GAS5

Long non-coding RNA growth arrest-specific 5 (GAS5) has recently become an attractive target for cancer therapy by regulating cell growth, invasion, and migration.

Growth arrest-specific 5 is a non-protein coding RNA that in humans is encoded by the GAS5 gene.

GAS5 noncoding RNA, which accumulates in growth arrested cells, acts as a decoy hormone response element for the glucocorticoid receptor (GR) and hence blocks the upregulation of gene expression by activated GR.

A number of studies have linked GAS5 to apoptosis and it may play a role in the progression of some types of cancer.

The GAS5 introns host several snoRNA sequences, including SNORD81, SNORD47, SNORD80, SNORD79, SNORD78, SNORD44, SNORD77, SNORD76, SNORD75 and SNORD74. These intronic sequences are more conserved than the exons of the host gene, these sorts of genes are often called “inside-out genes”.

It was recently discovered that the nonsense-mediated degradation pathway can regulate the function of the GAS5 in mammalian cells.

Shen et al. from the Department of Epidemiology, Department of Neurosurgery, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, China, measured the levels of six known oncogenic lncRNAs-CRNDE, GAS5, H19, HOTAIR, MALAT1, and TUG1 in serum samples from 106 patients with primary glioblastoma and analyzed their association with outcomes. High levels of HOTAIR were associated with decreased probability of 2-year overall survival (adjusted hazard ratio [HR] = 2.04; 95% confidence interval [CI] = 1.08-9.76), and disease-free survival (adjusted HR = 1.82; 95% CI = 1.04-6.17). High levels of GAS5 were associated with increased probability of 2-year overall survival (adjusted HR = 0.44; 95% CI = 0.18-0.99), and disease-free survival (adjusted HR = 0.46; 95% CI = 0.16-0.98). HOTAIR and GAS5 levels could serve as reciprocal prognostic predictors of survival and disease progression in patients with glioblastoma [1)].

Its role in glioma chemoresistance remains elusive. In a study of Huo and Chen, the expression of GAS5 was decreased in glioma cell lines, and lower levels of GAS5 were observed in U138 and LN18 glioma cells that had low sensitivity to cisplatin. Functional assay confirmed that knockdown of GAS5 enhanced cell resistance to cisplatin in U87 cells, which had a relatively high expression of GAS5. Conversely, elevation of GAS5 increased cell sensitivity to cisplatin in U138 cells that had a relatively low expression of GAS5. Mechanistically, cisplatin exposure evoked excessive autophagy concomitant with an increase in autophagy-related LC3II expression and a decrease in autophagy substrate p62 expression, which was reversely muted after GAS5 overexpression. In addition, GAS5 restored cisplatin-inhibited mammalian target of rapamycin (mTOR) activation. Preconditioning with mTOR antagonist rapamycin engendered not only mTOR inhibition but also abrogated GAS5-mediated depression in cisplatin-evoked autophagy. Notably, blocking the mTOR pathway also attenuated GAS5-increased sensitivity to cisplatin in U138 cells. Cumulatively, these findings indicate that GAS5

may blunt the resistance of glioma cells to cisplatin by suppressing excessive autophagy through the activation of mTOR signaling, implying a promising therapeutic strategy against chemoresistance in glioma [2].

1)
Shen J, Hodges TR, Song R, Gong Y, Calin GA, Heimberger AB, Zhao H. Serum HOTAIR and GAS5 levels as predictors of survival in patients with glioblastoma. Mol Carcinog. 2018 Jan;57(1):137-141. doi: 10.1002/mc.22739. Epub 2017 Oct 10. PubMed PMID: 28926136.
2)
Huo JF, Chen XB. Long non-coding RNA growth arrest-specific 5 facilitates glioma cell sensitivity to cisplatin by suppressing excessive autophagy in an mTOR-dependent manner. J Cell Biochem. 2018 Oct 14. doi: 10.1002/jcb.27900. [Epub ahead of print] PubMed PMID: 30317677.