Development of novel dual inhibitor of CXC Chemokine receptor 4 and Mcl-1 against Multiple Myeloma

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Multiple myeloma (MM) is a neoplastic plasma-cell disease. It is characterized by clonal proliferation of malignant plasma cells in the bone marrow (BM) microenvironment, monoclonal protein in blood or urine, and associated organ dysfunction. The treatment options approved by FDA are immune-modulatory agents, proteasome inhibitors, and autologous stem cell transplantation (ASCT). Unfortunately, MM remains uniformly fatal owing to intrinsic or acquired drug resistance and the median survival time is 3 to 5 years. Thus, there is a great need for novel strategies to combat MM. The intimate relationship of myeloma cells to BM microenvironment is “hallmark of myeloma.” The homing of MM cells to the BM, mediated by the gammacrine stromal cell-derived factor-1α (SDF-1α) and its receptor CXCR4 has important functional sequelae. The BM microenvironment, constituting cells secrete chemokines, cytokines, and growth factors such as interleukin 6 (IL-6), vascular endothelial growth factor (VEGF). SDF-1α, and tumor necrosis factor a (TNFα) etc.1

These growth factors contribute in activation of several signaling pathways including nuclear factor-kB (NF-κB), phospholipidinositol 3 kinase (PI3-K/Akt), Ras-Raf-MAPK kinase (MEK) extracellular signal regulated kinase (ERK), and the Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3). Activation of these pathways has been associated with increased expression of several anti-apoptotic proteins such as Bcl2, Bcl-xl, Mcl-1, and XIAP.2

Mcl-1 is one of the most highly amplified genes in a variety of human cancers including MM and contributes in drug resistance.1 Thus, Mcl-1 becomes unique target to overcome drug resistance in MM.2

Gambogic acid (GA) is a xanthine derived from the resin of Garcinia hanburyi (also called mangosteens). We have previously shown that GA inhibits CXCR4 in MM.3

We modified GA by adding MCL1 inhibitor moieties in order to develop this molecule as a dual inhibitor of CXCR4 and MCL1. We investigated whether the gambogic acid (GA) analog(s) can modulate survival and drug resistance of MM cells.

Abstract

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Introduction

MM cells are highly dependent on the bone marrow (BM) microenvironment for growth and survival.1

Migration of cells through the blood to the BM niches requires active navigation, a process termed homing.2

One of the most extensively studied chemokines in homing is stromal cell-derived factor-1α (SDF-1α) also known as CXC Chemokine ligand 12 (CXCL12) and its receptor, CXCR4.2

The BM microenvironment constituting cells secrete chemokines, cytokines, and growth factors such as interleukin 6 (IL-6), vascular endothelial growth factor (VEGF). SDF-1α, and tumor necrosis factor a (TNFα) etc.1

These growth factors contribute in activation of several signaling pathways including nuclear factor-kB (NF-κB), phospholipidinositol 3 kinase (PI3-K/Akt), Ras-Raf-MAPK kinase (MEK) extracellular signal regulated kinase (ERK), and the Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3). Activation of these pathways has been associated with increased expression of several anti-apoptotic proteins such as Bcl2, Bcl-xl, Mcl-1, and XIAP.2

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Figure 1. Intimate relationship between MM and BM microenvironment. BMSCs secrete cytokine a growth factors, these growth factors activate several pathways in MM. GA targets these pathways.

Figure 2. A, GA interacts with CXCR4 and modulates the expression of CXCR4 protein of MM cells

Figure 3. A, GA analog reduces the survival of MM cells. MM cells (RPMI 8226 and U266) were treated with different concentration of GA, and its analogs for 48h. Cell viabilities were assessed using MTT assay. As shown in the figure treatment of GA and its analog effectively kill MM cells. Prism software was used to plot the graph. B, Effect of GA on cell survival protein suppression. The human MM RPMI 8226 cells were treated with the indicated amount of GA analog for 24h. Treatment of GA analog modulates expression of anti-apoptotic proteins such as Mcl-1, Bcl-2, and caspase 3.

Conclusions and future directions

GA analog reduces cell viability and induces apoptosis through inhibition of Mcl-1

References