Moreover, in vivo, silencing of β-arr1 or macitentan treatment inhibited metastasis in sensitive and resistant EOC xenografts, providing evidence that blockade of ETAR/β-arr1-driven EMT can overcome chemoresistance and inhibit tumor progression. Collectively, our findings provide insights into how ETAR controls EMT transcriptional responses and tumor initiating trait, deciphering a novel function for β-arr1 for nuclear compartmentalization of ETAR signalling influencing the mechanism of acquired resistance, EMT and stem-cell like features.


(Pro)renin receptor in breast cancer and its possible pathophysiological role in breast cancer proliferation
Kazuhito Takahashi, Koji Ohba, Hiroshi Nishiyama, Kiriko Kaneko, Takuo Hirose, Kazuhito Totsune, Hironobu Sasanoda, Takashi Suzuki

aDepartment of Endocrinology and Applied Medical Science, Tohoku University Graduate School of Medicine, Japan
bDepartment of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Graduate School of Medicine, Japan
cDepartment of Social Welfare, Faculty of Synthetic Welfare, Tohoku Fukushi University, Japan
dDepartment of Anatomic Pathology, Tohoku University Graduate School of Medicine, Japan
eDepartment of Pathology and Histotechnology, Tohoku University Graduate School of Medicine, Japan

E-mail address: ktaka-md@med.tohoku.ac.jp (K. Takahashi)

The endothelin system is an important paracrine or autocrine system for cancer cell proliferation. Endothelin-1 and endothelin receptors are expressed in various types of cancers including breast cancer. (Pro)renin receptor ((P)RR) is a specific receptor for renin and prorenin. Receptor-bound prorenin becomes enzymatically active in converting angiotensinogen to angiotensin I, and binding then activates phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), independent of angiotensin II generation. Furthermore, (P)RR is associated with vasoconstrictor-type H+-ATPase (V-ATPase), which may be independent of angiotensin II generation. The aim of the present study is to clarify the pathophysiological role of (P)RR in breast cancer. We investigated (P)RR expression in 69 clinical cases of breast carcinoma by immunohistochemistry and its correlation with clinicalopathological parameters. Effects of (P)RR on cell proliferation and ERK1/2 phosphorylation were examined in cultured human breast carcinoma cells. Immunohistochemistry showed that (P)RR immunoreactivity was detected in carcinoma cells of breast carcinoma tissues, and was correlated with Ki-67 expression. The (P)RR specific small interference RNA or caspase inhibition of V-ATPase activity inhibited cell growth of breast carcinoma cell lines (MCF-7 and SK-BR-3). Prorenin stimulated the phosphorylation of ERK1/2 in MCF-7 cells. Treatment of MCF-7 cells with endothelin-1 had no significant effects on (P)RR expression levels. The present study has raised the possibility that, in addition to the endothelin system, (P)RR is involved in the pathophysiology of breast cancer by stimulating the proliferation of breast carcinoma cells via the association of V-ATPase and/or phosphorylation of ERK1/2.


Poly-gamma-glutamic acid attenuates angiogenesis and inflammation in experimental colitis
Mi Jeong Sung, Munghugs Davaaersen, Jin-Taek Hwnag, Jae Ho Park, Myung Sunny Kim, Shiyaju Wang

Korea Food Research Institute, Gyeonggi-Do, South Korea
E-mail address: dulle5@kfri.re.kr (M. Jung)

Poly-gamma-glutamic acid (PGA), naturally secreted from various strains of Bacillus, has anti-inflammatory activity. In inflammatory bowel disease (IBD), inflammation is promoted and sustained by angiogenesis; however, the role played by PGA in this condition is unclear. Therefore, we evaluated PGA effects on angiogenesis and inflammation in a dextran sulfate sodium (DSS)-induced mouse colitis model. Experimental colitis was induced in male C57BL/6 mice by administering 3% DSS. Disease activity index (DAI), histopathological scores, microvacular density, myeloperoxidase activity, and VEGF-A and VEGFR2 expression were compared among control mice, DSS-treated mice, and mice receiving 3% DSS along with PGA at 50 mg/kg body weight per day, or 3% DSS with PGA at 200 mg/kg body weight per day. We found that PGA significantly attenuated weight loss, DAI, and colon shortening. PGA also significantly reduced histopathological evidence of injury. Moreover, PGA significantly attenuated DSS-induced blood vessel densities. Furthermore, PGA attenuated DSS-induced expression of VEGF-A and its receptor, VEGFR2. In addition, PGA treatment led to reduced recruitment of leukocytes to the inflamed colon. Therefore, our results indicate that PGA has potential application in conditions marked by inflammatory-driven angiogenesis and mucosal inflammation.


Identification of bladder endothelin-1 receptors and binding characteristics of bosentan and ambrisentan
Ayaka Osano

Pharmacokinetics and Pharmacodynamics, Japan
Clinical Pharmacology and Genetics, Japan
E-mail address: s12134@u-shizuoka-ken.ac.jp (A. Osano)

Endothelin (ET)-1 induces prolonged contractile responses in isolated bladder muscle strips. ET-like immunoreactivity was identified in detrusor muscles, epithelium and vascular endothelium. Selective ETA receptor antagonists have ameliorating effects on urinary dysfunction. The current study aimed to identify bladder ET-1 receptors using radioligand binding assay and characterize receptor binding of clinically used ET-1 receptor antagonists. ET-1 receptors were measured in rat bladder using [125I]ET-1, and binding parameters of dissociation constant (Kd), and the maximal number of binding sites (Bmax) for [125I]ET-1 were estimated. The inhibition of specific [125I]ET-1 binding was measured in the presence of ET-1 and its receptor antagonists. Specific [125I]ET-1 binding in rat bladder was saturable and of high affinity, which characterized selective labeling of bladder ET-1 receptors. ET-1, bosentan, ambrisentan, and CI-1020 inhibited specific [125I]ET-1 binding in a concentration-dependent manner at nanomolar ranges of IC50. Nonlinear least squares regression analysis revealed the presence of high- and low-affinity ET-1 receptor sites for ambrisentan and CI-1020. Bosentan significantly increased Kd for bladder [125I]ET-1 binding without affecting Bmax, while ambrisentan increased Kd with a concomitant reduction in Bmax. Thus, bosentan seems to bind bladder ET-1 receptor in a competitive and reversible manner while ambrisentan may bind to bladder ET-1 receptors, partially in a non-competitive manner in addition to a competitive manner. Oral administration of bosentan caused a dose-dependent decrease in Bmax for bladder [125I]ET-1 binding, suggesting significant binding of bladder ET-1 receptors in vivo. These results indicate that pharmacologically relevant ET-1 receptors exist in rat bladder and they may become a promising target for the development of novel therapeutic agents for bladder dysfunction.