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Review

Maslinic acid as an effective anticancer agent

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Abstract: Maslinic acid (2α,3β-dihydroxyolean-12-en-28-oic acid) is a naturally occurring pentacyclic triterpenic compound. Maslinic acid is gradually gaining attention as an excellent pharmacologically active product because of its premium biological properties. In this review we will focus on chemopreventive properties of Maslinic acid against different cancers. Seemingly, available data is limited and we have yet to unravel how Maslinic acid therapeutically targeted oncogenic cell signal transduction cascades in different cancers. Moreover, there are visible knowledge gaps about the ability of Maslinic acid to modulate oncogenic and tumor suppressor microRNAs in various cancers.

Key words: Cancer; Signaling; Apoptosis; Maslinic Acid.

Introduction

Maslinic acid has been shown to exert health promoting effects. There is sufficient evidence related to ability of Maslinic acid to ameliorate worsening conditions of diabetes, obesity and inflammation. Maslinic acid has also shown tremendous potential to inhibit cancer in different studies. Maslinic acid has a molecular weight of 472.71 g/mol. Hydrogen bond donor count of Maslinic acid is 3 and acceptor count is 4. Topological polar surface area of Maslinic acid is 77.8 A^2. There has been an exponential growth in the discovery of natural products having characteristically unique potential to improve worsening disease conditions (1,2). There has been a rapidly growing interest in exploring the cancer suppressive effects exerted by different natural products (3,4,5,6). In this review we will focus on Maslinic acid mediated anticancer effects. In the upcoming section we will summarize on the ability of Maslinic acid to regulate different proteins in colon cancer.

Colon cancer

Colon cancer is multifaceted and difficult to treat (7,8,9). Various reports have demonstrated that Maslinic acid effectively suppressed colon cancer. It had previously been reported that Maslinic acid metabolized into majority of monohydroxylated metabolites whereas phase II derivatives were not detected (10). Higher concentration of Maslinic acid was detected in the intestine which clearly suggested that it might be useful and advantageous in the prevention of colon cancer. Maslinic acid-enriched diet markedly reduced intestinal tumorigenesis in Apc(Min/+) mice (11).

In this section we will summarize role of Maslinic acid in prevention/suppression of colon cancer.

Apoptotic pathway has been extensively studied in different cancers and overwhelming list of natural products provided evidence of ability of natural products to induce apoptosis in drug-resistant cancer cells. Apoptosis is a programmed cell death. Molecular studies have focused on intrinsic and extrinsic pathways of apoptosis. Extrinsic apoptotic pathway is triggered by activation of caspase-8. Caspase-8 switched caspase-3 to its active form to induce apoptosis. Intrinsic pathway is triggered by entry of truncated BH3-interacting domain death agonist (BID) into mitochondrion. Entry of tBID into mitochondrion promoted release of Second mitochondria-derived activator of caspase (SMAC) and cytochrome-c into the cytoplasm. Cytochrome-c, apoptotic protease activating factor and pro-caspase-9 formed a multi-protein complex known as apoptosome. Apoptosome induced activation of caspase-9. It is relevant to mention that FasL, TNF-related apoptosis-inducing ligand (TRAIL) and Tumor necrosis factor (TNF) proteins have been shown to induce apoptosis in cancer cells.

FADD overexpression was noted to enhance apoptosis in SW480 cells. Adenovirus-mediated overexpression FADD induced regression tumor growth in xeno-

grafted mice (12).

It was surprising to note that Maslinic acid functionalized extrinsic pathway in colon Caco-2 adenocarcinoma cells (13). Caspase-8 and caspase3 were found to be increased in cancer cells treated with Maslinic acid. However, cytochrome c remained unchanged which clearly suggested that Maslinic acid did not trigger intrinsic pathway (13). Maslinic acid also induced activation of c-Jun N-terminal kinase (JNK) in Caco-2 adenocarcinoma cells (14). However, Maslinic acid has been shown to differentially target different colon cancer cell lines. Maslinic acid effectively functionalized intrinsic pathway in HT29 cells (15). It triggered release of cytochrome-c and induced activation of caspase-9 in HT29 cells. Excitingly, levels of JNK and p53 were also noted to be enhanced in Maslinic acid HT29 cancer cells (16).

Lung cancer

Cutting edge research has helped us to develop a better comprehension of lung cancer and the mechanisms which underlie its development and progression (17,18, 19).

Inhibitor of apoptotic protein (IAPs) family has tremendous capacity to interfere with the process of programmed cell death. Hallmark characteristic of an IAP protein is the presence of the baculovirus IAP repeat (BIR) domain that mediated protein–protein interactions. XIAP structurally interacted and inhibited caspase 3 and caspase 9. Studies had shown that linker region between the BIR1 and BIR2 domains contained specific amino acids which were noted to interact with active sites of caspase-7 and caspase-3. Excitingly, BIR3 domain of XIAP interacted with homo-dimerization surface of caspase-9. It has been shown that caspase-9 required a dimerization-directed structural reorganization to generate an active catalytic pocket and subsequently XIAP interfered with dimerization of caspase-9.

Maslinic acid induced activation of caspase-8,-9 and caspase-3 in lung cancer A549 cells. Maslinic significantly reduced survivin, XIAP, c-IAP1 and c-IAP2 in lung cancer cells (Bai et al, 2016). However, Maslinic acid markedly enhanced Direct IAP-binding protein with low pI (SMAC/DIABLO). Maslinic acid morphologically altered lung cancer cells as evidenced by chromatin condensation, karyopyknosis and fragmented nucleus, which are key features of apoptosis (20). Maslinic acid induced downregulation of HIF-1α, VEGF, survivin and inducible-nitric oxide synthase (iNOS) both under hypoxic and normoxic conditions (21). Treatment of cells with YC-1, an inhibitor of HIF-1α, significantly abrogated maslinic acid-triggered decrease in the levels of HIF-1α, VEGF, iNOS and survivin (21).

Gastric cancer

Maslinic acid was found to be effective against gastric cancer. Deregulated JAK-STAT signaling is frequently noted in gastric cancer (22). Janus kinase (JAK) belongs to the family of non-receptor tyrosine kinases. Activation of JAKs occurs upon ligand-receptor interaction that induces multimerization. Ligand-receptor interaction brought two JAKs in closer proximity and consequently allowed trans-phosphorylation. Functionally active JAKs phosphorylated receptor and signal transducer and activator of transcription (STAT) proteins. STATs exist in the cytoplasm of resting cells as inactive homodimers. However, ligand-receptor interaction induced activation of STAT proteins by JAKs. JAKs phosphorylated tyrosine residues of receptors. Phosphor-tyrosyl residues of the receptor acted as a binding site for STAT proteins which were further phosphorylated by JAKs. Activated STATs sequestered away from the receptor and reoriented themselves into an anti-parallel dimeric form, where the SH2 domain of one STAT interacted with phosphor-tyrosine of the other STAT. STAT dimers accumulated in the nucleus and transcriptionally regulated expression of myriad of target genes.

Many natural products (thymoquinone and piperlongumine) have been shown to inhibit STAT3 signaling in gastric cancer (23; 24). Maslinic acid was also found to be very effective against JAK-STAT signaling (Wang et al, 2017). Maslinic acid efficiently inhibited JAK2 and STAT3 in gastric cancer cells (shown in figure). BCL2-associated agonist of cell death (BAD) and BCL2 associated-X (BAX) proteins played significant role in induction of apoptosis. Maslinic acid dose dependently enhanced the levels of BAD and BAX in gastric cancer cells (25).

It will be important to see how Maslinic acid modulates negative regulators of JAK-STAT signaling in different cancers. Different molecules particularly, suppressor of cytokine signaling (SOCS) and protein inhibitor of activated STAT (PIAS) have been shown to interfere with JAK-STAT signaling and it will further improve our understanding about ability of Maslinic acid to target JAK-STAT signaling at multiple levels.

Maslinic acid mediated targeting of protein network in prostate cancer

Increasingly it is being realized that prostate cancer (PCa) progression and gradual development of resistance against various therapeutics are frequently driven by aberrantly activated androgen receptor-directed signaling pathways that can be therapeutically targeted. High-throughput technologies, have enable the analyses of signaling networks in individual tumors and started to play a central role in advancement of personalized therapy by discovering biomarkers of pathway activity and clinically effective drug targets. To maximize translatability, different models of PCa bone metastases have been developed, which include animal models, bone implant models, cell line injection models and patients-derived xenografted models. Synthetic and natural products are currently being tested for efficacy and these chemicals have been tested in different PCa models for analysis of their efficacy against tumor growth and metastasis.

Maslinic acid considerably repressed both the basal and EGF-triggered migratory capacity of prostate cancer DU145 cells (26). EGF increased secretion of pro-MMP-9, but Maslinic acid sufficiently decreased secretion of pro-MMP-9. Furthermore, Maslinic acid also effectively blocked secretion of pro-MMP-2. There was a dose-dependent increase in TIMP-2 secretion in

cancer cells treated with Maslinic acid. Moreover, EGF was noted to stimulate secretion of pro- and active-uPA however, maslinic acid significantly suppressed secretion of these proteins. Maslinic acid strongly inhibited VEGF secretion in prostate cancer cells kept under hypoxic and normoxic conditions. Maslinic acid inhibited phosphorylation of AKT/PKB and extracellular signal-regulated kinase 1/2 (26).

Targeting of NF-κB and its associated Target Genes in Pancreatic and Gallbladder Cancers

Increasingly it is being realized that a series of stimuli play role in activation of the canonical pathway of NF-κB. Functionally active inhibitor of Kappa-B kinase (IKK) phosphorylated IκB on serine residues and induced poly-ubiquitinylation and degradation of IκB. Following the IκB degradation, cytosolic NF-κB dimers accumulated in the nucleus and transcriptionally modulated expression of myriad of genes (shown in figure).

TNFα has been noted to induce apoptosis in cancer cells. However, TNFα has also been shown to induce activation of NF-κB in treated cancer cells (27). Therefore, researchers focused on identification of the molecules which can inhibit NF-κB in different cancers. Therefore, keeping in view the need for inhibition of NF-κB, Maslinic acid was used in combination with TNFα to maximize its efficacy against pancreatic cancer cells. Maslinic acid not only inhibited TNFα-mediated degradation of IκBα but also blocked nuclear accumulation of NF-κB. Maslinic acid remarkably inhibited tumor growth in mice xenografted with pancreatic cancer cells (27). Maslinic acid worked synergistically with Gemcitabine and exerted inhibitory effects on constitutively active NF-κB and NF-κB-driven target genes including MMP-2, MMP-9, cyclin D1, BCL-2 and BAX. Maslinic acid and Gemcitabine effectively induced regression of tumors in mice implanted with EH-GB2 cells (28).

Structural modifications

Maslinic acid is a naturally occurring pentacyclic triterpenic compound. Structurally modified triterpenoids have been noted to demonstrate stronger biological activities (29). Most recently, several C-28 amide derivatives of maslinic acid were semi-synthesized for evaluation of biological properties. Some of the diamine conjugates and a PEGylated diamine conjugate of Maslinic acid inhibited proliferation and induced apoptosis in B16-F10 cells (29). Maslinic acid derivatives bearing 1,5- and 1,4-di-substituted triazoles were found to be efficacious against colon SW480 cancer and breast cancer EMT-6 cells (30). Acetylated Maslinic acid derivative ("EM2") containing a benzylamide structure differentially targeted cancer cells. EM2 dose-dependent inhibited B164A5 and A375 cells (31).

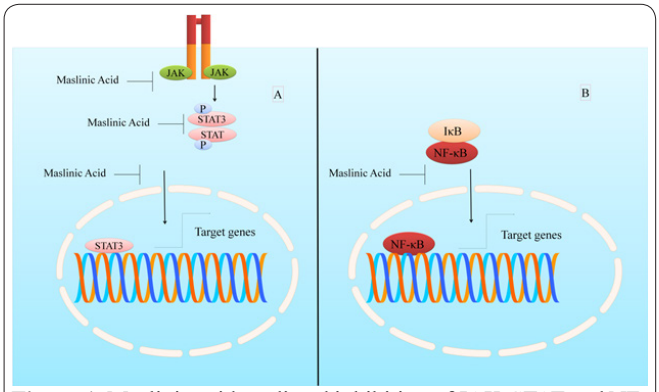

Figure 1. Maslinic acid mediated inhibition of JAK-STAT and NF-κB-triggered pathway.

Moreover, 3D-QSAR model has recently been used as a tool to virtually screen efficacy of Maslinic acid analog (P-902) (32). P-902 was comparatively analyzed with standard anticancer drug topotecan. ADMET analysis of best-hit compound P-902 demonstrated that it was considered safer in pharmacological and toxicological studies. Overall intrinsic clearance of P-902 in liver microsomes was 11.051 µL/min/mg. P-902 was within the range of standardized toxicological parameters and considered to be appropriate for further high-throughput analysis (32).

Bioavailability

Liquid chromatography tandem mass spectrometry was used for quantification of Maslinic acid in plasma and urine (33). Oleanolic acid was metabolized as both glucuronide and sulfate conjugates whereas Maslinic acid was mainly excreted as glucuronide (33).

Reverse-phase high-performance liquid chromatography (HPLC) coupled to mass spectrometry (MS) detected concentration of Maslinic acid in cancer cells (34). This study was effective in evaluation of the concentration of Maslinic acid taken up by different cancer cells. Maslinic acid-incorporation curve and the lower percentage of incorporation of Maslinic acid into HT29 cells pinpointed towards exquisite role of carrier proteins that interacted with Maslinic acid with low affinity at lower concentrations (34). However, increasing concentration of Maslinic acid induced an increase in the uptake of Maslinic acid by cancer cells. Maximum uptake/transport was dependent on the number of carrier proteins present in the membrane of cancer cells (34).

Ability of maslinic acid to modulate signaling pathways: More questions than answers

Maslinic acid is gradually gaining appreciation because of its ability to induce apoptosis and inhibit cancer. However, we still have outstanding questions related to ability of Maslinic acid to modulate multiple signaling pathways. Deregulation of spatio-temporally controlled pathways particularly PDGF/PDGFR, VEGF/VEGFR and EGF/EGFR need extensive research.

Maslinic acid has been shown to potently induce apoptosis in cancer cells however, it needs to be tested in TRAIL-resistant cancer cell lines. Keeping in view differential killing activity of TRAIL, it will be very advantageous if Maslinic acid stimulated expression of TRAIL-receptors on surface of cancer cells. On a similar note Maslinic acid can be used in combination with either microRNA mimics or miRNA inhibitors to maximize apoptotic rate in cancer cells.

Likewise, mTOR signaling has been extensively studied in different cancers and it will be essential to see how Maslinic acid regulated mTORC1 and mTORC2 in various cancers. Our recent study showed that Maslinic acid induced autophagy via downregulation of HSPA8,

a heat shock protein in pancreatic Panc-28 cancer cells (35). Maslinic acid inhibited the proliferation and induced autophagy of Panc-28 cells by regulating the expression levels of autophagy related proteins. HSPA8 knockdown significantly inhibited cell viability and enhanced the cytotoxic effects exerted by Maslinic acid, whereas HSPA8 overexpression substantially enhanced cell viability and interfered with the effects of Maslinic acid (35). It is relevant to mention that Maslinic acid mediated inhibitory effects on tumor growth have been insufficiently studied in xenografted mice. It is vital to analyze if Maslinic acid strongly inhibits tumor growth and metastasis in xenografted mice. Preclinical studies can be designed strategically and Maslinic acid can be combined with different chemotherapeutic drugs or various other natural products to study growth inhibitory effects and reversal of multi-drug resistance. Therapeutic targeting of metastasis is extremely challenging and future studies must also emphasize on analysis of the ability of Maslinic acid to inhibit multiple steps of metastasis. Although bioavailability of Maslinic acid is significant however, different methodologies must be designed to maximize its biodistribution. In accordance with this concept, nanotechnologically assisted methods can prove to be helpful in remarkable increase in delivery of Maslinic acid to target cells/sites.

Conclusion

Maslinic acid has been shown to inhibit proliferation of cancer cells and induce apoptosis. However, there are various facets of molecular oncology which still have to be to uncovered. Future studies must converge on identification of signal transduction cascades which can be therapeutically targeted by Maslinic acid. Various studies have provided evidence of considerable bioavailability of Maslinic acid, therefore we must move forward and use high-throughput technologies to discover how Maslinic acid exerts its effects at transcriptional, post-transcriptional, translational and post-translational level to inhibit cancer.

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