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Role of Galectin-3 in Tumour Metastasis[1]

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Abstract—We used metastatic variant of B16 melanoma (B16F1) to study lung colonization galectin-3-deficient (gal-$3^{-/-}$) C57BL/6 mice. In vivo study showed that compared with gal-$3^{+/+}$ mice, gal-$3^{-/-}$mice exhibited resistance to lung colonization of B16F1 melanoma cells ($p < 0.03$). In vitro assays showed higher number of attached malignant cells in the tissue section derived from gal-$3^{+/+}$ mice ($p < 0.001$) and tumor specific cytotoxicity of lymphoid cells of tumour inoculated gal-$3^{-/-}$ suggesting that galectin-3 is considered as therapeutic target.

Key words: Galectin-3, malignant melanoma, metastasis, B16F1.

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Galectin-3, a lectin with specificity for beta galactosides, that is overexpressed in a variety of tumour and immune cells in response to various stimuli. This protein interacts with a numerous complementary glycoconjugates and regulates many biological functions and signaling pathways in normal and cancer cells. The expression of Galectin-3 is modulated in many different tumour types [1] and, in general, expression of this protein is associated with poor prognosis and acquisition of a metastatic phenotype [2]. For example, its overexpression in human melanoma correlates with metastatic progression and with negative clinical outcome [3]. Recent observations from Krishnan et al. [4] suggest that Galectin-3 constitutively expressed on the lung vascular endothelial cells plays a key role in the adhesion of circulating murine melanoma cells to lungs. During the last years, an extensive accumulation of data has changed the perspective of this multifunctional protein. It was therefore postulated that Galectin-3 is involved in tumour progression and metastasis by modulating various biological events, including cell adhesion, migration, angiogenesis, and immune escape [2, 5].

Galectin-3 have recently attracted the attention of as novel regulator of immune cell homeostasis [6, 7]. Among the 15 galectin members, Galectin-3 is expressed in many immunocompetent and inflammatory cells including macrophages and activated T lymphocytes [8–10]. Galectin-3 affects differentiation and growth of various immune cells: it activates several lymphoid and myeloid cells, such as mast cells, neutrophils, monocytes and T cells, resulting in mediator release, superoxide anion production, and cytokine production [11–13]. Galectin-3 has been shown to induce apoptosis in T lymphocytes, including human T leukaemia cell lines, human peripheral blood mononuclear cells (PBMC), and activated mouse T cells [14, 15]. Zubieta et al. [16] demonstrated that Galectin-3 expression correlated with apoptosis of tumour-associated lymphocytes in human melanoma biopsies. A recent study also found that Galectin-3 secreted by tumours facilitates tumour immune escape by killing tumour reactive CD8+T cells and promotes tumour growth in a mouse model of colorectal cancer [17].

However, there is still scarce information available on how Galectin-3 regulates metastasis in vivo. The hematogenous phase of metastasis is a dynamic and coordinated multistep process. During this phase, the tumour cells are directly confronted with effector mechanisms of the host immune system [18]. It appears that one of the critical steps in hematogenous phase of metastasis is the adhesion of circulating tumour cells to the vascular endothelium in targeted organs. This process is thought to be regulated by the specific expression of various adhesion molecules and their ligands on the surface of tumour cells and endothelial cells [19]. In this regard, some evidence indicate that Galectin-3 and its glycoconjugate ligands are engaged in this process [5]. We used metastatic variant of B16 melanoma (B16F1) to study lung colonization and tumor cell adhesion in order to directly demon-

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