Novel Aspects of Mevalonate Pathway Inhibitors as Antitumor Agents

Martin Thurnher, Oliver Nussbaumer, and Georg Gruenbacher

Abstract

The mevalonate pathway for cholesterol biosynthesis and protein prenylation has been implicated in various aspects of tumor development and progression. Certain classes of drugs, such as statins and bisphosphonates, inhibit mevalonate metabolism and therefore have also been tested as antitumor agents. This concept is strongly supported by the recent finding that mutant p53, which is present in more than half of all human cancers, can significantly upregulate mevalonate metabolism and protein prenylation in carcinoma cells. The first evidence that mevalonate pathway inhibitors may have the potential to reverse the malignant phenotype has already been obtained. Moreover, recently discovered immunomodulatory properties of statins and bisphosphonates may also contribute to their known anticancer effects. Drug-induced inhibition of protein prenylation may induce sequential cellular stress responses, including the unfolded protein response and autophagy, that eventually translate into inflammasome-dependent and caspase-1-mediated activation of innate immunity. This review focuses on these novel capabilities of mevalonate pathway inhibitors to beneficially affect tumor biology and contribute to tumor immune surveillance.

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Introduction

Mevalonate synthesis and metabolism

In the first committed step of the mevalonate pathway (1), which is inhibited by statins (2, 3), hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase converts HMG-CoA to mevalonic acid (mevalonate; Fig. 1). Mevalonate is further metabolized to isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). Farnesyl pyrophosphate (FPP) synthase, which is inhibited by bisphosphonates (4, 5), catalyzes sequential condensation reactions of DMAPP with 2 units of IPP to form FPP, and geranylgeranyl pyrophosphate (GGPP) synthase catalyzes yet another condensation reaction to form GGPP. FPP is the precursor in cholesterol and steroid biosynthesis as well as in the biosynthesis of dolichols, which are membrane anchors during the formation of N-linked oligosaccharides. Both FPP and GGPP serve as adjuncts for a posttranslational modification at the C-terminus of a variety of important cellular proteins, which is referred to as protein prenylation (6).

Protein prenylation

Protein prenylation creates a lipidated hydrophobic domain and plays a role in membrane attachment or protein–protein interactions, which in most cases is an essential requirement for the biologic function of proteins. Prenylation occurs on many members of the Ras and Rho family of small guanosine triphosphatases (GTPases). Three enzymes [farnesyltransferase (FTase), geranylgeranyltransferase (GGTase) I, and GGTase II] can catalyze protein prenylation. FTase uses FPP (C15) as a prenyl donor to transfer a farnesyl group to the C-terminal CaaX motif (C is cysteine, A is usually an aliphatic residue, and X is any amino acid). GGTases use GGPP (C20) as a prenyl donor to transfer a geranylgeranyl moiety to their target proteins (Fig. 1). It has been shown that GGTase can prenylate some of the substrates of FTase and vice versa. Prenylation, however, is not restricted to proteins containing the CaaX sequence, and also occurs on many members of the Rab family of Ras-related G-proteins. Rab prenylation is catalyzed by GGTase II, which is also referred to as Rab GGTase. Rab proteins do not have a consensus sequence, such as the CaaX box; instead, most of them contain a CC or CXC C-terminal sequence. Rab proteins are bound by the Rab escort protein over these more-conserved regions and then presented to the Rab GGTase. Rab GGTase often transfers 2 geranylgeranyl groups to the C-terminal cysteines of Rab proteins.

Protein prenylation inhibitors as antitumor agents

Many proteins that participate in signaling pathways to which tumors are frequently addicted, such as the members of the Ras superfamily, are prenylated. This observation...
mic blasts were found to develop a form of chemoresistance most from statin-based anticancer therapy (11). Statins may data suggest that statins can lower the risk of certain cancers preclinical and some clinical observations, epidemiologic important anticancer effect of statins (5, 8). In addition to proteins (rather than farnesylation of Ras) seems to be an nylation (Fig. 2). Inhibition of geranylgeranylation of Rho phosphate, and thus due to the inhibition of protein pre- HMG-CoA reductase (8). This apoptotic response is in part that depends on HMG-CoA reductase, and chemosensitivity could be restored by blockade of HMG-CoA reductase with statins (12).

Enhanced mevalonate metabolism and statin sensitivity in cancer cells carrying mutant p53
Recent work showed that mutant p53, which is present in more than half of all human cancers, can significantly upregulate mevalonate pathway activity in cancer cells (Fig. 2), which contributes to maintenance of the malignant phenotype (13). Simvastatin used at clinically achievable concentrations was shown to reduce 3-dimensional growth of cancer cells expressing a single mutant p53 allele. Moreover, simvastatin was able to induce extensive cancer cell death in these cells and a significant reduction of their invasive phenotype. Intriguingly, the morphologic changes observed with either statin treatment or mutant p53 depletion by short hairpin RNA were virtually the same and were not observed in wild-type p53-expressing cells. In iso- prenoid add-back experiments, supplementation with GGPP was sufficient to restore the invasive phenotype in the presence of HMG-CoA reductase inhibition, showing that upregulation of protein geranylgeranylation is an important effect of mutant p53 (13). Mutant p53 may thus be an important marker for distinguishing the subset of tumors that are sensitive to statin-induced apoptosis.

Statins have also been shown to have immunomodulatory activity. Modulation of protein prenylation is consid- ered a key mechanism by which statins alter inflammatory and immune responses (6). Although it is well established that statins by themselves are predominantly anti-inflam- matory and immunosuppressive agents (6), an increasing number of studies are showing that statins may induce strong proinflammatory responses when appropriate costi- mulatory signals are provided (Table 1).

Bisphosphonates likewise affect tumor biology and also exhibit immunomodulatory properties
Bisphosphonates, which are drugs that prevent bone resorption, are used to treat osteoporosis and similar dis- eases but have also been approved for the treatment of metastatic bone disease of hematopoietic tumors such as multiple myeloma (4) and nonhematopoietic tumors such as breast (14) and prostate cancer (15). Whereas statins inhibit HMG-CoA reductase, the first committed step in the mevalonate pathway, bisphosphonates act downstream of HMG-CoA reductase to inhibit FPP synthase (Fig. 1). How- ever, both bisphosphonates and statins eventually cause FPP and GGPP deprivation and thus failure to perform farnesylation and geranylgeranylation of small GTPases of the Ras superfamily. With regard to bisphosphonates, it is the inhibition of Ras signaling due to the disruption of membrane anchoring of these GTPases that eventually stops osteoclast-mediated bone resorption (5).

Prenyltransferase inhibitors
In contrast to statins and bisphosphonates, which inhibit protein prenylation by depleting FPP and GGPP,
Prenyltransferase inhibitors directly inhibit the transfer of FPP or GGPP by FTase and GGTase, respectively. FTase inhibitors (FTI) can be analogues of FPP that compete with FPP for binding to FTase, CAAX peptidomimetics that compete with RAS-CAAX motif for FTase, or both analogues and peptidomimetics (16). FTIs can prevent H-Ras farnesylation and thus reverse H-Ras–induced transformation (17). With regard to hematologic malignancies, populations of patients with acute myelogenous leukemia and myelodysplastic syndromes showed promising response rates to FTI monotherapy (18). The FTI tipifarnib [also known as R115777; trade name Zarnestra (Selleck Chemicals)], which inhibits Ras kinase prenylation, has been tested in a phase II study in older patients (median age, 74 years) with previously untreated acute myelogenous leukemia. Complete remission was achieved in 14% of the patients, and partial remission or hematologic improvement was observed in 9%. The median duration of complete remission was 7.3 months, and the median survival of complete responders was 18 months. Inhibition of farnesylation of the surrogate protein HDJ2 occurred in most of the bone marrow samples that were tested (19). GGTase inhibitors (GGTI) can be GGPP analogues and CAAL (where L denotes leucine) peptidomimetics or bisubstrate analogues (20). Despite their potent antiproliferative and proapoptotic properties in both in vitro and in vivo models, clinical development of GGTS has been problematic owing to their toxicity (21). Little is known about the immunomodulatory effects of prenyltransferase inhibitors.

Figure 1. Mevalonate metabolism. The mevalonate pathway produces isoprenoid precursor units, which are required for the biosynthesis of a variety of important molecules that contribute to diverse cellular functions, ranging from cholesterol synthesis to N-glycosylation and protein prenylation. Statins and bisphosphonates are 2 classes of drugs that inhibit mevalonate metabolism and thus inhibit protein prenylation. Modulation of protein prenylation is considered a key mechanism by which statins and bisphosphonates alter inflammatory and immune responses. In mevalonate kinase deficiency, a rare hereditary autoinflammatory syndrome, inhibition of protein prenylation results in similar inflammatory responses. Bisphosphonates also induce the accumulation of IPP, a phosphoantigen that is specifically recognized by certain γδ T lymphocytes.
Protein Prenylation Inhibitors Can Induce Stress Responses and Generate Danger Signals That Translate into Innate Immune Responses

Protein prenylation inhibitors induce the unfolded protein response

Prenylated proteins constitute up to 2% of total cellular protein (6), indicating that pharmacologic modulation of protein prenylation must markedly affect cellular physiology. Inhibition of protein prenylation causes stress to the endoplasmic reticulum (ER) because prenylated Rab proteins (22) are involved in almost every route of intracellular trafficking (23). Such stress to the ER prompts the mammalian cell to initiate the unfolded protein response (UPR), an evolutionarily conserved program to cope with ER stress (24). Exposure of macrophages to fluvastatin was shown to activate a cytoprotective UPR, which included the expression of the chaperone glucose-related protein [GRP78 (25)].

The UPR induces the lysosomal degradation pathway of autophagy

During the past few years, it has become increasingly clear that not only does ER stress induced by unfolded protein aggregation activate the UPR, the UPR in turn induces the lysosomal degradation pathway of autophagy (26), a catabolic cellular process of self-digestion that helps the cell get
rid of damaged organelles, misfolded proteins, and invading microorganisms (27). Autophagy involves the sequestration of cytoplasmic cargo within double-membrane vesicles and the delivery of its contents to the lysosome for degradation. Initial steps include vesicle nucleation and elongation to form the phagophore. The edges of the phagophore then fuse to assemble the autophagosome, a double-membrane compartment that sequesters the cytoplasmic material. Finally, fusion of the autophagosome with a lysosome forms an autolysosome, where degradation of the captured material together with the inner membrane occurs (27).

Recent work has shown that the UPR is specifically initiated to promote the initiation of autophagosome formation (26, 28, 29). However, what happens if autophagic proteins, which are frequently prenylated, are depleted and the process of autophagy is aborted?

Aborted autophagy alerts the innate immune system

According to recent observations in knockout mouse models, blocking of autophagy can induce innate immune responses (30). Macrophages from mice with deletion of autophagy genes such as LC3B, beclin 1, and Atg16L are more prone to inflammasome-mediated cleavage and activation of caspase-1, leading to the maturation and secretion of interleukin (IL)-1β and IL-18 (30, 31) because autophagy physiologically serves to eliminate active inflammasomes in order to temper inflammation and restore homeostasis (31). In similarity to the genetic deletion of autophagy proteins, which are frequently prenylated, are depleted and the process of autophagy is aborted?

### Box 1. Cellular stress responses induced by mevalonate pathway inhibitors

1. Inhibition of protein prenylation causes stress to the ER and initiates the UPR.
2. The UPR involves several sequential steps to restore ER homeostasis: a boosting of protein folding capacity, enhanced clearance of misfolded proteins, and a slowdown of mRNA translation.
3. Alarm signaling during the UPR engages signal transduction pathways that are often also associated with innate immune responses.
4. ER stress induced by unfolded protein aggregation not only activates the UPR but also induces the lysosomal degradation pathway of autophagy to digest the stressed organelle.
5. When all rescue measures fail and autophagy cannot be completed, because autophagy depends on prenylated proteins such as Rab, a final eradicative measure is taken: Inflammasome-dependent caspase-1 activation induces inflammation and alerts innate lymphocytes that kill the heavily stressed cell.

### Table 1. Immunostimulatory effects of statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Target cell</th>
<th>Costimulus</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>Endothelial cells</td>
<td>IL-1 and TNF</td>
<td>CAM upregulation</td>
<td>(51)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>BM-derived DC</td>
<td>LPS</td>
<td>TNF-α, IL-6, IL-12</td>
<td>(52)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Macrophages</td>
<td>LPS</td>
<td>TNF-α</td>
<td>(53)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Monocytes</td>
<td>PHA</td>
<td>T cell IFN-γ</td>
<td>(54)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>CD56+ DC</td>
<td>IL-2</td>
<td>NK cell IFN-γ</td>
<td>(36)</td>
</tr>
</tbody>
</table>

Abbreviations: BM, bone marrow; CAM, cell adhesion molecules; DC, dendritic cell; IL, interleukin; LPS, lipopolysaccharide; NK, natural killer; PHA, phytohemagglutinin.

Mevalonate pathway inhibitors can induce innate lymphocyte activation

In line with all of these observations, statins were recently shown to induce the depletion of prenyl pyrophosphates in human dendritic cells (DC), the professional antigen-presenting cells of the immune system (34, 35). Prenyl pyrophosphate deprivation seemed to generate danger signals, because it translated into caspase-1 activation (Box 1; Fig. 2). Caspase-1 cleaved the proforms of IL-1β and IL-18 and enabled the release of bioactive cytokines. The statin-treated DCs thus acquired the capability to potently activate IL-2–primed natural killer (NK) cells (36). NK cells are known to contribute to innate immune responses against neoplastic cells because NK cells usually recognize and attack tumor cells that lack MHC class I molecules (37, 38). The statin-induced response of IL-2–primed NK cells could be abolished completely when cell...
catures were reconstituted with the isoprenoid pyrophosphate GGPP, which allows protein geranylgeranylation to occur despite statin-mediated inhibition of HMG-CoA reductase. Statins also acted directly on human carcinoma cells to induce apoptosis, and, intriguingly, IFN-γ produced by NK cells cooperated with statins to enhance tumor cell death in a synergistic fashion (Fig. 2; ref. 36).

The first evidence of the immunomodulatory effects of bisphosphonates was obtained when expansion of γδ T lymphocytes was observed in patients who had acute-phase reactions after their first treatment with the bisphosphonate pamidronate (39). Inhibition of FPP synthase by bisphosphonates leads to accumulation of the mevalonate pathway intermediate IPP (Fig. 2), a phosphoantigen that can be specifically recognized by Vδ2 Vγ9+ γδ T lymphocytes (40). γδ T cells are assigned to the innate arm of the immune system and contribute to immune surveillance of tumors (41), a concept that has been tested in clinical trials (Table 2). Moreover, activated γδ T lymphocytes can costimulate the activation of NK cells to enhance immune surveillance (Fig. 2; ref. 38).

Bisphosphonates may exert additional immunomodulatory effects by regulating myeloid differentiation. In a murine model of breast cancer, bisphosphonate treatment reduced the number of myeloid-derived suppressor cells and concomitantly tumor size (42). In the same mouse model, a marked reduction of tumor-associated macrophages and their repolarization toward an M1 phenotype were observed upon zoledronate treatment (43). In a murine model of mesothelioma, zoledronate was shown to impair myeloid differentiation, leading to a reduction in tumor-associated macrophages but also an increase in immature myeloid cells with myeloid-derived suppressor cell characteristics (44). Along the same line, zoledronate has been shown to inhibit DC differentiation from monocytes and to impair DC activation via Toll-like receptor 4 (45, 46).

However, until recently, the potential immunomodulatory effects of bisphosphonates, which arise from the inhibition of protein prenylation, have been less well examined. Zoledronate, the most potent bisphosphonate currently available, not only induces γδ T-cell activation (40) but also was recently shown to be capable of inducing NK cell activation (47). This effect also depended on DCs (34) and was due to zoledronate-mediated inhibition of isoprenoid pyrophosphate formation (Fig. 2). In contrast to statins, both FPP and GGPP supplementation abolished NK cell activation in response to zoledronate, indicating that both farnesylation and geranylgeranylation regulate innate immunity. The depletion of isoprenoid pyrophosphates resulted in caspase-1 activation and maturation of active IL-1β and IL-18. The 2 cytokines induced IFN-γ production in IL-2–primed NK and in γδ T lymphocytes (47). Intriguingly, the caspase-1 inhibitor YVAD (47) abrogated zoledronate-induced intracellular IFN-γ production not only in NK cells but also in γδ T lymphocytes (47), indicating that caspase-1–mediated cytokine maturation is the central mechanism underlying innate lymphocyte activation in response to the bisphosphonate zoledronate (Fig. 2). Together with other reports (30, 48), these studies strongly suggest that the depletion of isoprenoid pyrophosphates induced by protein prenylation inhibitors induces cellular stress and activates the UPR-autophagy pathway, culminating in caspase-1–mediated cytokine maturation and innate lymphocyte activation (Box 1; Fig. 2; refs. 36, 47).

In vivo evidence for the link between isoprenoid pyrophosphate deprivation and caspase-1 activation, which has been observed during drug-induced inhibition of mevalonate metabolism (36, 47), was recently obtained in a genetic human disease, mevalonate kinase deficiency [MKD (49)]. In this rare hereditary, auto-inflammatory syndrome, the enzyme is inactive due to mutations of the encoding gene. Lack of mevalonate kinase, the second enzyme of the mevalonate pathway (Fig. 1), results in downstream GGPP deprivation followed by Nalp3 inflammasome-dependent caspase-1 activation and maturation of bioactive IL-1β. The inflammatory phenotype of MKD, which includes periodic fevers, is consistent with many of the well-known biologic effects of IL-1β (50).

Conclusions and Future Directions
The increased activity of mevalonate metabolism, particularly in cancer cells carrying mutant p53, may

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**Table 2. Immunostimulatory effects of bisphosphonates**

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Tumor type</th>
<th>Experimental system</th>
<th>Costimulus</th>
<th>Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmitronate</td>
<td>Multiple myeloma</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(39, 55)</td>
<td></td>
</tr>
<tr>
<td>Palmitronate</td>
<td>Lymphoid malignancies</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(56)</td>
<td></td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Breast and prostate cancer</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(57, 58)</td>
<td></td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Breast cancer</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(59)</td>
<td></td>
</tr>
<tr>
<td>BrHPP</td>
<td>Renal cell carcinoma</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(60)</td>
<td></td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Non-small cell lung cancer cells</td>
<td>IL-2</td>
<td>γδ T-cell expansion</td>
<td>(61)</td>
<td></td>
</tr>
<tr>
<td>Zoledronate</td>
<td>CD56+ PBMCs <em>in vitro</em></td>
<td>IL-2</td>
<td>NK-cell activation</td>
<td>(47)</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: BrHPP, BromoHydrin PyroPhosphate; PBMC, peripheral blood mononuclear cell.*

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distinguish tumor cells from nonmalignant cells and may render such tumor cells particularly sensitive to mevalonate pathway inhibition. Statins have already been shown to be able to reverse the malignant phenotype by inhibiting protein geranylgeranylation (Fig. 2; ref. 13). Mevalonate pathway inhibitors may also be used to induce cellular stress responses and to generate danger signals that tumor cells, in contrast to pathogens, usually lack. Cellular stress induced by mevalonate pathway inhibitors can translate into inflammatory and innate immune responses that may improve the efficacy of tumor immune surveillance (36, 47). Bisphosphonates may be particularly promising because they meet several requirements. They inhibit protein prenylation and, similarly to statins, may be able to reverse the malignant phenotype. Their ability to induce the accumulation of IPP (Fig. 2) and to recruit γ6 T cells into the antitumor immune response is already well established (40, 41). By inhibiting protein prenylation, bisphosphonates can also induce caspase-1–dependent activation of NK cells (47), which may join γ6 T cells in the antitumor immune response (Fig. 2). Clinical studies of mevalonate pathway inhibitors should therefore be designed to exploit their beneficial effects on tumor biology and their stimulatory effects on tumor immune surveillance simultaneously.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: M. Thurnher, O. Nußbaumer, G. Grünbacher

Writing, review, and/or revision of the manuscript: M. Thurnher, O. Nußbaumer, G. Grünbacher

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