenase isoforms in murine chronic granulomatous inflammation. Implications for future anti-inflammatory therapy. J Pathol, 176: 413-420, 1995.
10) Crofford LJ, Wilder RL, Ristimaki AP, Sano H, Remmers EF, Epps HR, Hla T: Cyclooxygenase-1 and -2 expression in rheumatoid synovial tissues. Effects of interleukin-1β, phorbol ester, and corticosteroids. J Clin Invest, 93 : 1095-1101, 1994.
11) Masferrer JL, Zweifel BS, Manning PT, Hauser SD, Leahy KM, Smith WG, Isakson PC, Seibert K: Selective inhibition of inducible cyclooxygenase 2 *in vivo* is antiinflammatory and nonulcerogenic. Proc Natl Acad Sci USA, 91: 3228-3232, 1994.
12) Niki H, Tominaga Y, Watanabe-Kobayashi M, Mue S, Ohuchi K: Possible participation of cyclooxygenase-2 in the recurrence of allergic inflammation in rats. Eur J Pharmacol, 320: 193-200, 1997.
13) Ziche M, Jones J, Gullino PM : Role of prostaglandin E_1 and copper in angiogenesis. J Natl Cancer Inst, 69: 475-482, 1982.
14) Form DM, Auerbach R: PGE_2 and angiogenesis. Proc Soc Exp Biol Med, 172: 214-218, 1983.
15) Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN: Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell, 93: 705-716, 1998.
16) Majima M, Isono M, Ikeda Y, Hayashi I, Hatanaka K, Harada Y, Katsumata O, Yamashina S, Katori M, Yamamoto S: Significant roles of inducible cyclooxygenase (COX)-2 in angiogenesis in rat sponge implants. Jpn J Pharmacol, 75: 105-114, 1997.
17) Beer DJ, Matloff SM, Rocklin RE: The influence of histamine on immune and inflammatory responses. Adv Immunol, 35: 209-268, 1984.
18) Falus A, Meretey K: Histamine: an early messenger in inflammatory and immune reactions. Immunol Today, 13: 154-156, 1992.
19) Nakaya N, Tasaka K: The influence of histamine on precursors of granulocytic leukocytes in murine bone marrow. Life Sci, 42: 999-1010, 1988.
20) Miyata K, Kamato T, Fujihara A, Takeda M: Selective and competitive histamine H_2-receptor blocking effect of famotidine on the blood pressure response in dogs and the acid secretory response in rats. Jpn J Pharmacol, 54: 197-204, 1990.
21) Schwartz JC, Pollard H, Quach TT: Histamine as a neurotransmitter in mammalian brain: neurochemical evidence. J Neurochem, 35: 26-33, 1980.
22) Hellstrand K, Hermodsson S : Histamine H2-receptor-mediated regulation of human natural killer cell activity. J Immunol, 137: 656-660, 1986.
23) Nielsen HJ, Kikuchi Y: Histamine-2 receptor antagonists as potential adjuvant treatment of malignant diseases. Adv Biosci, 89: 319-334, 1993.
24) Suonio E, Tuomisto L, Kangas L: The role of histamine in cancer growth as assessed by the mouse subrenal capsule assay. Adv Biosci, 89: 349-374, 1993.
25) Zauberman H, Michaelson IC, Bergmann F, Maurice DM: Stimulation of neovascularization of the cornea by biogenic amines. Exp Eye Res, 8: 77-83, 1969.
26) Tsurufuji S, Sato H, Min K-R, Ohuchi K: Difference in the anti-inflammatory effect of indomethacin between acute and chronic stages of carrageenin-induced inflammation. J Pharmacobio Dyn, 1: 8-14, 1978.
27) Ghosh AK, Hirasawa N, Niki H, Ohuchi K: Cyclooxygenase-2-mediated angiogenesis in carrageenin-induced granulation tissue in rats. J Pharmacol Exp Ther, 295: 802-809, 2000.
28) Houck KA, Ferrara N, Winer J, Cachianes G, Li B, Leung DW: The vascular endothelial growth factor family: identification of a fourth molecular species and characterization of alternative splicing of RNA. Mol Endocrinol, 5: 1806-

1814, 1991.

29) Tischer E, Mitchell R, Hartman T, Silva M, Gospodarowicz D, Fiddes JC, Abraham JA: The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. J Biol Chem, 266: 11947-11954, 1991.

30) Bacic M, Edwards NA, Merrill MJ: Differential expression of vascular endothelial growth factor (vascular permeability factor) forms in rat tissues. Growth Factors, 12: 11-15, 1995.

31) Sowter HM, Corps AN, Evans AL, Clark DE, Charnock-Jones DS, Smith SK: Expression and localization of the vascular endothelial growth factor family in ovarian epithelial tumors. Lab Invest, 77: 607-614, 1997.

32) Ghosh AK, Hirasawa N, Ohuchi K : Enhancement by histamine of vascular endothelial growth factor production in granulation tissue *via* H_2 receptors. Br J Pharmacol, 134: 1419-1428, 2001.

33) Majima M, Hayashi I, Muramatsu M, Katada J, Yamashina S, Katori M: Cyclo-oxygenase-2 enhances basic fibroblast growth factor-induced angiogenesis through induction of vascular endothelial growth factor in rat sponge implants. Br J Pharmacol, 130 : 641-649, 2000.

34) Yamashita M, Ichinowatari G, Yamaki K, Ohuchi K: Inhibition by auranofin of the production of prostaglandin E_2 and nitric oxide in rat peritoneal macrophages. Eur J Pharmacol, 368: 251-258, 1999.

35) Niisato N, Ogata Y, Furuyama S, Sugiya H: Histamine H_1 receptor-induced Ca^{2+} mobilization and prostaglandin E_2 release in human gingival fibroblasts. Possible role of receptor-operated Ca^{2+} influx. Biochem Pharmacol, 52: l015-1023, 1996.

36) Shayo C, Davio C, Brodsky A, Mladovan AG, Legnazzi BL, Rivera E, Baldi A: Histamine modulates the expression of *c-fos* through cyclic AMP production via the H_2 receptor in the human promonocytes cell line U937. Mol Pharmacol, 51: 983-990, 1997.

37) Marconcini L, Marchio S, Morbidelli L, Cartocci E, Albini A, Ziche M, Bussolino F, Oliviero S: *c-fos*-induced growth factor/vascular endothelial growth factor D induces angiogenesis *in vivo* and *in vitro*. Proc Natl Acad Sci USA, 96: 9671-9676, 1999.

38) Hoper MM, Voelkel NF, Bates TO, Allard JD, Horan M, Shepherd D, Tuder RM: Prostaglandins induce vascular endothelial growth factor in a human monocytic cell line and rat lungs via cAMP. Am J Respir Cell Mol Biol, 17: 748-756, 1997.

39) Hirasawa N, Watanabe M, Mue S, Tsurufuji S, Ohuchi K: Downward regulation of neutrophil infiltration by endogenous histamine without affecting vascular permeability responses in air-pouch-type carrageenin inflammation in rats. Inflammation, 15: 117-126, 1991.

40) Hirasawa N, Ohuchi K, Watanabe M, Tsurufuji S: Machanism of the inhibitory action of cyclooxygenase inhibitors on leukocyte infiltration: involvement of endogenous histamine. Eur J Pharmacol, 144: 267-275, 1987.

41) Lawson JA, Adams WJ, Morris DL: Ranitidine and cimetidine differ in their *in vitro* and *in vivo* effects on human colonic cancer growth. Br J Cancer, 73: 872-876, 1996.

42) Tsukamoto Y, Niwa Y, Arisawa T: Relapse of peptic ulcer after quick healing induced by proton pump inhibitors. Jpn J Clin Med, 50: 174-180, 1992.

43) Ghosh AK, Hirasawa N, Ohtsu H, Watanabe T, Ohuchi K: Defective angiogenesis in the inflammatory granulation tissue in histidine decarboxylase-deficient mice but not in mast cell-deficient mice. J Exp Med, 195: 973-982, 2002.

44) Kahlson G, Rosengren E: New approaches to the physiology of histamine. Physiol Rev, 48: 155-196, 1968.

45) Theile DR, Kane AJ, Romeo R, Mitchell G, Crowe D, Stewart AG, Morrison WA: A model of bridging angiogenesis in the rat. Br J Plastic Surgery, 51: 243-249, 1998.

46) Sorbo J, Jakobsson A, Norrby K: Mast-cell histamine is angiogenic through receptors for $histamine_1$ and $histamine_2$. Int J Exp Pathol, 75: 43-50, 1994.

47) Watanabe T, Taguchi Y, Sasaki K, Tsuyama K, Kitamura Y: Increase in histidine decarboxylase activity in mouse skin after application of the tumor promoter tetradecanoylphorbol acetate. Biochem Biophys Res Commun,100: 427-432, 1981.

48) Endo Y: Induction of histidine and ornithine decarboxylase activities in mouse tissues by recombinant interleukin-1 and tumor necrosis factor. Biochem Pharmacol, 38: 1287-1292, 1989.

49) Shiraishi M, Hirasawa N, Oikawa S, Kobayashi Y, Ohuchi K: Analysis of histamine-producing cell at the late phase of allergic inflammation in rats. Immunol, 99: 600-606, 2000.