ATR在浸润性乳腺癌组织中的表达和临床意义

《现代肿瘤医学》[ISSN:1672-4992/CN:61-1415/R] 期数: 2019年11期 页码: 1903-1906 栏目: 论著（胸部肿瘤） 出版日期: 2019-04-30

Title: Expression of ATR in invasive ductal breast cancer tissues and its clinical significance

作者: 胡晓华[1]; 王 宁[2]; 王雅杰[2]
1.上海交通大学医学院附属第九人民医院肿瘤科，上海 201999; 2.上海第二军医大学附属长海医院肿瘤科，上海 200433

Author(s): Hu Xiaohua[1]; Wang Ning[2]; Wang Yajie[2]
1.Oncology Department，Shanghai Ninth People's Hospital，Shanghai Jiaotong University School of Medicine，Shanghai 201999， China；2.Department of Oncology，Changhai Hospital of Second Military Medical University，Shanghai 200433，China.

关键词: 乳腺癌; ATR; 免疫组织化学

Keywords: breast cancer; ATR; immunohistochemistry

分类号: R737.9

DOI: 10.3969/j.issn.1672-4992.2019.11.013

文献标识码: A

摘要: 目的：探讨共济失调毛细血管扩张突变基因Rad3相关蛋白（ATR）在浸润性乳腺癌组织中的表达及其临床意义。方法：收集289例乳腺癌改良根治术后病理标本，构建组织芯片，采用免疫组化方法检测组织中ATR的表达，并分析其与临床病理参数之间的关系。结果：ATR在乳腺癌组织中的阳性表达率为70.6%（204/289）。ATR阳性表达率在肿瘤直径>2 cm组高于≤2 cm组，在TNM分期Ⅱ-Ⅲ期组高于Ⅰ期组，在孕激素受体（PR）阳性组高于PR阴性组，在人类表皮生长因子受体2（HER-2）阳性组高于HER-2阴性组，在非三阴性乳腺癌组高于三阴性乳腺癌组，差异均有统计学意义（P<0.05）；ATR的表达与患者发病年龄、月经状态、组织学分级、淋巴结转移情况、雌激素受体（ER）水平、p53状态无明显相关（P>0.05）。结论：浸润性乳腺癌组织中ATR的高表达可能与乳腺癌的进展相关。

Abstract: Objective：To investigate protein expression of ATR(ataxia telangiectasia mutated and Rad3 related protein) in invasive ductal breast cancer tissues and the relevant clinical significance．Methods：Totally 289 cases of invasive ductal breast cancer tissue were collected to construct tissue microarrays．Immunohistochemistry was used to detect protein expression of ATR．The correlation between protein expression and clinicopathological parameters was explored．Results：The positive rate of ATR in breast cancer tissues was 70.6%(204/289)．The protein expression was significantly higher in the cases with tumor size>2 cm，TNM stageⅡ-Ⅲ，PR-positive，HER-2-positive and non-triple-negative breast cancer(P<0.05).No statistically significant difference was found in ATR expression according to different ages，menopausal status，histological grade，regional lymph node metastasis，ER and p53 status．Conclusion：Detection of ATR protein expression by immunohistochemistry may help to investigate the biological behavior of the breast cancer．

参考文献/REFERENCES

[1]Siegel R，Naishadham D，Jemal A．Cancer statistics，2012［J］．CA Cancer J Clin，2012，62(1)：10-29.
[2]Marechal A，Zou L.DNA damage sensing by the ATM and ATR kinases［J］.Cold Spring Harbor Perspectives in Biology，2013，5(9)：a012716.
[3]Roos WP，Thomas AD，Kaina B.DNA damage and the balance between survival and death in cancer biology［J］.Nature Reviews Cancer，2016，16(1)：20-33.
[4]Fokas E，Prevo R，Hammond EM，et al.Targeting ATR in DNA damage response and cancer therapeutics［J］.Cancer Treat Rev，2014，40(1)：109-117.
[5]Cimprich KA，Shin TB，Keith CT，et al.cDNA cloning and gene mapping of a candidate human cell cycle checkpoint protein［J］.Proc Natl Acad Sci USA，1996，93(7)：2850-2855.
[6]Shiotani B，Zou L.ATR signaling at a glance［J］.J Cell Sci，2009，122(3)：301-304.
[7]Lempiainen H，Halazonetist D.Emerging common themes in regulationg of PIKKs and PI3Ks［J］.EMBO J，2009，28(20)：3067-3073.

[8]Moreno NC，Garcia CCM，Rocha CRR，et al.ATR/Chk1 pathway is activated by oxidative stress in response to UVA light in human Xeroderma pigmentosum variant cells［J］.Photochemistry and Photobiology，2018.doi：10.1111/php.13041.
[9]Saini P，Li Y，Dobbelstein M.Wee1 is required to sustain ATR/Chk1 signaling upon replicative stress［J］.Oncotarget，2015，6(15)：13072-13087.
[10]Ling H，Lu LF，He J，et al.Diallyl disulfide selectively causes checkpoint kinase-1 mediated G2/M arrest in human MGC803 gastric cancer cell line［J］.Oncology Reports，2014，32(5)：2274-2282.
[11]Shen T，Zhou H，Shang C，et al.Ciclopirox activates ATR-Chk1 signaling pathway leading to Cdc25A protein degradation［J］.Genes & Cancer，2018，9(1-2)：39-52.
[12]Couch FB，Bansbach CE，Driscoll R，et al.ATR phosphorylates SMARCAL1 to prevent replication fork collapse［J］.Genes Dev，2013，27(14)：1610-1623.
[13]Tibbetts RS，Cortez D，Brumbaugh KM，et al.Functional interactions between BRCA1 and the checkpoint kinase ATR during genotoxic stress［J］.Genes Dev，2000，14(23)：2989-3002.
[14]Durocher F，Labrie Y，Sourcy P，et al.Mutation analysis and characterization of ATR sequence variants in breast cancer cases from high-risk French Canadian breast/ovarian cancer families［J］.BMC Cancer，2006，6：230.
[15]Marsh A，Healey S，Lewis A，et al.Mutation analysis of five candidate genes in familial breast cancer［J］.Breast Cancer Res Treat，2007，105(3)：377-389.
[16]Cimprich KA，Cortez D.ATR：An essential regulator of genome integrity［J］.Nat Rev Mol Cell Bil，2008，9(8)：616-627.
[17]Luo J，Solimini NL，Elledge SJ.Principles of cancer therapy：Oncogene and non-oncogene addiction［J］.Cell，2009，136(5)：823-837.
[18]Gutierrez C，Schiff R.HER2：Biology，detection，and clinical implications［J］.Arch Pathol Lab Med，2011，135(1)：55-62.
[19]Bartkova J，Horejsi Z，Koed K，et al.DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis［J］.Nature，2005，434(7035)：864-870.
[20]De Mattos-Arruda L，Ng CKY，Piscuoglio S，et al.Genetic heterogeneity and actionable mutations in HER2-positive primary breast cancers and their brain metastases［J］.Oncotarget，2018，9(29)：20617-20630.
[21]Abdel-Fatah TM，Middleton FK，Arora A，et al.Untangling the ATR-CHEK1 network for prognostication，prediction and therapeutic target validation in breast cancer［J］.Molecular Oncology，2015，9(3)：569-585.
[22]Di Benedetto A，Ercolani C，Mottolese M，et al.Analysis of the ATR-Chk1 and ATM-Chk2 pathways in male breast cancer revealed the prognostic significance of ATR expression［J］.Scientific Reports，2017，7(1)：8078.
[23]Josse R，Martin SE，Guha R，et al.ATR inhibitors VE-821 and VX-970 sensitize cancer cells to topoisomerase I inhibitors by disabling DNA replication initiation and fork elongation responses［J］.Cancer Research，2014，74(23)：6968-6979.
[24]Andrs M，Korabecnya J，Nepovimova E，et al.Small molecules targeting ataxia telangiectasia and Rad3-related（ATR) kinase：An emerging way to enhance existing cancer therapy［J］.Current Cancer Drug Targets，2016，16:200-208.
[25]Mohni KN，Thompson PS，Luzwick JW，et al.A synthetic lethal screen identifies DNA repair pathways that sensitize cancer cells to combined ATR inhibition and cisplatin treatments［J］.PLoS One，2015，10(5)：e0125482.
[26]Yang ZY，Sun CY，Liu Y，et al.Suppression of ATR reverses the cisplatin resistance in ovarian cancer SKOV3 cells［J］.Chinese Journal of Oncology，2014，36（11）：805-810.［杨宗元，孙朝阳，刘毅，等.抑制共济失调毛细血管扩张突变基因RAD3相关蛋白逆转卵巢癌SKOV3细胞顺铂耐药［J］.中华肿瘤杂志，2014，36（11）：805-810.］

备注/Memo: National Natural Science Foundation of China(No.81372854）；国家自然科学基金（编号：81372854）

更新日期/Last Update: 2019-04-30