microRNA deregulation in thyroid cancer

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In cancer microRNAs are often dysregulated with their expression patterns being correlated with clinically relevant tumor characteristics. Recently, microRNAs were shown to be directly involved in cancer initiation and progression. Despite the large amount of data showing strong correlations between cancer phenotype and microRNAs aberrant expression, very little is known about the molecular mechanisms inducing such deregulation. Thyroid carcinomas comprise a heterogeneous group of neoplasms with distinctive clinical and pathological characteristics. Activating mutations in Ras genes are frequently found in poorly differentiated and in anaplastic thyroid carcinomas. We have recently shown that oncogenic activation of Ras is able to change the expression of several microRNAs in thyroid epithelial cells. One of the top aberrantly expressed ones is miR-21, a microRNA prevoiusly reported overexpressed in a wide variety of cancers and causally linked to cellular proliferation, survival and migration. By using an inducible Ras oncogene we demonstrated that constitutively active Ras induce overexpression of miR-21 at very early times after its activation, and that such overexpression is maintained at later times as well as in chronically Ras-transformed cells. Analysis of a panel of thyroid tumors with different hystotypes revealed that miR-21 is overexpressed mainly in anaplastic carcinomas, thus correlating with the most aggressive phenotype. Interestingly, this induction seems to be cell-type specific, since the inducible Ras oncogene is unable to increase miR-21 levels in cultured fibroblasts. Moreover, our data show that at least two different Ras downstream pathways are necessary to induce miR-21 expression. We then asked if the ability of Ras in inducing miR-21 overexpression is verified *in vivo*. To answer this question we analyzed the expression of this microRNA in a mouse model of Ras-induced lung tumorigenesis, showing that Ras constitutive activation is able to increase miR-21 levels in normal lung and that the Ras-initiated lung cancer progression is accompained by a further increase in miR-21 expression. Taken together, our data strongly suggest that the oncogenic activation of Ras could be responsible for the increased expression of miR-21 frequently observed in human cancers.