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MODULATION OF MICRORNA EXPRESSION: A NEW THERAPEUTIC AVENUE FOR INHERITED RETINAL DISEASE?

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Modulation of microRNA expression: a new therapeutic avenue for inherited retinal disease?

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Inherited Retinal Dystrophies (IRDs) constitute one of the most frequent causes of genetic blindness in the western world. The most frequent and severe forms are Retinitis Pigmentosa (RP), Leber Congenital Amaurosis (LCA), macular dystrophies (MD) and cone and cone-rod dystrophies (CD and CRD, respectively). Despite their remarkable genetic heterogeneity, retinal degeneration due to photoreceptor cell death (PD) is the common outcome of most forms of IRDs Currently, there are no effective therapies for IRDs and the high genetic and clinical heterogeneities of these conditions constitute a limiting factor for the rapid development of effective gene-based therapeutic strategies. MicroRNAs (miRNAs) are short non-coding RNAs that control fundamental biological processes by targeting networks of functionally correlated genes. Due to their reportedly pervasive control of many pathophysiological processes and to their easy manipulation, miRNAs may represent ideal gene-independent therapeutic tools for IRDs.
Our main goal is to identify miRNAs putatively able to modulate PD processes and to potentially exert a protective effect on IRD progression. We found that the expression modulation in the retina, via AAV-mediated delivery, of the miRNAs miR-204 and miR-181a/b is able to slow down photoreceptor cell death and to improve visual function in different IRD mouse models. Moreover, to identify additional miRNAs with a potentially beneficial role in PD, we are carrying out an unbiased high content screening utilizing an in vitro PD model: we have already identified a few promising hits, currently under characterization. This project may pave the way towards the implementation of gene-independent therapeutic strategies for IRDs that can be used as alternative or in complementation to gene-based approaches.

Modulazione dell'espressione di microRNA: una nuova strategia terapeutica per le malattie retiniche ereditarie?

Le distrofie retiniche ereditarie (IRD) costituiscono una delle più frequenti cause di cecità ad origine genetica nel mondo occidentale. Tra le forme più frequenti e gravi vi sono la retinite pigmentosa (RP), l'Amaurosi Congenita di Leber (LCA), e le distrofie maculari (MD). Attualmente non esistono terapie efficaci per le IRD e l'elevata eterogeneità genetica e clinica di queste condizioni costituisce un fattore limitante allo sviluppo di terapie appropriate. I microRNA (miRNA) sono piccoli RNA non codificanti

che controllano processi biologici fondamentali attraverso la regolazione genica. Proprio a causa di questa loro attivita' e della loro facilita' di manipolazione, i miRNA potrebbero rappresentare, in linea di principio, degli ideali agenti terapeutici per le IRD. Lo scopo principale di questo progetto e' quello di identificare microRNA in grado di esercitare un effetto protettivo nelle malattie retiniche ereditarie indipendentemente dal difetto genetico responsabile. Utilizzando modelli appropriati, abbiamo dimostrato che i microRNA miR-204 e miR-181 sono in grado di rallentare la progressione di alcune forme di IRD e potrebbero quindi in futuro rappresentare degli strumenti terapeutici per queste condizioni.

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Malattie retiniche ereditarie

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