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| Title        | miR-27b suppresses tumor progression by regulating ARFGEF1 and focal adhesion signaling |
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## 論文内容の要旨

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| 氏 名 ( 松山 麗伊 )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                    |
| 論文題名                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | miR-27b suppresses tumor progression by regulating ARFGEF1 and focal adhesion signaling<br>(miR-27bはARFGEF1およびfocal adhesionシグナルを制御することでがん悪性を抑制する) |
| 論文内容の要旨                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                    |
| <p>The non-receptor tyrosine kinase c-Src is frequently activated during progression of colon cancers. However, the molecular mechanisms underlying c-Src activation and c-Src-induced tumor progression remain to be elucidated. Previously, we showed that c-Src upregulation causes repression of a subset of miRNAs that target several genes implicated in tumor progression. In this study, I found that among these c-Src-regulated miRNAs, miR-27b is repressed not only by c-Src upregulation but also by activation of K-Ras/H-Ras. Inhibitor studies suggested that the PI3K pathway is involved in the repression of miR-27b, implicating miR-27b in a wider range of colon cancers. Indeed, miR-27b was repressed in various colon cancer cell lines and tumor tissues. Re-expression of miR-27b in human colon cancer HCT116 cells caused morphological changes, and suppressed tumor growth, cell adhesion, and invasive ability. I also identified ARFGEF1 and paxillin as novel targets of miR-27b, and found that miR-27b-mediated regulation of ARFGEF1 is crucial for controlling anchorage-independent growth, and that of paxillin is important for controlling cell adhesion and invasion. Furthermore, re-expression of miR-27b suppressed the activation of c-Src induced by integrin-mediated cell adhesion, suggesting that repression of miR-27b may contribute to c-Src activation in cancer cells. These findings demonstrate that miR-27b functions as a tumor suppressor by controlling ARFGEF1 and the paxillin/c-Src circuit at focal adhesions.</p> |                                                                                                                                                    |

## 論文審査の結果の要旨及び担当者

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**論文審査の結果の要旨**

申請者は、がん原遺伝子産物c-Srcによるがん化に伴い発現が低下するMicroRNA(miRNA)に着目し、miRNAを介したc-Srcによるがん化制御機構の解明に取り組んだ。その結果、miRNA-27b(miR-27b)が、ヒト大腸がんにおいても発現が低下していること、そして、がん細胞の増殖、浸潤などを抑制する機能を持つことを明らかにした。またそのメカニズムとして、miR-27bががん悪性化シグナルに関わる複数の遺伝子の発現を調節していることを発見し、その中でも特に、がん増殖の制御にはARFGEF1、細胞接着・浸潤能の制御にはPaxillinの発現調節が重要であることを見出した。さらに、miR-27bががん悪性化に重要なIntegrinを介したSrc活性化を抑制することを明らかにした。

以上の成果は、Srcがん化シグナルの理解を進展させる新たな知見であり、学位授与に値すると考える。