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A RASSF1A as a Mechanosensitive Regulator of Cancer Stemness

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Abstract

Population of cancer stem cells in solid tumors represents a major factor of resistance to conventional therapy that influences patient survival. We recently identify RASSF1A as a novel regulator of cancer stemness that plays a key role in regulation of mechanical properties provided by ECM in lung cancer. We showed that epigenetic loss of RASSF1A promotes YAP1 nuclear accumulation which, via P4HA2 expression, drives ECM remodeling associated with Cancer Stem Cell (CSC) plasticity during malignant carcinogenesis.

Keywords: Cancer stem cells • RASSF1A • Stiffness • Tumor microenvironment

Description

Populations of Cancer Stem Cells (CSCs), also referred as Tumor Initiating Cells (TICs) has been observed in many types of solid tumors including hematologic malignities. CSCs usually represent a small part of "immortal" self-renewal cancer cells within the tumor tissue, with ability to differentiate into various cell types. This unique capability not only allows them to evade chemo-and radiotherapy, but also to develop recurrent tumors after patients undergo conventional therapy [1]. Several studies described CSCs *via* their phenotypic cell surface molecules, which are derived from adult or normal embryonic stem cells markers, *via* resulting from accumulation of genetic or epigenetic modifications in tumors [2]. Notably, cancer stem cells display excessive potential of plasticity within the tumor microenvironment, which gives them great competence to be involved in many essential processes of tumor growth, epithelial-mesenchymal transition, and metastatic dissemination to the distant organs or cell proliferation [3]. Given the several remarkable capacities of CSCs, it is not unexpected that cancer stem cells are able to escape from the immune system and educate cells in surrounding tumor environment to produce specific factors and cytokines favorable for malignant progression [4]. Additionally, alteration of mechanical properties of tumor microenvironment, including increased stiffens, elevated crosslinking or deposition of extracellular matrix initiates stemness in cancer cells [5].

We recently reported the novel function of Hippo pathway scaffold RASSF1A, as a key regulator of cancer stemness in lung tumors. RASSF1A protein has been broadly validated as a tumor supressor in the most of the cancers, where its epigenetic silencing correlates with poor prognosis and overall survival [6].

We demonstrated that loss of RASSF1A leads to constitutive activity of transcriptional regulator YAP1, and furthermore bestowed a greater mechanosensitive control on YAP1 nuclear localization. Thus, RASSF1 may be intricately involved in sensing mechanical forces in the cells thought interaction with Rho-kinases [7] and suppress YAP1 only on the soft matrices. Activated YAP1 in the nucleus leads to expression of prolyl 4-hydroxylase aplha-2 (P4HA2) and alteration of mechanical properties of extracellular matrix that in turns promotes cancer stemness re-programming and metastatic dissemination in lung adenocarcinoma *in vitro* and *in vivo*. P4HA2 enzyme catalyzes formation and stabilization of collagen I, the major component of extracellular matrix, which directly regulates biophysical properties of surrounding tumor environment [8] High tissue stiffness and elevated collagen I deposition within the tumor microenvironment prevent RASSF1A expression, and together *via* β -catenin/YAP1 associated regulation promote transcription of the pluripotency genes NANOG, SOX2 and OCT4, that in turns induces emergence of cancer stem cell population. These data are in line with our previous report showing elevation of Embryonic Stem Cells (ESCs) markers in human tumors when RASSF1A is methylated and a direct role for RASSF1A in promoting ESC differentiation [9,10]. Additionally, we elucidated that epigenetic silencing of RASSF1A together with deregulation of P4HA2 levels, are the major factors behind the poor clinical prognosis due to occurrence of cancer stem cells in tumors. Therefore, pursuing new therapy against P4HA2 may be critical strategy how to deregulate stiffness in tumor microenvironment and thus eradicate the incidence of cancer stem cells formation.

Re-activation of Hippo signaling pathway by re-expression of RASSF1A protein fails to stimulate both stiffness of tumor microenvironment, and YAP-associated P4HA2 expression in RASSF1 methylated cells. Notably, we also found that RASSF1A expression in lung adenocarcinoma impairs metastatic dissemination, and ability to sustain cancer stem cells by RASSF1A promoted differentiation. Given that RASSF1A presence restricts tumor formation *in vivo*, it was alluring to discover a direct positive correlation between mRNA levels of RASSF1A and overall survival in patients with lung adenocarcinoma. Interestingly, re-activation of Hippo signaling pathway by RASSF1A expression or impairing P4HA2 function, supports the differentiation status of lung adenocarcinoma *in vivo* and *in vitro*, and upregulation of lung differentiation markers TTF-1 and Mucin 5B in lung adenocarcinoma patients, with associated improvement in clinical prognosis. In addition to mechanisms that are involved in lung cancer progression, it is very appealing to assume that RASSF1A methylation and elevated stiffness of tumor microenvironment contribute to aggressive lung adenocarcinoma by impairing differentiation status and stimulating pluripotency within lung tumors.

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Conflict of Interest

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