Chapter 8

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In conclusion, RBL exhibited binding to both normal human PBMC and leukemic T cells, but induced opposite effects in the two cell types. RBL induced proliferation, cytokine production and activation of immune effector cells in normal human blood cells. On the other hand it inhibited proliferation and induced cytotoxicity in human leukemic cell lines Molt-4 and Jurkat.

RBL induced T-cell activation as evidenced by phosphorylation of ZAP-70 and downstream activation of MAPK and STAT signaling pathways that resulted in IL-2 secretion and IL-2Rα expression. RBL-induced proliferation was blocked by neutralizing IL-2 suggesting the importance of IL-2 in RBL-induced proliferation. RBL stimulated the secretion of other Th1 (IFNγ, IL-12) and Th2 (IL-4 and IL-19) cytokines suggesting the activation of both Th1 and Th2 type cells. RBL-induced proliferation and cytokine secretion were blocked by inhibiting p38 MAPK and STAT signaling pathways thus implicating these pathways in RBL-induced mitogenesis. The findings also suggested that RBL can induce proliferation of isolated T cells without any co-stimulation by associated APCs. The study revealed that RBL might exert its biological activities in lymphocytes by binding to CD45, thus implicating a role for CD45 in RBL-induced mitogenic activity.

The immunomodulatory activity of RBL was further explored by studying its effect on monocytes. RBL induces the differentiation of monocytes into macrophage-like cells that exhibits mature macrophage and stimulated secretion of cytokines and phagocytosis. A comparison of the responses of primary cultures of monocytes and monocytic cell lines to RBL revealed that THP-1 cells did not mimic the response in primary monocytes. Interestingly, differentiation of primary monocytes to macrophage-like cells and functionality was better achieved with RBL than with PMA+LPS stimulation suggesting RBL has a high potential for antimicrobial agent. This property of RBL adds to its properties as an immunomodulator.

RBL exposure induced inhibition of proliferation and cytotoxicity in leukemic cells. Studies also revealed a significant role for caspase-8 mediated pathway in RBL-induced apoptosis by cleavage of Bid, loss of MMP and down regulation of anti-
apoptotic proteins BcL-2 and Bel-XL. Considering the cytotoxic effect and the immunomodulatory properties of RBL, RBL has the potential to be a useful tool in cancer research. Few reports are reported to display differential responses in normal and tumor cells. Native jacalin is mitogenic to T cells [103;318;319], and acts as inhibitor of proliferation of HT29 cells [296;320;321]. Mistletoe lectins have been shown to exhibit broad immunostimulatory activity and antitumor effects and have been used in adjuvant cancer therapy [322;323].

Lectins have been utilized as powerful tools for studying lymphocyte differentiation, modeling of antigen activation, initiation of cell division and growth when investigating the status of immunological disorders in patients. To this end, only some well-known plant mitogenic lectins such as PHA-L, Con A, and PWM (Pokeweed mitogen) are commercially available [324]. It is one of the aims of natural complementary medical therapy to stimulate natural resistance in order to restrain cancer progression or improve defective immunological conditions. Mitogenic lectins have been used as therapeutic agents for the management of malignant tumors due to their capacity to induce global immunostimulation by nonspecific activation of CD4+/− and CD8 +/− cells and also the monocyte macrophage lineage. Defective immunological functions of cells of the macrophage lineage have been observed in immunocompromised patients and contributes to the pathogenesis of HIV-1 infection and other immunological disorders [325]. As RBL enhances monocyte/macrophage function like cytokine secretion and phagocytosis, the use of this immunomodulator is of potential clinical interest as adjunctive immunotherapy in immunosuppressed individuals.

In sum, RBL may be visualized as double-edged sword wherein on one hand it acts as an immunomodulator and stimulates immune response by inducing proliferation and secretion of cytokines by normal lymphocytes and activation of monocyte/macrophage lineage, on the other it induces apoptosis in cancer cells. Therefore, with potential of RBL as an exceptional and novel mitogenic lectin with immunomodulatory and anticancer property is of great significance. With its multi-faceted properties, RBL is promising candidate for therapeutic applications in cancer and immune disorder-related diseases.