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Mini Review

Co-expression of MRP1 and STAT3 in Various Type of Cancers May Indicate Constitutive Resistance to Cancer Chemotherapy

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Abstract

Cancer resistance is a major hurdle for cancer treatment. Understanding how cancers become resistant to chemotherapeutic agents i.e. mechanisms underlying the resistance is pivotal to a success of cancer chemotherapy. Multidrug-resistant associated protein 1 (MRP1) and signal transducer and transcription activator 3 (STAT3) are two factors, in addition to other factors, that play significant roles in cancer biology and cancer resistance. Both MRP1 and STAT3 proteins are ubiquitously expressed in various types of tissue. MRP1 is an efflux transporter. Overexpression of MPR1 has been associated with treatment failure in many malignant neoplasia due to a decreased intracellular accumulation of chemotherapeutic agents. STAT3 is a pleiotropic transcription factor, which can be activated through several factors such as growth factors and cytokines via Janus kinase (JAK)-STAT signaling pathways. STAT3 target genes include cyclin D1, Bcl-xL, c-myc, Mcl1, VEGF, reflecting STAT3's involvement in diverse cellular processes. Additionally, STAT3 can upregulate MRP1 therefore co-expression of MRP1 and STAT3 are often observed in various types of cancers. Hence, the co-expression of MRP1 and STAT3 may suggest a cancer resistant phenotype. Inhibition of STAT3 activation could reverse the resistant phenotype of cancer by obliterating the expression of MRP1. Currently, there is no direct STAT3 inhibitor approved by the US Food and Drug Administration. However, suppressing MRP1 expression can be achieved by blocking IL-6 signaling pathway e.g. by anti-IL-6 monoclonal antibody, tocilizumab. Because IL-6R signaling causes an activation of STAT3, which has been associated with IL-6 induces drug resistance, incorporation of anti-IL-6 into pharmacotherapy regimens may be beneficial to cancer patients. Thus, comprehensive clinical trials, pharmacological and toxicological studies as well as translational researches with regards to cancer resistance and MRP1 and STAT3 expression status are warranted.

Keywords: *Multidrug-Resistant Associated Protein 1 (MRP1); Signal Transducer and Transcription Activator 3 (STAT3)*

Introduction

Cancer resistance is one of the key challenges in treatment of cancer. Understanding how cancers become resistant to chemotherapeutic agents is pivotal to a success of cancer chemotherapy. Several mechanisms of resistance have been associated with and/or linked to resistant phenotype of cancers, which include, but not limited to, upregulation of DNA repair systems, overexpression of efflux transporters, and increased expression of anti-apoptotic proteins [1]. These resistances are either inherited or acquired following exposure of tumors to chemotherapeutic agents. This short article focuses on multidrug-resistant associated protein 1 (MRP1) and signal transducer and transcription activator 3 (STAT3), the two factors that play significant roles in cancer biology and cancer resistance.

Tissue expression of MRP1

MRP1, also known as ABCC1, is a member of the ATP-binding cassette (ABC) transporter protein superfamily, sub-family C, ABCC1 [2]. MRP1 protein is ubiquitously expressed in most tissues where the expressions may vary from tissues to tissues (Table 1).

	High	Medium	Low/undetectable
Brain		Cerebral cortex	Amygdala, basal ganglia, thalamus, hypothalamus, midbrain, pons and medulla, cerebellum, spinal cord
Endocrine tissue			Thyroid gland, parathyroid gland, adrenal gland, pituitary gland
Respiratory system		Lung, nasopharynx	Bronchus
Gastrointestinal tract	Duodenum, rectum	Colon	Stomach
Biliary tract		Gallbladder	Liver
Pancreas		Pancreas	
Kidney and urinary bladder	Kidney		Bladder
Male tissues	Testis		Seminal vesicle, prostate
Female tissues	Ovary, endometrium	Fallopian tube	
Skin		Skin	
Bone marrow and lymphoid tissues	Appendix, tonsil	Bone marrow	Thymus, spleen, lymph node

Table 1: *Expression levels of MRP1 protein in normal tissues [3].*

MRP1 plays a significant role in transporting glutathione and glucuronide conjugates including chemotherapeutic agents e.g. paclitaxel, vincristine and doxorubicin. Growing evidence of increased MRP1 expression have been reported in various types of cancers such as non-small-cell lung cancer [4], ovarian cancer [5], and colorectal cancer [6], suggesting a role of MRP1 in cancer resistance.

Tissue expression of STAT3

STAT3 is a transcription factor. It is one of the seventh members of the STAT family, STAT1-STAT4, STAT5α, STAT5β, and STAT6 [7]. Similar to MRP1, STAT3 proteins are ubiquitously expressed at various levels in cytosol of broad range of tissues (Table 2).

	High	Medium	Low/undetectable
Brain		Cerebral cortex, basal ganglia, cerebellum	Amygdala, thalamus, hypothalamus, midbrain, pons and medulla, spinal cord
Endocrine tissue	Thyroid gland, adrenal gland		Parathyroid gland, pituitary gland
Respiratory system	Lung, bronchus, nasopharynx		
Gastrointestinal tract	Stomach, duodenum, colon, rectum		
Biliary tract	Gallbladder	Liver	
Pancreas	Pancreas		
Kidney and urinary bladder	Kidney, bladder		
Male tissues	Testis, seminal vesicle		Prostate
Female tissues	Ovary, fallopian tube. breast	endometrium	Breast
Skin	Skin		
Bone marrow and lymphoid tissues	Appendix, tonsil, spleen, lymph node	Bone marrow	Thymus

Table 2: *Expression levels of STAT3 protein in normal tissues [3].*

STAT3 can be activated through several factors such as growth factors and cytokines via Janus kinase (JAK)-STAT signaling pathways. STAT3 target genes include cyclin D1, Bcl-xL, c-myc, Mcl1, VEGF [7], reflecting STAT3's involvement in diverse cellular processes such as cell growth, proliferation, apoptosis, induction of an acute phase response in hepatocytes, embryogenesis, and stimulation of T cell survival [8]. More specifically, persistently activated STAT3 increases cancer cell survival, proliferation, and metastasis while suppressing anti-tumor immunity [7].

Because STAT3 can upregulate MRP1 therefore it is not that uncommon to observe co-express MRP1 and STAT3 in various types of cancers (Table 3). For instance, a study in ovarian cancer cell line, OVCAR3, has demonstrated that MRP1 was upregulated via IGF-1-mediated STAT3. The expression of MRP1 was completely obliterated by a STAT3 inhibitor [9].

Solid tumors	Activated STAT	MRP1 expression [3]	References
Breast cancer	1, 3	Low/undetectable	Bromberg J [10]
Prostate cancer	3	Low/undetectable	Bromberg J [10]
Brain tumors	1, 3	Medium (cerebral cortex)	Bromberg J [10]
Colon cancer	3	Medium	Corvinus FM [11]
Lung cancer	1, 3	Medium	Bromberg J [10]
Melanoma	3	Medium	Bromberg J [10]
Pancreatic cancer	3	Medium	Bromberg J [10]
Ovarian cancer	3	High	Bromberg J [10]
Rectal cancer	3	High	Zhang BD [12]
Renal carcinoma	3	High	Bromberg J [10]
Testicular cancer	3	High	Abe T [13]

Table 3: *Expressions of activated STAT proteins and MRP1 in solid tumors.*

Currently, there is no STAT3 inhibitor approved by the US Food and Drug Administration. However, a blockade of STAT3 can be achieved by anti-IL-6 such as tocilizumab. Because IL-6R signaling causes an activation of STAT3, which has been associated with IL-6 induces drug resistance in renal cell carcinoma [14], incorporation of anti-IL-6 into the treatment regimens may be beneficial to the patients. In fact, roles of IL-6 inhibitors in cancer treatments have already been reported. For instance, inhibition of IL-6 signaling significantly reduced primary tumor growth and recurrences in orthotopic xenograft models of pancreatic cancer [15]. Furthermore, a combination therapy with IL-6 receptor blockade with tyrosine kinase inhibitor (TKI) has been shown to overcome TKI resistance of renal cell carcinoma [16] and of colon cancer stem-like cells [17].

Conclusion

Several solid tumors co-express MRP1 and STAT3, which may contribute to poor clinical outcomes due to cancer resistance. In such cancers, chemotherapies in combination with a STAT3 inhibitor e.g. via blockade of IL-6R signaling pathway appears to have potential benefits in treatment outcomes. Thus, comprehensive clinical trials, pharmacological and toxicological studies as well as translational researches with regards to cancer resistance in relation to MRP1 and STAT3 expression status are warranted.

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