

Gene regulation by microRNAs in cellular systems

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A central gene regulatory mechanism, recently identified, is regulation by small non-coding RNAs termed microRNAs. MicroRNAs control gene expression by binding to mRNA targets and leading them to facilitated mRNA degradation and translation inhibition. Currently there are hundreds of reported human miRNAs predicted to control at least half of the human transcriptome. MicroRNAs were observed to be important for a diverse range of biological processes such as differentiation and development, and to play a pivotal role during pathogenesis. I will present our computational and experimental efforts in identifying: (i) the complete microRNA repertoire; (ii) the characteristics of effective microRNA targeting; and (iii) novel functions microRNAs play in the cellular context.

Loss of miRNA activity in adult beta cells causes overt diabetes

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With the discovery of miRNAs, a large set of cellular regulators, we sought to explore their relevance to pathogenesis of diabetes. To this end we have obtained a conditional Dicer1 allele, the chief miRNA processing enzyme, and knocked out miRNA function specifically in mature beta cells through an inducible RIP-Cre recombination system. Our results show that miRNA loss in beta cells results in a striking diabetic phenotype, although histological studies did not reveal any change in tissue architecture. At the cellular level, Dicer^{null} beta cells show a dramatic decrease in insulin mRNA and protein levels. Strikingly, Dicer^{null} beta cells retain beta cell markers, such as MafA, Pdx1 and Nkx6.1, suggesting that regulation of insulin gene expression is affected in a relatively isolated fashion. Clues for the mechanism underlying reduction of insulin transcription emerged when we uncovered the increased expression of the insulin-associated transcriptional repressors, BETA3, Sox6, Insm1 and TLE4 in the mutant islets. We conclude that miRNAs are important in tuning the fine balance between transcriptional activators and repressors in the mature beta cell, proposing an intriguing, novel etiology for diabetes.

microRNA microRNAs and estrogen regulation

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microRNAs in the growth plate in nutritional induced growth changes

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The association between nutrition and growth is a common knowledge, however, in spite of the enormous effort of pediatric endocrinologists, dieticians and scientists, our understanding of the interaction of nutrition and linear growth in children is still lacking. The exact mechanism by which the body signals the EGP to grow or attenuate growth is still unclear. In the last couple of years our group has been extensively involved in trying to elucidate the mechanism governing the association between nutrition and growth. We have, together with others, identified the role of leptin in regulation of linear growth and we have shown that HIF1a, a transcription factor that is essential for EGP growth and development is responsive to nutritional status.

MicroRNAs (miRNAs) are small endogenous RNAs that regulate target mRNAs by binding to their 3'-UTRs. They have been reported to be involved in a variety of functions, including skeletal development and longitudinal growth.

Prompted by reports showing miRNA expression in cartilage, we investigated the potential role of miRNAs in regulating growth attenuation and Catch-up (CU) growth in the mature EGP. CU growth is a period of accelerated growth that occurs when growth inhibitory conditions resolve.

To study the mechanisms regulating nutritional induced CU growth, pre-pubertal rats were subjected to 10 days of 40% food restriction, followed by a renewal of the regular food supply. We found that under these mild food restriction conditions humerus and EGP lengths were significantly smaller compared to control. When food restriction was removed, there was an instantaneous increase in weight and EGP length, later accompanied by an increase in humerus length. Nutritional manipulation induced dramatic changes in the expression of numerous genes; however, no significant change was detected in known growth-related genes. Using miRNA microarrays, we found that numerous miRNAs were expressed in the postnatal EGP. Furthermore, nutritional manipulation led to significant changes in the expression of several miRNAs, including the cartilage-specific miR-140. We also noted a dramatic change in several potential targets of these miRNAs, which are expressed in the EGP. Some may have an anti-proliferative effect on the EGP or bone.

These results may have important implications for understanding the mechanism of the EGP growth. The present study is the first, to our knowledge, to show the involvement of miRNA in growth regulation in the post-natal EGP and the first to show the effect of nutrition on miRNA expression in vivo. Involvement of miRNA in the regulation of growth may open a new era of research and may enable the development of new treatment for children with growth abnormalities.