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DISSERTATION SUMMARY

Ceramide mediated apoptotic pathway is involved in galectin-1 induced apoptosis in Jurkat T lymphocytes

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Galectin-1, a member of the S-type mammalian lectin family is characterized by high affinity for β-galactoside on complex glycoconjugates and by a highly conserved carbohydrate recognition domain (CRD). Galectin-1 induces apoptosis of immature cortical thymocytes, activated peripheral T lymphocytes and T leukemia cell lines. According to this function, galectin-1 is a potential valuable therapeutic agent in autoimmune and inflammatory diseases. In spite of the increasing interest, the molecular mechanism of the apoptotic process is not well understood yet.

In the present study, we examined the possible involvement of protein kinase C (PKC) and ceramide in apoptosis induced by galectin-1. Recently, we showed that $p56^{lck}$, the non-receptor tyrosine kinase is involved in the galectin-1 triggered apoptosis. The literature data indicated that ceramide, an apoptotic lipid second messenger also dependent on the presence of functional lck. Upon this finding we have been analysing whether galectin-1 acts through the ceramide mediated apoptotic pathway. The latter was analysed by exogenously added C6-ceramide, as a model. We found that: 1) Phorbol 12,13-dibutyrate (PDBu) inhibited the galectin-1 induced apoptosis by 50-100%. Since PDBu directly activates PKC, we suggest that PKC activation counteracts galectin-1-mediated apoptosis similarly to that induced by ceramide. 2) A caspase-8 inhibitor did not affect the apoptosis either induced by galectin-1 or ceramide. In order to clearly determine whether caspase-8 is requisite for galectin-1 mediated apoptosis we compared the sensitivity of the wild type and the caspase-8 deficient (J-$C8^{mut}$) Jurkat cells. Both cell lines were similarly sensitive to galectin-1 and ceramide but the caspase 8 mutant was resistant to apoptosis initiated via the TNF receptor. 3. To gain a direct evidence for the role of the ceramide pathway in this process we used fumonisin B1 a specific inhibitor of ceramide synthesis. This drug did not inhibit the effect of galectin-1 indicating that production of ceramide upon galectin-1 stimulation did not occur through the synthetic route. Further we studied whether the catabolic production of ceramide is involved in galectin-1 induced apoptosis. For this purpose we used another inhibitor of ceramide-mediated apoptosis, sphingosine-1 phosphate (S1P). S1P inhibited the galectin-1 or ceramide induced apoptosis similarly. Thus, S1P, likely generated via PKC-mediated activation of sphingosine kinase, downregulates the galectin-1 apoptotic pathway. Taken together, our results strongly suggest that galectin-1 induced apoptosis is mediated by the intracellular ceramide level, leading to the activation of a caspase cascade.

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