Degranulation Age-Induced Reprogramming of Mast Cell Degranulation
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Age-Induced Reprogramming of Mast Cell Degranulation

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Mast cell degranulation can initiate an acute inflammatory response and contribute to the progression of chronic diseases. Alteration in the cellular programs that determine the requirement for mast cell degranulation would therefore have the potential to dramatically impact disease severity. Mast cells are exposed to increased levels of PGE2 during inflammation. We show that although PGE2 does not trigger the degranulation of dermal mast cells of young animals, in older mice, PGE2 is a potent mast cell stimulator. Intradermal administration of PGE2 leads to an EP3 receptor-dependent degranulation of mast cells, with the number of degranulated cells approaching levels observed in IgE- and Ag-treated controls. Taken together, these studies suggest that the ability of PGE2 to initiate mast cell degranulation changes in the aging animal. Therefore, elevated PGE2 levels might provide an important pathway by which mast cells are engaged to participate in inflammatory responses in the elderly patient. The Journal of Immunology, 2005, 175: 5701–5707.

Activated mast cells undergo degranulation, a series of biological and morphological changes that lead to secretion of inflammatory mediators from cytoplasmic granules. Large numbers of mast cells are present in the dermis and, when activated, release a number of stored inflammatory mediators, including histamine, TNF-α, IL-1, IL-4, IL-6, IL-8, IL-13, platelet-activating factor, and leukotriene C4 (1). Although traditionally mast cells are associated with acquired immune responses, where the cells are activated by the binding of Ag-IgG or -IgE complexes to FcRs or the recognition of Ags by FcεRI-bound IgE, they can also be activated by the presence of certain microorganisms as well as C3a and C5a, generated by nonspecific activation of the complement system. A large body of evidence supports a role for mast cells in innate immune responses (2, 3), including response to tissue injury and activation through TLR signaling in response to LPS and peptidoglycan (4). It has also been shown that mast cells are required for normal levels of edema and leukocyte infiltration in response to PMA, an agent that induces acute inflammation (5). In these models, mast cell degranulation is presumed to be independent of engagements of the FcRs. More recently, a role for mast cells has been documented in chronic diseases, such as inflammatory arthritis, allergic encephalomyelitis, and asthma (6–8).

The ability of PGE2 to modulate mast cell function has been noted for many years, and the ability of PGE2 to both enhance mast cell degranulation and inhibit the release of mast cell mediators has been reported (9–13). PGE2 levels increase during tissue injury and infection and in chronically inflamed lesions. PGE2 is important as a mediator of acute inflammation, which is characterized by changes in the caliber and permeability of the microvasculature, the exudation of fluid and plasma proteins, and the migration of leukocytes, predominantly neutrophils, into the injured area (1). The identification of PGE2 in rat inflammatory exudates led to the initial proposal of a role for PGs in inflammation (14), and this idea was supported by the observation of increased levels of PGE2 in numerous types of experimental inflammation models and clinical studies. The observation that PGE2 was a potent vasodilator led to the more specific theory that the ability of PGE2 to alter protein plasma extravasation was an indirect consequence of its actions on vascular smooth muscle (15), and this contention was supported by the observation that injection of PG into human skin induced dose-dependent erythema (16, 17). However, other reports suggested that PGE2 alone was able not only to elicit erythema, but also to alter vascular permeability. Kaley et al. (18) demonstrated that PGE2 was equipotent with bradykinin and histamine in causing vascular leakage in rat skin; however, other studies indicated that the increase in vascular permeability might not be due to a direct action of PGE2, but was perhaps secondary to endogenous histamine release (19). High doses of PGE2 produced only small changes in vascular permeability in guinea pig or rabbit skin (20–22), also suggesting that PGs do not contribute to edema by a direct effect on blood vessel permeability.

The realization that PGE2 could modulate the function of most inflammatory cells raised the possibility that PGE2 acted through a number of different mechanisms to modulate acute inflammation: indirectly through its activation of tissue leukocytes, and directly through its actions on the vasculature. Furthermore, the discovery that PGE2 could activate a family of cell surface receptors raised the possibility that the proinflammatory actions of PGE2 might be specific to only a single receptor or a subset of receptors (23).

PGE2 mediates its effects by binding to specific cell surface G protein-coupled receptors, of which there are four subtypes, designated EP1, EP2, EP3, and EP4 (24). The diverse actions of PGE2 are believed to be related to the fact that EP receptors couple to various G proteins to affect different inflammatory mediators. EP2 and EP4 receptors are coupled to Gαi and activate adenylylcyclase, leading to increased levels of intracellular cAMP. EP1 receptor activation is associated with increases in intracellular Ca2+; however, its coupled G protein remains unidentified (23). EP3 is unique among the prostaglandin receptors, in that many isoforms of the receptor are produced from the EP3 gene. EP1 isoforms couple to Gαi, Gαs, or Gαq to mediate the regulation of adenylylcyclase; however, in most systems extensively studied, Gαi predominates (25, 26).

PGE has been shown to enhance IL-6 production by rat mast peritoneal cells (27), and additional studies using rat peritoneal...
cells and bone marrow mast cells (BMMCs) have indicated that although PGE alone cannot induce mast cell degranulation, administration of PGE in addition to IgE/Ag-mediated activation results in synergistically increased activation of BMMCs and enhanced IL-6 production. Pharmacological studies have indicated that these increases in mast cell degranulation and IL-6 production are mediated through the EP1 or EP3 receptors (28), and other investigations, using EP receptor-deficient BMMCs, have concluded that EP3 is the primary mediator for these responses, at least in these immature cells (13).

In the present study we examine the effects of PGE on inflammation in vivo. We show that PGE can induce cutaneous inflammation in mice, and that this response is mast cell dependent. Using EP receptor-deficient mice, we show that the EP receptor expressed by mast cells has the predominant role in PGE-induced inflammation. We also show that the extent of this inflammation varies between strains of inbred mice and that the age of the mouse is the most important factor determining the response of the mast cell to PGE2.

Materials and Methods

Mice

The generation of mice deficient in EP1, EP2, EP3, and EP4 receptors has been previously reported (29–32). Mast cell-deficient mice (WBB6F1/J-KitW–/–; 8–12 wk old) were purchased from The Jackson Laboratory. All mice used were bred and maintained in specific pathogen-free animal facilities at University of North Carolina in accordance with the institutional animal care and use committee guidelines.

PGE-induced ear edema

Mice were injected i.v. with 0.5% Evan’s Blue dye (Sigma-Aldrich) in PBS at a concentration of 10 ml/kg body weight. Mice were then anesthetized, and 20 μl of PGE2 (0.5 μg) was injected intradermally into the right ear, whereas the left ear was injected with an equal amount of PBS. One-half hour after intradermal injection, mice were killed by CO2, and ears were cut off close to the base of the ear. Ear biopsies were incubated in 1 ml of 0.9% sodium borate for 48 h. The absorbance of the formamide extracts was measured at 610 nm for quantification of serum protein extravasation.

Passive cutaneous anaphylaxis

Passive cutaneous anaphylaxis was performed as described previously (33). Briefly, animals were lightly anesthetized, and the right ears were injected intradermally with 20 ng of murine monoclonal anti-DNP IgE diluted in 20 μl of PBS. The left ears were injected with 20 μl of PBS. Twenty-four hours later, animals were injected i.v. with 100 μl of 0.9% PBS containing 100 μg of DNP-albumin and 1% Evan’s Blue dye. Animals were killed 90 min after i.v. injection, and ears were cut off close to the base of the ear.耳 biopsies were incubated in 1 ml of formamide at 55°C for 48 h. The absorbance of the formamide extracts were measured at 610 nm for quantification of serum protein extravasation.

Bone marrow transplantation

EP1+/– and EP2–/– animals served as donors for mast cell-deficient (W/Wv) mice. Bone marrow transplantation was performed as previously described (34). Briefly, femurs from donors were flushed with 4 ml of PBS to obtain bone marrow cell suspensions. Bone marrow cell suspensions were filtered through Miracloth (22- to 25-μm pores; Calbiochem-Novabiochem). Cell suspensions were washed twice with PBS and resuspended in 0.5 ml of PBS. Recipients then received whole bone marrow cells by tail vein injection. Transplanted mice were fed normal mouse chow without antibiotic supplementation. Seven months after transplantation, reconstituted mice were injected intradermally with PGE2 in the ears to examine the formation of edema, as described above.

Histological analysis

Ear tissue from EP1+/– and EP2–/– animals was harvested and fixed in 10% formalin. Tissue was embedded in paraffin, and 5-μm sections were stained with toluidine blue. Ear biopsies treated with PGE and IgE were fixed in 0.1 M sodium cacodylate buffer for 4 h at room temperature and returned to 4°C overnight for additional fixing. Samples were then processed in the automated Reichert Lynx EM tissue processor. Specimens were embedded in Spurr’s resin and polymerized overnight at 70°C. Sections (1 μm thick) were cut and stained with 1% Toluidine Blue-O in 1% sodium borate for light microscopy. Mast cells were identified according to their cytoplasmic granules. They were considered normal if <10% of the granules exhibited fusion, moderate if 10–50% of the granules exhibited fusion, or extensively degranulated if >50% of the cytoplasmic granules exhibited fusion and extrusion from cells.

Statistical analysis

Data are presented as the mean ± SEM. Statistical analysis was performed using two-sample Student’s t test for unequal variances or single-factor ANOVA, where indicated. The p values reported have been adjusted using the Bonferroni method to account for multiple comparisons.

Results

PGE induces cutaneous inflammation in mice

We first examined the ability of s.c. application of PGE2 and PGE1 to induce an inflammatory response. To monitor this response, we injected mice with Evan’s Blue dye, which binds to serum proteins and allows changes in vascular permeability to be monitored by determining the levels of dye in a tissue. Wild-type 129/SvEv mice received an intradermal injection of PGE in the right ear, whereas the left ear was injected with vehicle (PBS). Mice were killed 0.5 h later, an ear tissue sample was removed, and the difference in the amount of dye in the tissue from the PGE-treated and vehicle-treated ears was determined (data not shown). Using this protocol, we found that PGE2 or PGE1 alone is sufficient to elicit a measurable change in vascular permeability in mouse dermis, and that this change was similar using either PGE2 or PGE1 (data not shown).

PGE induced edema formation in EP receptor-deficient mice

to determine whether the observed inflammation was the result of the specific action of PGE2 and to define the receptor(s) mediating this action, we examined the impact of loss of each of the four PGE2 receptors on this response. We first examined the roles of the two G protein-coupled PGE2 receptors, EP2 and EP4, in PGE-mediated plasma extravasation. Comparison of age-matched 129/SvEv mice and congenic EP2–/– animals failed to support a role for this receptor in PGE-induced edema formation (data not shown). Similarly, no significant difference was observed in the response of EP3–/– animals compared with littermate controls (data not shown). Activation of both the EP1 and the EP4 PGE receptors can lead to an increase in intracellular Ca2+; thus, these receptors are likely candidates for mediating the proinflammatory actions of PGE. The EP1 mutation was introduced into an ES cell line established from DBA/1J embryos and has been maintained on this genetic background (30). Comparison of wild-type DBA/1J and congenic EP1–/– mice indicated a similar level of induced edema formation in both groups of mice, suggesting that PGE activation of the EP1 receptor did not play a part in this response (Fig. 1A). Two congenic EP2–/– mice lines have been generated, one on the 129/SvEv background and a second on the C57BL/6 genetic background. PGE-induced edema formation was significantly attenuated in both of these lines compared with wild-type controls (Fig. 1B: p = 0.0003 for EP1–/– vs wild-type C57BL/6; Fig. 1C: p = 0.006 for EP2–/– vs wild-type 129/SvEv; by Student’s t test).

PGE fails to induce edema in mast cell-deficient mice

Mast cells are an important constituent of the dermis, and we have previously shown that PGE can potentiate degranulation of
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Wild-type and EP1-deficient mice exhibited edema in response to PGE1. P3-deficient mice (Fig. 3; 14) demonstrate a significantly reduced level of inflammation compared with both C57BL/6 and 129/SvEv (9) mice. No significant decrease in edema resulting from passive anaphylaxis was observed in the EP3−/− animals. This suggests that the mast cells of EP3−/− mice are mostly normal in both number and function (Fig. 2).

Two possible models can be proposed to explain the lack of response to PGE in the W/WV and EP3−/− mice. First, it is possible that PGE acts directly on EP3 receptors present on mast cells. Alternatively, EP3 might bring about the release of mediators by other cells, which then act on the mast cells, causing them to degranulate and release mediators that increase vascular permeability.

To distinguish between these two possibilities, W/WV mice were reconstituted with either wild-type or EP3-deficient mast cells. As expected, reconstitution of W/WV mice with wild-type mast cells significantly restored the dermal response to PGE1 (Fig. 3; 37). In addition, immune responses can change in magnitude over the lifetime of the animal. We therefore sought to determine whether the magnitude of the response to intradermal application of PGE is dependent either directly or indirectly on the presence of mast cells.

BMMCs (13). To determine whether mast cells play a part in PGE-mediated edema formation, we treated mast cell-deficient (W/WV) and EP3−/− mice with PGE. We show that the response in the mast cell-deficient W/WV background reveals reduced edema in response to PGE1. EP3-deficient mice (n = 12) demonstrate a significantly reduced level of inflammation compared with both C57BL/6 and 129/SvEv (p = 0.0003; n = 14) and 129/SvEv (p = 0.0006; n = 15) wild-type mice. *p ≤ 0.01; **p ≤ 0.001.


PGE-induced edema appears to be largely dependent on the expression of EP3 receptors and the presence of mast cells. A possible explanation for these findings is that the PGE-stimulated EP3 receptor is required for normal development or function of mast cells. To test this, we examined the number and morphology of the mast cells in the EP3+/+ and EP3−/− mice. No difference in the number or histological appearance of dermal mast cells in EP3+/+ mice was noted (data not shown), suggesting that the EP3 receptor is not required for normal mast cell development; however, this does not rule out a possible alteration in the ability of these cells to degranulate and release mediators capable of altering vascular physiology. To determine whether the EP3−/− mast cells can degranulate and stimulate edema formation, we examined edema formation induced by passive anaphylaxis in the two populations of animals. No significant decrease in edema resulting from passive anaphylaxis was observed in the EP3−/− animals. This suggests that the mast cells of EP3−/− mice are mostly normal in both number and function (Fig. 2).

FIGURE 1. PGE1-induced edema formation in EP receptor-deficient mice. A, Loss of the EP1 (n = 5) receptor has no effect on the level of PGE-stimulated inflammation. Wild-type and EP1-deficient mice exhibited similar responses to vehicle, and although treatment with PGE1 caused an increase in inflammation, this increase was not significantly different between the wild-type and deficient mice. B and C, The EP3 receptor appears to play a role in PGE1-induced inflammation. Examination of EP3-deficient mice on both the C57BL/6 and 129/SvEv backgrounds reveals reduced edema in response to PGE1. EP3-deficient mice (n = 12) demonstrate a significantly reduced level of inflammation compared with both C57BL/6 (p = 0.0003; n = 14) and 129/SvEv (p = 0.0006; n = 15) wild-type mice. *p ≤ 0.01; **p ≤ 0.001.

FIGURE 2. Normal degranulation of EP3+/+ and EP3−/− mast cells. EP3+/+ (n = 10) and EP3−/− (n = 11) mice exhibit increased inflammation in response to IgE stimulation compared with the response to vehicle. No difference in edema formation was noted between EP3+/+ and EP3−/− mice, suggesting that mast cells from EP3−/− mice are degranulating normally (p = 0.731, by two-sample Student’s t test with unequal variances).

Large differences have been noted between mouse strains in the inflammatory response elicited by various stimuli and, in particular, in the role of arachidonic acid metabolites in this response (37). In addition, immune responses can change in magnitude over the lifetime of the animal. We therefore sought to determine whether the magnitude of the response to intradermal application of PGE is dependent either directly or indirectly on the presence of mast cells in the dermis.

Induction of cutaneous inflammation by PGE increases in older mice

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Comparison of PGE and passive anaphylaxis in young and old mice

This increased inflammation in older mice could result from an increase in mast cell size or number or from an increase in the mediators released upon mast cell degranulation. Histological examination of mast cells from C57BL/6 young and old mice revealed no difference in the number of mast cells (data not shown). To determine whether there was a difference in the release of inflammation mediators or in the response of the tissues to the released mediators, we examined passive anaphylaxis in young and old C57BL/6 mice, directly comparing this to the change in responsiveness to PGE. Young (2-mo-old) and old (6-mo-old) mice were loaded overnight with monoclonal IgE to DNP. The next day, serum proteins were labeled with Evan’s Blue, and mice were treated with an intradermal injection of Ag in one ear and with PGE in the other. Unlike PGE, IgE mediated a robust response in the young mice: the tissue extravasation was 3 times that induced by PGE (Fig. 5). Similar to PGE, IgE/Ag-mediated mast cell degranulation and edema formation was increased in the older mice. Although this increase was significant (Fig. 5; p = 3.6 × 10^{-5}), the increase represented a change of ∼30% over that in wild-type animals. In comparison, edema formation in response to PGE was increased by >200% in the older animals (p = 4 × 10^{-5}).

We next determined whether the temporal difference between mouse strains in the development of responsiveness to PGE was easily explained by differences in the accumulation and/or maturation of mast cells in the various mouse lines. To address this point, we measured cutaneous anaphylaxis in 2- and 4- to 5-mo-old 129/SvEv and C57BL/6 mice. All mice received an intradermal injection of anti-DNP monoclonal IgE into the pinna of the left ear. Twenty-four hours later, mice received an i.v. injection of Evan’s Blue containing anti-DNP and an intradermal injection of PGE in the right ear, and edema formation was monitored. As expected and consistent with the results shown in Fig. 4A, both these mouse strains displayed only a small increase in edema formation in response to PGE at 2 mo of age (Fig. 4B). Again, consistent with the experiments shown in Fig. 4A, a robust response to PGE was observed in 4-mo-old C57BL/6 mice, whereas 129/SvEv mice continued to respond poorly (Fig. 4B). In contrast, the responses of 129/SvEv and C57BL/6 mice to IgE/Ag did not differ significantly at either 2 or 4–5 mo of age. Thus, the delayed development of responsiveness to PGE in 129/SvEv mice vs C57BL/6 mice cannot easily be explained by a difference between these strains in either the number of dermal mast cells or the response of the tissue to inflammatory mediators released by mast cells.

Degranulation of mast cells by PGE and IgE in young and old mice

We next determined whether there was a correlation between the inflammatory response to PGE and mast cell degranulation. Young (2-mo-old) and old (>6-mo-old) mice received an i.v. injection of 20 ng of monoclonal IgE. The next day, the mice received an intradermal injection of IgE on the right ear and PGE on the left ear. After 90 min, the mice were killed, the pinna was harvested, and mast cell degranulation was evaluated, as described by Takai et al. (33). As shown in Fig. 6 and consistent with the small change in vascular permeability, few mast cells responded to PGE in the young animals. In contrast, IgE resulted in 60% of the mast cells degranulating either completely or partially in these animals. In older animals, however, the percentage of mast cells degranulated by injection of PGE approached that observed with IgE. Thus, although the tissue mast cell of the 8-wk-old mouse is virtually unresponsive to PGE, the addition of this lipid mediator alone in the aged mouse is sufficient to initiate degranulation of >50% of dermal mast cells.
Discussion

Soon after its isolation, the inflammatory actions of PGE₂ were investigated by direct injection of this lipid into skin (16, 17). Although the proinflammatory actions of PGE₂ were generally observed, reports differed on the ability of PGE₂ alone to induce all the cardinal signs of inflammation. For example, although PGE₂ was generally observed to sensitize the tissue to pain and cause erythema, the ability of PGE₂ to mediate changes in vascular permeability was not observed in all systems. A number of studies showed that PGE₂ acted primarily to amplify edema formation initiated by other inflammatory mediators, such as histamine (18, 19). Our studies provide some clarification of these results. First, similar to earlier studies, we found that PGE alone can induce edema formation. However, this action is dependent on the presence of mast cells in the tissue, because no protein extravasation was observed in the mast cell-deficient W/WV mice. This observation is consistent with a model in which PGE alone has limited ability to alter the permeability of the postcapillary venules, but, rather, acts by stimulating tissue mast cells to release bioactive mediators, such as platelet-activating factor, leukotriene C₄, and histamine. These mediators, either alone or in synergy with PGE₂, change the permeability of these vessels. The variable previous reports on the proinflammatory acts of PGE₂ could reflect the difference in the number of mast cells present in the tissues studied and/or, as discussed below, in the age of the subjects or animals in which these studies were conducted.

The availability of mice lacking specific receptors provides a useful tool for determining the contributions of individual EP receptors to the physiological actions of PGE. We have used this approach in this study to examine the mechanism by which PGE

5-mo-old 129/SvEv and C57BL/6 mice. Mice received an intradermal injection of DNP-IgE mAb into the pinna of the left ear, and 24 h later, mice received an i.v. injection of Evan’s Blue containing anti-DNP (C). At the same time the right ear was treated with an intradermal injection of PGE (B). A pronounced difference in the responses of 129/SvEv and C57BL/6 mice to PGE was observed, particularly in the 4- to 5-mo-old animals (*, p = 1.83 × 10⁻⁶; #, p = 2.2 × 10⁻⁷). In contrast, the inflammation observed after treatment with Ag did not differ between the two strains at either age (p > 0.5; n = 8 for each group).

![Comparison of edema induced by passive anaphylaxis and PGE in young and old mice.](image)
mediates edema formation. We report that plasma protein extravasation in response to PGE is not observed in animals lacking the EP3 receptor. The involvement of EP3 in this response together with the results of previous studies both from our laboratory (13) and others (28) indicate that EP3 could alter mast cell function and suggest that perhaps the PGE-induced edema formation was mediated in part through its actions on resident mast cells. We show by reconstitution of W/WV mice that EP3 receptor expression is necessary for PGE-mediated plasma extravasation. However, our studies differ in one important aspect from our previous studies with bone marrow-derived cultures of mast cells. Our current studies suggest that PGE alone is sufficient to mediate the degranulation of mast cells.

Previously, using BMMCs, we had shown that although PGE2 acting through the EP3 receptor could increase intracellular Ca2+ in BMMCs, EP3 activation alone was not sufficient to mediate the degranulation of BMMCs (13). PGE2 activation of the EP3 receptor did, however, augment degranulation and cytokine production by BMMCs. Our findings were consistent with previous pharmacological studies of rat peritoneal mast cells, which were shown not to degranulate in response to PGE alone, although these cells did produce cytokines without additional signals (27). There are a number of possible explanations for the differential actions of PGE in vivo and in vitro. First, it is possible that PGE elicits the production of another mediator(s) in the in vivo model that, together with PGE, activates the mast cell. Such mediators would not be available in the in vitro systems. We previously reported that EP3 was able to degranulate BMMCs treated with PMA (13). Thus, the production of a mediator in vivo in response to PGE that is capable of activating protein kinase C could synergize with PGE in triggering mast cell degranulation.

Alternatively, it is possible that the response of a mature connective tissue mast cell to PGE differs from that of an immature BMMC or from the response of peritoneal mast cells. It is interesting to speculate that as the mast cell matures within various tissue compartments, it acquires characteristics that make it sensitive to regulation of mediators such as PGE and that these pathways provide a means by which to participate in the innate immune response.

We have found that the amount of edema induced by subdermal injection of PGE was dependent on the age of the mice tested. Inflammation was minimal in very young mice, but inflammation increased significantly with age in mice from all genetic backgrounds examined. There are a number of explanations for this increased inflammation. First, it is possible that the number of mature mast cells might increase with age in mice. Hart et al. (38) have observed an age-dependent increase in dermal mast cell numbers in BALB/c mice; however, this increase was not observed in mice on a C57BL/6 genetic background. We also failed to observe a change in mast cell number in C57BL/6 mice. A second possible explanation is that the level of mediators released by mast cells increases as they age. This would be consistent with the observation that vascular permeability was also greater when the mast cells of older mice were triggered by IgE. Harada et al. (39), who have also examined the potentiation of passive anaphylaxis in young and old mice, found that cataract Shionogi, diazepam sensitive, and C57BL/6J mice exhibit an increase in passive anaphylactic shock that is age dependent. However, it is unlikely that this alone can account for the dramatic change in the response to PGE in the old and young animals, because the IgE response was enhanced by only 30%, whereas the response to PGE increased >200-fold. These results suggest that the increased inflammation observed is unlikely to be due to a generalized increase in mast cell number, size, or the mediators released upon degranulation.

Another possible explanation for the increase in inflammation with age is that the degranulation of the mast cell does not change with age, but, rather, other changes in the tissue occur that increase the sensitivity of the tissue to the release of mast cell mediators. Again, this explanation is not consistent with the modest change in the response of the older mice in the passive anaphylaxis model.

A more likely explanation is that as the dermal mast cells mature, the program regulating mast cell responses to various stimuli changes, and this reprogramming may begin to favor activation by non-FcR pathways. The mast cell may then become more sensitive to increased innate inflammatory mediators and less dependent on an active adaptive immune system. This interpretation is consistent with the dramatically increased number of degranulated mast cells present in the PGE-treated tissue of older mice compared with younger mice.

A role for mast cells has been demonstrated in numerous inflammatory diseases. Many of these diseases, including, most recently, arthritis and atherosclerosis, are more frequent in older populations, and nonsteroidal anti-inflammatory drugs are commonly used to treat these disorders. It is intriguing to speculate that the efficacy of nonsteroidal anti-inflammatory drugs in these patients might in part reflect the inhibition of mast cell deregulation via this PGE2/EP3 pathway.

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Disclosures
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