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REVIEWARTICLE

GALECTIN-3 IN MODULATING INFLAMMATION IN ADIPOCYTES AND MACROPHAGES

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Abstract

Previous studies on endogenous galectin-3 proved its role in the pathogenesis of asthma, heart attack and obesity. Galectin-3 applied therapeutically as gene therapy suppresses the inflammatory response in a rat asthma model thus presenting novel therapeutic approach to the treatment of several diseases. Despite availability of enormous data concerning galectin-3 expression, the mechanisms of regulation of galectin-3 expression are relatively poorly defined. Galectins are either pro-inflammatory or anti-inflammatory, such as galectin-1, may be employed as anti-inflammatory agents, while others, such as galectin-3, are evidently suitable targets for anti-inflammatory drugs. Investigating galectin-3 in the immune response has demonstrated that this protein displays pro- and anti-inflammatory roles depending on the target cell type, whether galectin-3 is acting exogenously or endogenously, its expression level and other inflammatory factors. It is therefore imperative that all these factors be taken into consideration should galectin-3 be used therapeutically.

Introduction:-

Galectin-3 entails a complex mechanism involving various transcription factors and signaling mediators and depends on cell type, degree and severity of stimuli and environmental conditions[1]. LGALS3, the gene coding for human galectin-3 is located on chromosome 14, locus q21-q22. LGALS3 promoters do not contain the TATA box upstream of the transcription initiation site. However, multiple GC motifs for binding of Sp1 transcription factor are found, which is a common feature of constitutively expressed, or the so-called housekeeping genes[2]. In addition to five putative Sp1 binding sites, the promoter region of the human LGALS3 gene contains 5 cAMP-dependent response elements (CRE), 4 AP-1 transcription factor binding sites and 1 AP-4-like consensus sequence, two NF-κB-like motifs, sis-inducible element (SIE) and a consensus basic helix-loop-helix (bHLH) core sequence[3-5]. Although the LGALS3 promoter is similar to that of a housekeeping gene, galectin-3 expression increases in response to serum stimulation, indicating it as an immediate-early gene. The presence of CRE and NF-κB-like sites in the promoter region suggests that galectin-3 expression could be regulated through metabolic/signaling pathways involving the cAMP-response element-binding protein (CREB) or the NF-κB transcription factor that is at the core of inflammatory pathways[6]. The involvement of NF-κB and Jun protein in the regulation of galectin-3 expression

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has been widely confirmed. Galectin-3, a unique chimera-type member, is widely expressed in numerous cells[7-8] (Figure 1).

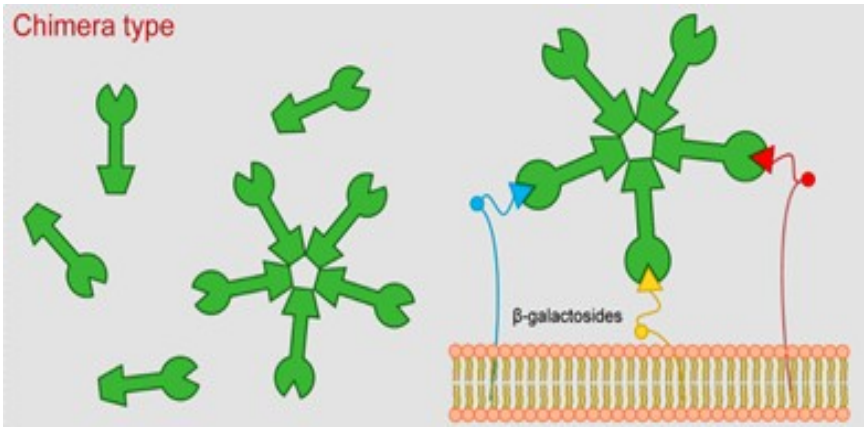

Figure 1:- Structure of galectin-3, chimera-type member of galectin family.

Functions and signaling in macrophages:
Galectin-3 might not be specific for a certain macrophage subtype, nevertheless, several basic macrophage functions were shown to be dependent on galectin-3[9]. Galectin-3 plays a critical role in the phagocytosis of apoptotic cells and IgG-opsonized material by macrophages. Galectin-3 can serve as a macrophage pattern recognition receptor[10]. This role has been assigned primarily to the extracellular, secreted galectin-3, conveyed by its CRD binding to glycan moieties on invading pathogens[11]. Pathogen recognition and binding could be an initial step leading to either pathogen cell death or phagocytosis and neutralization of the pathogen inside the macrophage[12-14]. Besides regulating inflammation and tissue remodeling through its roles in phagocytosis, pattern recognition and signaling, an emerging view connects galectin-3 to intracellular sorting and trafficking of glycoproteins[15].

Galectin-3 and adipose tissue:
In fibroblast culture, exogenous galectin-3 has been reported to promote cell proliferation. These findings suggest that galectin-3 expression may be capable of affecting adipocyte proliferation and thereby afford a mechanism through which obesity might be treated/regulated[16]. In human subcutaneous adipose tissue, galectin-3 was found predominantly in the preadipocyte fraction. Many intracellular binding partners for galectin-3 have been identified, which include Bcl-2, Gemin4, CBP70, cystidine/histidine-rich protein (Chrp), cytokeratins and β-catenin. Protein-protein rather than lectin-glycoconjugate interactions account for majority of intracellular interactions with galectin-3, except in the case of cytokeratins[17]. Gemin4, macromolecular spliceosome complex coordinates pre-mRNA splicing, plays an important role in the post-transcriptional process. Galectin-3 interaction with Gemin4 is regarded as a critical event in spliceosome assembly[18].

Bcl-2 was the first discovered cytosolic partner of galectin-3[19]. Galectin-3 has significant sequence similarity with the anti-apoptotic protein Bcl-2, most remarkably the NWGR motif conserved amongst the Bcl-2 family is also found in Galectin-3[20]. Interactions with Bcl-2 can be inhibited by lactose and other saccharides, despite Bcl-2 not being a glycoprotein. It is speculated that the CRD of galectin-3 could be responsible for this molecular interaction or conformational changes induced upon binding of lactose to galectin-3 may facilitate its interaction with Bcl-2[21]. These interactions between galectin-3 and Bcl-2 may be partly responsible for the effects on cell growth and apoptosis, but also suggest that galectin-3 may influence mitochondrial integrity and reactive oxygen species (ROS) generation[22]. Other galectin-3 ligands involved in apoptotic signaling have recently been identified; CD95 (APO-1/Fas) is a member of the death receptor family, Nucling is involved in the regulation of apoptosis and Alix/AIP1 is also involved in the regulation of apoptotic events[23].

Galectin-3 has been shown to activate Protein Kinase B (Akt/PKB), a Ser/Thr protein kinase involved in regulating the inhibition of apoptosis and the stimulation of cell proliferation, further linking galectin-3 with uncontrolled cell growth and cancer[24-27]. Ras proteins are important small GTPases, which can affect cell proliferation, differentiation, survival and death. Galectin-3 is a specific binding partner of activated K-Ras but does not interact with other members of the Ras family, including activated H-Ras or N-Ras[28]. This specific binding promotes the

activation of phosphatidylinositol 3-kinase (PI3-K/Akt), while Raf-1 augments extracellular signal-regulated kinase (ERK) activation[29]. On the other hand, Galectin-1 binds to both activated H-Ras and K-Ras thus deflecting the Ras signal towards Raf-1 and away from PI3-K. K-Ras is the most important Ras oncoprotein in human tumours and as galectin-1 and galectin-3 levels vary amongst normal and cancer cells, it is possible to conclude that the ratio of these galectins defines the outcome of oncogenic K-Ras transformation[30].

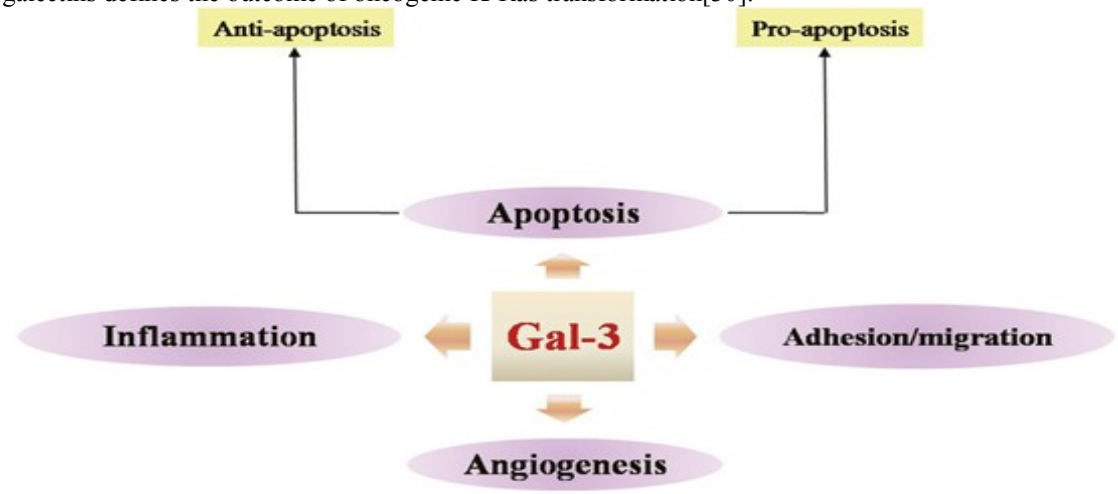

Figure 2:-The functions of galectin-3 in the cells.

Extracellular functions:

Once outside the cell, galectins interact with various cell surface β-galactosides containing glycans via the CRD. In vivo galectin-3 binds to ligands containing lactose as the basic unit of recognition[31]. In general, galectins bind to Type I Gal β1,3 GlcNAc or Type II Gal β1,4 GlcNAc units with higher affinity to polylactosamine chains. Expression of these glycan structures depends on the activity of glycosyltransferases[32]. β1, 6-N-acetylglucosaminyl transferase (Mgat5, GnT-V) promotes the addition of N-acelyllactosamine on N-glycans, thus creating the preferred ligands for galectin-3. The majority of extracellular functions and subsequent signal transduction of galectin-3 are thought to be due to the CRD binding to Mgat5-modified N-glycans on various cell surface receptors[33]. This is followed by the galectin forming oligomers via its N-terminal domain, thus functioning as a biological cross-linker among several glycoproteins. Previous data has shown that a truncated form of galectin-3 lacking the N-terminal domain, while still able to bind ligands, cannot exert its functions. Recent data has reinforced this proposal by demonstrating oligomerization of galectin-3 at a cellular level in biological settings.

Integrins are highly glycosylated due to multiple glycosylation sites and galectin-3 is a binding partner of α3β1 integrin on the cell surface of endothelial cells[34]. A complex is formed between the integrin, galectin-3 and the NG2 proteoglycan which may potentiate transmembrane signaling responsible for endothelial cell motility and morphogenesis[35]. This interaction may be important in angiogenesis and tumour vascularization.Binding of galectin-3 to Mgat5-modified N-glycans of epidermal growth factor (EGF) and transforming growth factor (TGF)-β receptors results in a delay of receptor removal by constitutive endocytosis[36]. Therefore, the galectin-3 lattice ensures upregulation of surface receptors and increased sensitivity to growth factors. For example, Mgat5-deficient mice display a loss of sensitivity to cytokines resulting in a loss of phosphorylation and nuclear translocation of ERK and reduced Smad2/3 phosphorylation. Galectin-3 may therefore function to regulate cytokine receptors primarily through its ability to bind Mgat5-modified N-glycans on surface glycoproteins. There is no known catalytic activity of galectin-3 to directly induce downstream signaling pathways[37].

Regulation of the immune response:

Galectin-3 is highly expressed and secreted from activated macrophages and acts as a powerful pro-inflammatory signal[38]. As stated above, extracellular galectin-3 mediates cell adhesion, activation and acts as a chemoattractant for various cell types. Numerous studies have been carried out investigating the effects of galectin-3 on the cells involved in immune responses (Figure 3). Galectin-3 promotes the respiratory burst in neutrophils and monocytes and this activity is dependent on the lectin property of the protein as it is inhibitable by lactose; it induces mediator release from mast cells and downregulates interleukin-5 (IL-5) production from eosinophils[39]. Galectin-3

promotes the survival of B cells by blocking the final differentiation into plasma cells thus allowing the rising of a memory B cell phenotype[40]. This process is important when the host meets a pathogen which it has previously encountered. Memory B cells enable the immune system to eliminate the secondary infection quicker and more effectively.

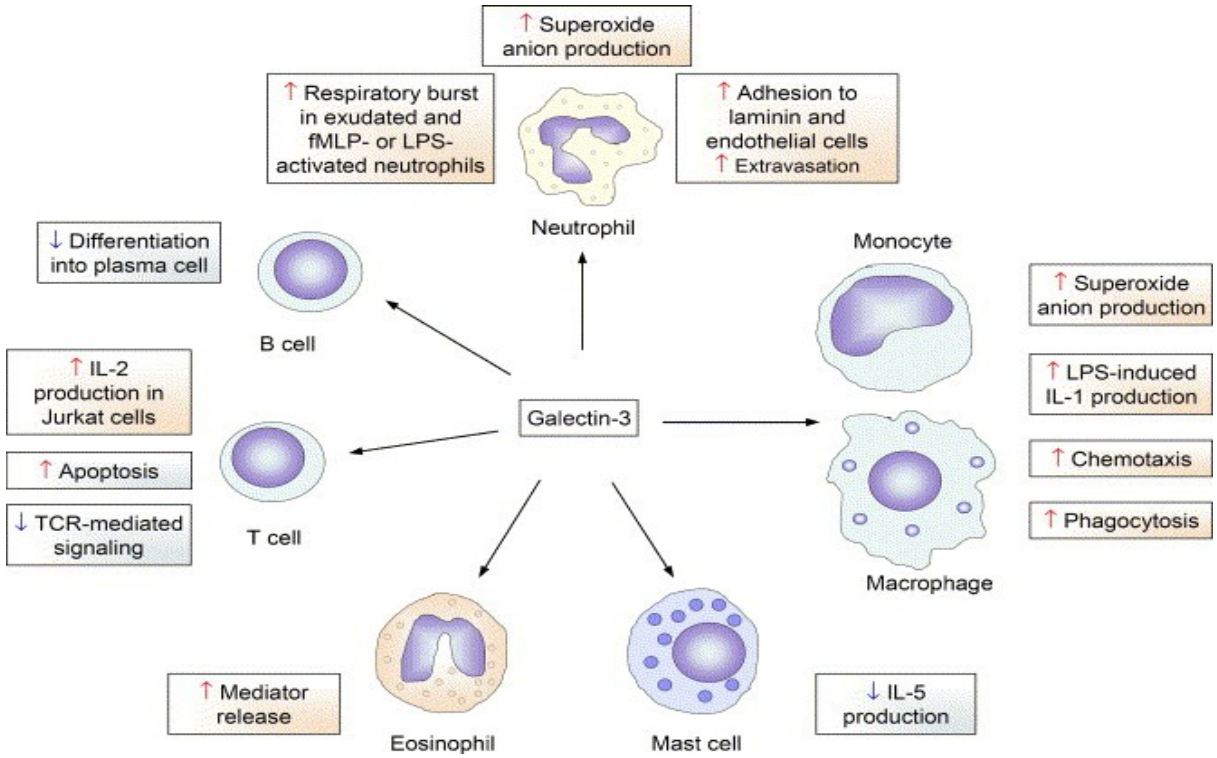

Figure 3:- The effect of galectin-3 on immune cell function (The effects of galectin-3 on immune cells. Red upwards arrows indicate positive effects, blue downwards arrows indicate negative effects, adopted from Dumicet al., 2006).

Monocyte and macrophage biology are also affected by galectin-3[41]. In addition to enhancing superoxide anion production from human monocytes, galectin-3 acts as a chemoattractant for monocytes and macrophages. At high concentrations the protein is chemotactic, that is to say cell migration is directed. At low concentrations galectin-3 is chemokinetic resulting in enhanced general motility. Galectin-3 positive macrophages show increased phagocytosis of Immunoglobulin-G (IgG)-opsonised erythrocytes and apoptotic thymocytes both in vitro and in vivo when compared to macrophages from galectin-3 knockout (galectin-$3^{+/-}$) mice[42]. Furthermore, peritoneal macrophages taken from suchmice are more prone to undergo apoptosis than wild type macrophages. Galectin-3 also promotes monocyte-monocyte interactions that ultimately lead to polykaryon (multinucleated giant cell) formation, a phenotype associated with chronic inflammatory and fibrotic diseases.The aforementioned effect on the different cells of the immune system signifies that galectin-3 must play an important role in certain disease states[43]. Intracellular galectin-3 could promote the survival of inflammatory cells resulting in persistence of inflammation confirmed by the finding that galectin-$3^{+/-}$ mice demonstrate a reduced inflammatory response after the induction of peritonitis. Galectin-3 recognizesgalactoside-containing glycoconjugates on pathogens and can bind to lipopolysaccharides (LPS) of a number of gram-negative bacteria implicating the importance of galectin-3 in pathogen recognition[44-45].

Conclusion:-

Galectin-3 bind to T cells to induce cell death in a carbohydrate-dependent manner. At first glance, it may appear that galectin-3 have redundant functions, suggesting that one galectin could substitute for the other. Indeed, several other galectins, including galectin-2, -7, and -9, also kill T cells. Similarly, the little that is known about galectin-mediated T cell death pathways supports the hypothesis that different galectins do not use identical mechanisms to kill T cells. In vivo, different galectins may act at different times in development, at different anatomic sites, or on

different cell populations, to regulate cell death. As the patterns of cell and tissue expression of many galectins overlap, we need to understand the different mechanisms used by different galectins to regulate T cell death.

Conflict of Interests:
The authors declare that there is no conflictofinterests exist among them regarding the publication of this paper.

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