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Expression and function of galectins in the endometrium and at the human feto-maternal interface

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ABSTRACT

Galectins are classified as lectins that share structural similarities and bind β-galactosides via a conserved carbohydrate recognition domain. So far 16 out of 19 identified galectins were shown to be present in humans and numerous studies revealed galectins as pivotal modulators of cell death, differentiation and growth. Galectins were highlighted to interact with both the adaptive and innate immune response.

In the field of reproductive medicine and placenta research different roles for galectins have been proposed. Several galectins, being abundantly present at the human feto-maternal interphase and endometrium, were hypothesized to significantly contribute to endometrial receptivity and pregnancy physiology. Hence, this review outlines selected aspects of galectin action within endometrial function and at the feto-maternal interphase. Further current knowledge on galectins in reproductive and pregnancy disorders like endometriosis, abortion or preeclampsia is summarized.

1. Introduction

Galectins are defined as lectins having galactose-binding ability and in addition an amino acid sequence that is characteristic for galectins [1,2]. Galectin (gal) is a name proposed by Hirabayashi and Kasai for a family of animal lectins [3]. In general, galectins are soluble and metal-independent in their activity [4]. They have features of cytoplasm proteins, including no disulfide bridges, no sugar chains, no signal sequences and in most cases their N-terminal amino acids are acetylated [5]. Galectins can be classified into three types on the basis of their structural architecture: proto, chimera and tandem-repeat types (Fig. 1) [6].

As members of the animal β-galactoside-binding proteins, galectins can recognize Galβ1-4GlcNAc sequences of cell surface oligosaccharides [6–8]. Gal-1 is described to bind especially to the Thomsen–Friedenreich (TF) antigen (Galβ1-3GalNAc) on placental cells [9–11].

They bind to glycoconjugates on the plasma membrane and in the extracellular matrix [12,13]. Most galectins contain multiple sugar-binding sites, due to the presence of two galectin-type CRDs in a single polypeptide or as a result of dimerization [14–16]. A common function of the galectins may be to crosslink galactose-containing structures found at cell surfaces and in the extracellular matrix or to crosslink different or the same type of cells [17–19]. Eight residues i.e. eight amino acids (Histidin, 2xAsparagin, 2xArginin, Valin, Tryptophan and Glutamic acid) that form the galactoside-binding site are conserved in most mammalian galectins [6,20].

2. Galectin expression and function in the human endometrium/decidua

The comparative analysis between galectin-related physiology and endometrial physiology, lead to the hypothesis that possibly galectins could be involved in endometrial function. It is well-accepted that implantation is considered an inflammatory process and as such is modulated by immune factors. In that context, implantation requires both the attraction and the regulation of leucocytes, processes in which galectins are already involved. Indeed galectins have been reported as apoptosis inducers in Th1 and Th17 cells, and as inducers of the differentiation of tolerogenic dendritic cells as well as of the regulatory T cells [21]. Finally, galectins could contribute to the defense against bacteria, which constantly challenge the endometrial immune system via the ascending route of the genital tract [22]. Galectins 1–4, 9 and 12 were reported in the human endometrium [23]. Out of these, only gal-1 and gal-3 were highly expressed [23]. Immunohistochemical staining revealed that gal-1 is mainly located in the endometrial

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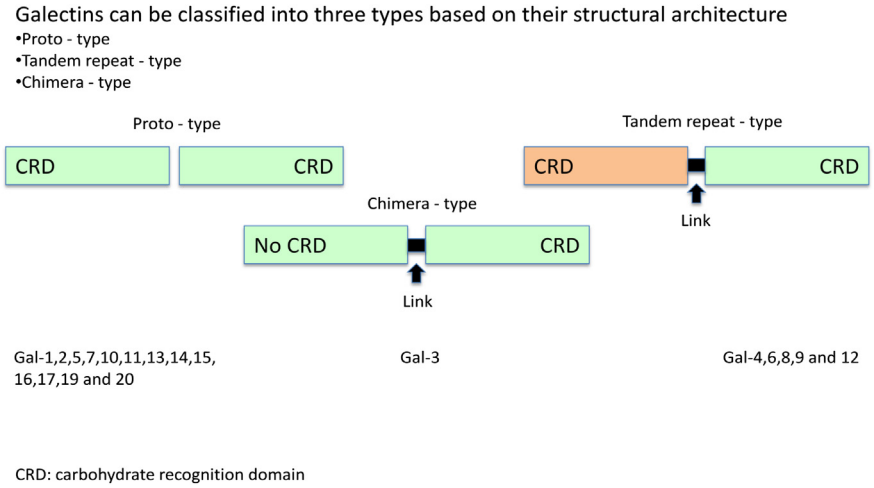

Fig. 1. Structure and carbohydrate-binding sites (CRD) of mammalian galectins. There are combinations of homologous CRDs (light green), heterologous CRDs (light green and orange) and combinations of CRD with non-CRD (light green and white). Galectins marked with a link are covalently connected. Proto galectins are non-covalently connected.

stroma, whereas gal-3 is found mainly in the endometrial glandular epithelium [23]. These galectins have differential patterns of expression throughout the menstrual cycle. Gal-1 is expressed throughout the menstrual cycle being significantly up-regulated in the late secretory phase and the early pregnancy decidua [23]. Recently, it was found that Gal-1 binds to the apical surface of both glandular and luminal epithelia and is significantly more abundant in the secretory phase as compared to the proliferative phase of the menstrual cycle [24]. In addition, there is a positive correlation of TF expression and galectin-1 binding in the human endometrium throughout the menstrual cycle and a positive correlation between MUC-1 expression and galectin-1 binding throughout the menstrual cycle. Taken together, the above findings formulate the hypothesis that the TF epitope is differentially expressed on MUC-1 during the menstrual cycle [24]. Therefore, gal-1 may be implicated in the process of implantation.

Gal-3 follows approximately the same pattern [23], being highly expressed during the window of implantation [25]. In mice, Gal-3 was shown to be expressed by the uteroplacental unit [25,26], being also up-regulated in the decidua 2–4 days after pregnancy establishment [27]. Gal-3 localization pattern alters in mice since it is initially expressed by the endometrial glandular epithelium and later on by the luminal epithelium [27].

Gal-1 seems also to play an immuno-modulatory role both in the human endometrium and the decidua. It has been shown that the uterine NK [8] cells – which comprise 70% of the immune cell population – selectively express gal-1 compared to the peripheral NK cell population [28,29]. It has been described that gal-1 secreted by the uNK cells, induces apoptosis of the activated decidual T cells, contributing to the maternal immunotolerance of the fetus [29]. To the same direction it has been shown that the regulatory T cells (Treg – $CD4^{+}CD25^{+}FOXP_{3}^{+}$) express both gal-1 and gal-10 [30,31]. Of note is the key role of Treg cells in modulating by immune reactions against the semi-allogenic fetus [32]. The importance of gal-1 has been further elucidated by Blois et al. [33]. Using a mouse model they showed that stress could down-regulate gal-1 in both myometrium and decidua. Additionally, they reported gal-1 knock-out mice to show higher rates of fetal losses compared to controls. These findings were reversed by treatment with recombinant gal-1. Gal-1 could modulate several immune mechanisms including the induction of tolerogenic dendritic cells, which in turn triggered the expansion of IL-10-expressing Treg cells in vivo.

The role of gal-3 in the endometrium and the decidua is still rather unclear. It was shown that gal-3 regulated endometrial cell proliferation and adhesion via the integrin β_3 [34]. Gal-3 silencing lead to reduced endometrial proliferation and adhesion [34]. The same group later on reported that gal-3 – secreted by BeWo trophoblast cells reduced endometrial cell (RL95-2) proliferation while inducing endometrial cell apoptosis, this being attributed to interaction of gal-3 with integrin β_3 [35]. Although initially such findings may seem contradictory, the authors supported both aspects of gal-3 function by highlighting the already published different effects that extracellular and cytoplasmic gal-3 exert on cell proliferation [36]. Cytoplasmic gal-3 was reported protecting T cells from apoptosis, promoting at the same time cell proliferation [37]. On the contrary treatment with recombinant gal-3 induced T cell apoptosis [38].

Initially it was shown that in case of: a) a gal-1 knock-out, b) a gal-3 knock-out, or even c) a double Gal-1/Gal-3 knock-out phenotype implantation could still occur [39,40]. However, further uprising evidence showed that in a mouse model, gal-3 knock-down resulted in a significantly reduced number of implanted embryos [27]. Such results combined with the corresponding findings regarding the role of gal-1 in expanding IL-10-expressing Treg cell population [33] indicate both gal-1 and gal-3 as contributors to the establishment of the immuno-privileged local environment which is a prerequisite for implantation and early fetal development [41].

The fact that both gal-1 and gal-3 are expressed during the secretory phase of the menstrual cycle as well as during pregnancy implied that they are under regulation by steroid hormones estrogen (E2) and progesterone (P4). Indeed it has been shown that both E2 and P4 up-regulate gal-1 expression in uterine tissues of ovariectomized mice [42]. This effect was abrogated by RU486 (a progesterone receptor antagonist) or ICI182780 (an estrogen receptor antagonist) [42]. Interestingly, an estrogen responsive element has been recognized in the gal-1 promoter [43]. To the same direction, in endometrial cells, gal-3 has also been shown as being regulated by E2 and P4 [44]. The E2/P4-induced gal-3 expression was further shown to protect endometrial cells from staurosporine-induced apoptosis [44]. Finally, endometrial cell gal-3 has been further reported to be induced by hCG, priming the endometrium for implantation [45].

Recently, gal-9 was reported as being exclusively expressed by the human endometrial glandular cells during the window of implantation as well as by the human decidua during early pregnancy [46]. Electron microscopy experiments elucidated further gal-9 localization: gal-9 was reported being located on the apical