Novel aspects of mevalonate pathway inhibitors
as antitumor agents

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Running head: Novel aspects of mevalonate pathway inhibitors

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Translational relevance

Biologically active metabolites generated in the mevalonate pathway have been implicated in tumor cell proliferation, survival, invasion and metastasis. The recent finding that mutant p53 enhances mevalonate metabolism in cancer cells along with the observation that mevalonate pathway inhibitors can reverse the malignant phenotype of these cancer cells reinforce the view that the mevalonate pathway is an important therapeutic target. Moreover, the recent discovery of immunostimulatory properties of mevalonate pathway inhibitors, which include caspase-1 mediated innate immune activation, further emphasizes the antitumor potential of mevalonate pathway inhibitors. The beneficial effects of mevalonate pathway inhibitors on tumor biology and on immune surveillance should be combined and simultaneously exploited in the therapy of tumors bearing mutant p53.
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 the statins and bisphosphonates, inhibit mevalonate metabolism and have therefore 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. 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, which eventually translate into inflammasome-dependent and caspase-1-mediated activation of innate immunity. The present review focuses on these novel capabilities of mevalonate pathway inhibitors to beneficially affect tumor biology as well as to contribute to tumor immune surveillance.
The mevalonate pathway for protein prenylation as a therapeutic target

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 IPP and DMAPP. Farnesyl pyrophosphate (FPP) synthase, which is inhibited by bisphosphonates (4, 5), catalyzes sequential condensation reactions of DMAPP with two 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 serves membrane attachment or protein-protein interactions, which in most cases is an essential requirement for their biological function. Prenylation occurs on many members of the Ras and Rho family of small guanosine triphosphatases (GTPases). Three enzymes can catalyze protein prenylation: farnesyltransferase, geranylgeranyltransferase I and geranylgeranyltransferase II. Farnesyltransferase (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). Geranylgeranyltransferases (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, but also
occurs on many members of the Rab family of Ras-related G-proteins. Rab prenylation is catalyzed by GGTase 2, which is also referred to as Rab GGTase. Rab proteins do not have a consensus sequence, such as the CaaX box, but most of them instead contain a CC or CXC C-terminal sequence. Rab proteins are bound by the Rab escort protein (REP) over these more conserved regions and then presented to the Rab GGTase. Rab GGTase often transfers two geranylgeranyl groups to the C-terminal cysteins of Rab proteins.

**Protein prenylation inhibitors as antitumor agents.** Many proteins, such as the members of the Ras superfamily, participating in signalling pathways that tumors are frequently addicted to, are prenylated. This observation prompted the development of protein prenylation inhibitors as potential anticancer drugs. Whereas prenyltransferase inhibitors directly inhibit protein prenylation, the statins and the bisphosphonates inhibit either mevalonate synthesis (statins) or mevalonate downstream metabolism (bisphosphonates) and thus also inhibit the formation of the downstream isoprenoids FPP and GGPP (Fig. 1), which are the substrates for farnesylation and geranylgeranylation, respectively (2, 3, 5, 7).

**Statins can affect tumor biology and exhibit immunomodulatory properties.** The statins, which were developed as lipid-lowering drugs to control hypercholesterolemia, inhibit HMG-CoA reductase, the first committed step of the mevalonate pathway (Fig. 1) (1). Statins not only prevent the formation of cholesterol but also block the protein prenylation branch. Downstream depletion of FPP and GGPP due to statin-mediated inhibition of HMG-CoA reductase results in failure of the cell to perform posttranslational protein prenylation (Fig. 1). Statins have been proposed as anticancer agents because of their ability to trigger apoptosis in a variety of tumor cells in a manner, which was sensitive and specific to the inhibition of HMG-CoA reductase (8). The apoptotic response was in part due to the
downstream depletion of geranylgeranyl pyrophosphate and thus due to the inhibition of protein prenylation (Fig. 2). Inhibition of geranylgeranylation of Rho proteins (rather than farnesylation of Ras) seems to be an important anticancer effect of statins (5, 8). In addition to preclinical and some clinical observations, epidemiologic data suggest that statins can lower the risk of certain cancers by up to 50% (9, 10). Mixed clinical responses in early phase 1/2 trials pointed to the importance of reliable markers for the subset of patients that may benefit most from statin-based anticancer therapy (11). Statins may have additional beneficial effects in cancer therapy. Leukemic blasts were found to develop a form of chemoresistance 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 has shown 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 the maintenance of the malignant phenotype (13). Simvastatin used at clinically achievable concentrations could reduce three-dimensional growth of cancer cells expressing a single mutant p53 allele. Moreover, simvastatin could induce extensive cancer cell death in these cells and significant reduction of their invasive phenotype. Intriguingly, the morphological 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 isoprenoid add-back experiments, supplementation with GGPP was sufficient to restore the invasive phenotype in the presence of HMG-CoA reductase inhibition demonstrating that upregulation of protein geranylgeranylation is an important effect of mutant p53 (13). Mutant p53 may thus be an important marker that distinguishes the subset of tumors that is sensitive to statin-induced apoptosis.
Statins have also been shown to have immunomodulatory activity. Modulation of protein prenylation is considered a key mechanism, by which statins alter inflammatory and immune responses (6). Although it is well established that statins by themselves are predominantly anti-inflammatory and immunosuppressive agents (6), an increasing number of reports has demonstrated that statins may induce strong proinflammatory responses, when appropriate co-stimulatory 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 diseases 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). However 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 signalling 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 (FTIs) 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).
Regarding hematological malignancies, AML and myelodysplastic syndromes (MDS) showed promising response rates to FTI monotherapy (18). The FTI tipifarnib (also known as R115777; trade name Zarnestra), which inhibits Ras kinase prenylation, has been tested in a phase 2 study in older patients (median age: 74 years) with previously untreated AML. Complete remission was achieved in 14% of the patients and partial remission or hematological 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 bone marrow samples tested (19). GTase inhibitors (GGTIs) can be GGPP analogues and CAAL (L denotes leucine) peptidomimetics or bi-substrate analogues (20). Despite their potent antiproliferative and pro-apoptotic properties in both in vitro and in vivo models, clinical development of GGTIs has been problematic owing to their toxicity (21). Little is known about immunomodulatory effects of prenyltransferase inhibitors.
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 has been 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 ER stress induced by unfolded protein aggregation not only activates the UPR but that the UPR, in turn, induces the lysosomal degradation pathway of autophagy (26), a catabolic cellular process of self digestion, which helps the cell to get rid of damaged organelles, misfolded proteins, and invading microorganisms (27). Autophagy involves the sequestration of cytoplasmic cargo within double-membrane vesicles and 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-membraned 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 demonstrated 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 knock out mouse models blocking of autophagy can induce innate immune responses (30). Macrophages from mice with deletion of autophagy genes such as LC3B, beclin 1 or Atg16L are more prone to inflammasome-mediated cleavage and activation of caspase-1, leading to the maturation and secretion of IL-1β and IL-18 (30, 31) because autophagy physiologically serves to eliminate active inflammasomes in order to temper inflammation and to restore homeostasis (31). Similar to the genetic deletion of autophagy proteins, the protracted administration of protein prenylation inhibitors will also favor the depletion of functional autophagic proteins, since some of them are subject to extensive prenylation (22, 32). In particular, Rab proteins, most of which are even doubly prenylated, are important for autophagosome formation. The early endosomal protein Rab5 has been shown to act at early formation stages. The late endosomal Rab7, which is essential for lysosome biogenesis, has also been shown to be involved in late stages of autophagosome maturation, presumably by facilitating fusion of autophagosomes with late endosomes and lysosomes (33). The Rab autophagic proteins are thus particularly sensitive targets of pharmacologic protein prenylation inhibitors. Box 1 summarizes the sequential stress responses induced by mevalonate pathway inhibition.

*Mevalonate pathway inhibitors can induce innate lymphocyte activation.* In line with all these observations, statins were recently shown to induce the depletion of prenyl pyrophosphates in human dendritic cells, the professional antigen-presenting cells of the immune system (34, 35). Prenyl pyrophosphate deprivation appeared to generate danger
signals since it translated into caspase-1 activation (Box 1 and Fig. 2). Caspase-1 cleaved the proforms of IL-1ß and IL-18 and enabled the release of the bioactive cytokines. The statin-treated dendritic cells 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 as NK cells usually recognize and attack tumor cells that lack major histocompatibility complex (MHC) class I molecules (37, 38). The statin-induced response of IL-2-primed NK cells could be abolished completely, when cell cultures 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 (36) (Fig. 2).

First evidence of 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 the accumulation of the mevalonate pathway intermediate IPP (Fig. 2), a phoshoantigen 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 (38) (Fig. 2).

Bisphosphonates may exhibit additional immunomodulatory effects by regulating myeloid differentiation. In a murine model of breast cancer, bisphosphonate treatment reduced the number of myeloid-derived suppressor cells (MDSCs) and concomitantly tumor size (42). In the same mouse model a marked reduction of tumor-associated macrophages (TAMs) 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 TAMs, but also in an increase of immature myeloid cells with MDSC characteristics (44). Along the same line, zoledronate has been shown to inhibit dendritic cell differentiation from monocytes and to impair dendritic cell activation via toll-like receptor 4 (45, 46).

However, the potential immunomodulatory effects of bisphosphonates, which arise from the inhibition of protein prenylation, have - until recently - been less well examined.

Zoledronate, the most potent bisphosphonate currently available, not only induces γδ T cell activation (40) but was recently shown to be also capable of inducing NK cell activation (47). This effect also depended on dendritic cells (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 two 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 (36, 47) (Box 1 and Fig. 2).
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), has recently been obtained in a genetic human disease (49). In mevalonate kinase deficiency (MKD), a 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 biological effects of IL-1β (50).

**Concluding remarks and future directions**

The increased activity of mevalonate metabolism, particularly in cancer cells carrying mutant p53, may distinguish tumor cells from non-malignant 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 (13) (Fig. 2). Mevalonate pathway inhibitors may also be used to induce cellular stress responses and to generate those danger signals, which tumor cells – in contrast to pathogens – usually lack. Cellular stress as 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 might be particularly promising since they meet several requirements. They inhibit protein prenylation and may – similar to statins – be able to reverse the malignant phenotype. Their ability to induce the accumulation of IPP (Fig. 2) and to recruit γδ 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 \( \gamma \delta \) T cells in the antitumor immune response (Fig. 2). Clinical studies of mevalonate pathway inhibitors should therefore be designed, which simultaneously exploit their beneficial effects on tumor biology and their stimulatory effects on tumor immune surveillance.
Disclosure of Potential Conflicts of Interest

The authors have declared that no conflict of interest exists.

Grant support

The work in the authors’ laboratory was supported by the COMET Center ONCOTYROL, which is funded by the Austrian Federal Ministries BMVIT/BMWFJ (via FFG) and the Tiroler Zukunftsstiftung / Standortagentur Tirol (SAT). We further appreciate the participation of the TILAK hospital holding company, who serves as a partner in the Oncotyrol research program. Oncotyrol approved the manuscript. We also thank Carola Hanisch for helpful comments and Wolfgang Horninger for continuous support.
Box 1. Cellular stress responses induced by mevalonate pathway inhibitors

- Inhibition of protein prenylation causes stress to the endoplasmic reticulum (ER) and initiates the unfolded protein response (UPR).
- The UPR involves several executive steps to restore ER homeostasis: the boosting of protein folding capacity, the enhanced clearance of misfolded proteins, the slowdown of mRNA translation.
- Alarm signaling during the UPR engages signal transduction pathways that are often also associated with innate immune responses.
- 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.
- 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>Co-stimulus</th>
<th>Response</th>
<th>Ref.</th>
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<tr>
<td>Simvastatin</td>
<td>endothelial cells</td>
<td>IL-1 and TNF</td>
<td>CAM upregulation</td>
<td>(51)</td>
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<tr>
<td>Lovastatin</td>
<td>BM-derived DC</td>
<td>LPS</td>
<td>TNFα, 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>

BM, bone marrow; CAM, cell adhesion molecules; DC, dendritic cell; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; NK, natural killer; PHA, phytohemagglutinin; TNF, tumor necrosis factor;
Table 2. Immunostimulatory effects of bisphosphonates

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Tumor type</th>
<th>Co-stimulus</th>
<th>Response</th>
<th>Ref.</th>
</tr>
</thead>
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<td></td>
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<tr>
<td>pamidronate</td>
<td>multiple myeloma</td>
<td>IL-2</td>
<td>γδ T cell expansion</td>
<td>(39, 55)</td>
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<tr>
<td>pamidronate</td>
<td>lymphoid malignancies</td>
<td>IL-2</td>
<td>γδ T cell expansion</td>
<td>(56)</td>
</tr>
<tr>
<td>zoledronate</td>
<td>breast &amp; prostate cancer</td>
<td>IL-2</td>
<td>γδ T cell expansion</td>
<td>(57, 58)</td>
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<tr>
<td>zoledronate</td>
<td>breast cancer</td>
<td>IL-2</td>
<td>γδ T cell expansion</td>
<td>(59)</td>
</tr>
<tr>
<td>BrHPP*</td>
<td>renal cell carcinoma</td>
<td>IL-2</td>
<td>γδ T cell expansion</td>
<td>(60)</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>
</tr>
<tr>
<td>zoledronate</td>
<td>CD56+ PBMCs in vitro</td>
<td>IL-2</td>
<td>NK cell activation</td>
<td>(47)</td>
</tr>
</tbody>
</table>

BrHPP, BromoHydrin PyroPhosphate; PBMCs, peripheral blood mononuclear cells;
Figure legends

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 two 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 (MKD), a rare hereditary auto-inflammatory 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.

Figure 2. Effects of mevalonate pathway inhibitors on tumor biology and immune surveillance. Mevalonate pathway inhibitors may directly act on tumor cells and change tumor cell biology. Tumor cells bearing mutant p53 have enhanced mevalonate pathway activity and may be particularly sensitive to inhibition. By inhibiting protein geranylgeranylation, mevalonate pathway inhibitors may be able to reverse the malignant phenotype by suppressing tumor cell invasive growth and survival. Mevalonate pathway inhibitors may also stimulate immune surveillance, i.e. the intrinsic potential of the immune system to control or eliminate cancer. Mevalonate pathway inhibition in dendritic cells (DC) may lead to antigen-specific γδ T cell activation via IPP accumulation (bisphosphonates) and antigen-nonspecific, cytokine-dependent activation of IL-2-primed γδ T cells and NK cells (statins and bisphosphonates). These innate lymphocytes can collaborate to produce large amounts of IFN-γ and exhibit potent antitumor cytotoxicity.
References


Three-dimensional growth
Invasive growth
Cell survival

Geranylgeranylation

Mutated p53
Tumor cell

NK cell

γδ T cell

IFN-γ

Costimulation

Proforms of IL-1β + IL-18

Caspase-1

Proforms of IL-1β + IL-18

Statins

HMG-CoA

Bisphosphonates

FPP/GGPP

IPMev

IPP

FPP

GGPP

Geranylgeranylation

↓ Three dimensional growth
↓ Invasive growth
↓ Cell survival

Tumor biology

HMG-CoA

Mev

IPP

FPP

Statins

Bisphosphonates

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Clin Cancer Res  Published OnlineFirst April 23, 2012.

Updated version

Author Manuscript
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-0489

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