2560 Bitter Taste Receptors System Is Expressed and Functional in Both HSCs and Leukemic Cells

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Hall GH (San Diego Convention Center)

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Acute Myeloid Leukemia (AML) is a clonal disease sprouting from a rare population of leukemic stem cells. Over the past years, increasing interest is gaining the contribution that cell-extrinsic factors have in AML generation and maintenance. In this context, the ability of leukemia cells to

detect changes in the microenvironment is important in responsiveness to environmental fluctuations.

Bitter taste receptors (T2Rs) are typical G-protein coupled receptors and are normally found on the surface of the tongue. Recent studies showed that T2Rs are widely expressed in various parts of human anatomy and have been shown to be involved in physiology of respiratory system, gastrointestinal tract and endocrine system. thus suggesting a wider function in "sensing microenvironment". We recently reported that AML cell lines OCI-AML3, THP-1, and AML primary cells expressed fully functional T2Rs subtypes. Gene expression profile analysis showed that after T2Rs activation, leukemic cell lines underwent down-regulation of genes involved in positive regulation of cell proliferation, migration, and cell-cycle. Whereas genes involved in cell adhesion and DNA repair were up-regulated. Functional assays supported these results (Blood 2017 130:3949).

In the present work, we further investigated the role of T2Rs in BM microenvironment by extending the analysis to AML primary samples and to normal hematopoietic stem cells (HSCs). Similarly to AML cell lines, T2Rs activation with high dose of agonist induced a reduction of cell viability associated to apoptosis induction, while non-toxic doses reduced cell migration and clonogenic capacity. In addition, T2Rs stimulation with agonist makes AML cell lines more prone to oxidative and metabolic stress. Leukemia cells displayed a quiescent phenotype in response to T2Rs activation suggesting that mitochondrial activity is significantly limited by T2Rs agonist treatment. Since no data are available on the presence and the function of T2Rs on normal hematopoietic stem cell counterpart, we characterized T2Rs expression on CD34+ cell isolated from healthy donor. CD34+ cells express several T2Rs subtype without significant differences compare to AML cells. Their activation with high dose of agonist reduced HSCs viability inducing apoptosis, while non-cytotoxic doses reduced clonogenic capacity and promoted migration.

Given the effect of T2Rs activation on crucial AML cell function, we tested the therapeutical potential of T2R agonist with and without conventional chemioterapic agent. Interestingly we observed that T2Rs agonist have a synergistic effect with cytarabine, reducing leukemia cell viability when combined with ARA-C compared to their use as single compound. The combination allowed to reach a high toxicity using lower doses of chemotherapic agent.

Overall our results indicate that T2Rs receptor system is expressed and functional in both leukemic cells and HSCs. In particular, in AML cells T2Rs activation is associated with quiescence induction and prevention of migration. T2Rs stimulation modulates HSCs function but their role

need to be further deepen. These data may suggest a role for microenvironment “bitter” molecules in regulating normal and leukemic hematopoiesis.