151 MicroRNAs as potential pharmacological targets for ocular diseases - Minisymposium

Sunday, May 03, 2015 3:15 PM–5:00 PM
1EF Mile High Blrm Minisymposium
Program #/Board # Range: 908–913
Organizing Section: Physiology/Pharmacology
Contributing Section(s): Anatomy/Pathology, Cornea, Genetics, Glaucoma, Retina

Program Number: 908
Presentation Time: 3:17 PM–3:34 PM
The role of microRNA profiles as diagnostic and prognostic biomarkers in ocular lymphoma
Sarah E. Coupland. University of Liverpool, Liverpool, United Kingdom.

Presentation Description: Purpose: Micro RNAs (miRNAs) are small (18 to 24 nucleotides) highly-conserved non-coding RNAs, which have multiple roles in negative regulation of gene expression including transcript degradation, transcript sequestering, and translational suppression, as well as possible involvement in positive regulation of gene expression via transcriptional and translational activation. The miRNA expression is deregulated in cancer through multiple mechanisms, such as gene amplification, deletion, mutation, and epigenetic silencing. There is now ample evidence that miRNAs are involved in the initiation and progression of cancer. MiRNA expression signatures are increasingly used for cancer classifications and have been associated with prognosis for some types. MiRNAs are stably present within microvesicles (exosomes) in many biofluids, including serum, plasma, cerebrospinal fluid, aqueous humor, and vitreous, and hence there is great potential for using miRNAs as biomarkers and potential therapeutic targets in cancer.

Methods: A literature review of publications addressing miRNAs in systemic, ocular and ocular adnexal lymphomas was performed.

Results: miRNA expression differs between lymphoma subtypes, and in lymphomas of differing anatomical compartments. For example, systemic and primary CNS diffuse large cell B-cell lymphoma (DLBCL) overexpress members of the miR-17-92 cluster (e.g. miR-92) and also miR-155, both of which are thought to be involved in B-cell lymphomagenesis, probably via the proto-oncogene MYC. However, PCNSL have differing expression patterns of up to 18 miRNAs when compared to nodal DLCBL: 13 were overexpressed, and 5 were downregulated in PCNSL. Further, preliminary data suggest that there are differing miRNAs expressed in vitreocentral lymphoma, compared to PCNSL. Finally, miRNA expression differences exist between ocular adnexal extranodal marginal zone B-cell lymphomas (EMZL) and DLBCL, possibly due to differences in MYC and NF-KB regulatory pathways.

Conclusions: Ocular lymphoma research is increasingly benefiting from technological advances in molecular pathology, and is improving our understanding of disease pathogenesis as well as the associated diagnostics, and may improve our prediction of disease response.

Commercial Relationships: Sarah E. Coupland, None

Program Number: 909
Presentation Time: 3:34 PM–3:51 PM
Role of microRNAs in the pathogenesis of macular pucker
Teresio Avitabile. Eye Clinic, University of Catania, Catania, Italy.

Presentation Description: Macular hole (MH) and epiretinal membrane (ERM) are disorders of the central area of the retina, site of the sharpest vision, characterized by vitreoretinal interface abnormalities, that lead to a severe visual impairment.

MiRNAs are an abundant class of naturally occurring, small noncoding RNA molecules that measure ~19–25 nucleotides in length. They play a major role as master regulators in RNA silencing and post-transcriptional regulation of gene expression by either one of two methods: cleavage of target miRNAs to induce their degradation or alternatively by translational repression of protein-coding genes.

MiRNAs have been identified as key mediators of a number of important biological processes such as cell development, cell differentiation, apoptosis or cell proliferation, thus implicating them in the process of carcinogenesis. A promising research field on miRNAs has been opened with the identification of miRNAs circulating in blood and other biological fluids. It has been recently shown that patients with different pathological phenotypes have a specific circulating miRNAs profile different than healthy individuals. These data suggest that modulation of dysregulated miRNAs with inhibitors (antagomirs) could have a key-role to design innovative targeted therapeutic strategies, as already investigated in other diseases. MiRNAs were identified in many ocular tissues and were shown to play a role in lens and retina development, ocular physiology, and in several ocular diseases. Aim of this study is to identify the complete expression profile of circulating miRNAs in vitreous humour (VH) and in serum of patients affected by MH and ERM and identification of dysregulated miRNAs in human VH, able to produce any changes in the vitreoretinal interface.

Commercial Relationships: Teresio Avitabile, None

Program Number: 910
Presentation Time: 3:51 PM–4:08 PM
MicroRNAs in glaucoma and regulating intraocular pressure
Colin E. Willoughby. Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom.

Presentation Description: MicroRNAs (miRNAs) are small (19-25 nucleotides), non-coding RNAs which are important regulators of eukaryotic gene expression in most biological processes. Tissue- and disease-specific alterations in the expression of miRNAs affect the abundance of proteins in different organs and their component parts. There is emerging experimental evidence deciphering the roles that miRNAs play in physiological and pathological states in the trabecular meshwork (TM). Mechanical and cellular stress, cellular senescence and TGFβ can induce alterations in miRNA expression in the TM. miRNAs play key roles in the outflow facility regulating cell contractility and the extra-cellular matrix in the TM. Intra-ocular pressure (IOP) can be modulated by miRNAs but further studies are required to fully understand the role of miRNAs in the TM and control of IOP. Our knowledge on the role of miRNAs in glaucoma pathogenesis is limited, although the cellular functions and genes miRNAs regulate in the TM have direct relevance to the pathophysiology of glaucoma. Understanding the role of miRNAs play in the TM and in glaucoma will not only improve our understanding of physiological and pathological states in the TM, but could provide new biomarkers of disease and novel therapeutic approaches. The ability to therapeutically manipulate miRNA expression and function with miRNA inhibitors or mimics has raised the possibility to develop a new class of glaucoma disease-modifying agents based on miRNA biology.

Commercial Relationships: Colin E. Willoughby, None

Program Number: 911
Presentation Time: 4:08 PM–4:25 PM
MicroRNAs in uveal melanoma: Another piece of the puzzle
Michele Reibaldi. Ophthalmology, University of Catania, Catania, Italy.

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**Presentation Description:**

Uveal melanoma is the most common primary intraocular malignancy in adults, with about 2000 new cases diagnosed in the United States each year. It may be located at any point in the uveal tract, with the choroid and ciliary body being more frequent locations than the iris and threatens not only the visual function but also the patient’s life. It is biologically distinct from cutaneous melanoma by a very strong propensity to metastasize the liver. It has been estimated that 50% of patients with uveal melanoma die from metastatic disease at 10 years, the liver being involved in up to 90% of individuals and the median survival being 4-5 months. Recently, the discovery of miRNAs as novel biomarkers in serum or plasma represented a new approach for diagnostic screening in blood. Moreover, several recent studies showed as circulating miRNAs fulfill a number of criteria of an ideal biomarker: such as accessibility through noninvasive methods; a high degree of specificity and sensitivity; the ability to differentiate pathologies; a long half-life within the sample; and the capability for rapid and accurate detection. Several studies have identified miRNAs in some types of cell-derived lipid vesicles secreted by cells. Among these, exosomes produced by cancer cells can contribute to the horizontal propagation of oncogenic miRNAs and their associated transforming phenotype among subsets of cancer cells. These secretory miRNAs may play a pivotal and general role as signaling molecules in physiological and pathological events. Beside the possibility of assessing the serum or plasma circulating concentrations of miRNAs, the possibility to dose such markers in other body fluids exists. In fact, in our previous work we already showed as expression of circulating miRNAs in vitreous humour changed in different eye pathologies, including uveal melanoma. Based on hypothesis, already proved for several neoplasias, that cancer cells in vitro and in vivo could be able to change the quantity of miRNAs secreted in body fluids with respect their physiological counterpart, the aim of this present work was to investigate whether patients affected by uveal melanoma could show different miRNA expression in vitreous humour and in the vitreal exosomes (biological fluid closest to site of primary tumour) but also in serum, respect to healthy donors.

**Commercial Relationships:** Michele Reibaldi, None

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**Presentation Description:**

MicroRNAs play a critical role within cells, regulating myriad cellular processes. However, microRNAs are also released form cells in extracellular vesicles which render them stable within the circulation. Pathological conditions such as diabetic retinopathy influence the microRNAs released by the affected cells and these changes can be detected in blood samples. This presentation will discuss how circulating microRNAs can be measured to provide diagnostic and prognostic information. Extracellular vesicles can also be used as part of a therapeutic strategy; the ability of vesicles released from endothelial progenitor cells to modulate angiogenesis and promote revascularisation will be reviewed. The delivery of microRNA-containing vesicles to vessels within the retina by intravitreal injection to modulate the pathologic angiogenesis which occurs in proliferative diabetic retinopathy will be described.

**Commercial Relationships:** David A. Simpson, None

**Support:** Fight for Sight Project grant ref 1444/1445

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**Presentation Description:**

The eye represents an extension of the brain and several ocular disorders were detected in patients with different central nervous system (CNS) diseases. miRNAs are abundant, endogenous, short, noncoding RNAs that act as important post-transcriptional regulators of gene expression by base-pairing with their target mRNA. Altered expression of certain miRNA molecules in the brains of patients with neurodegenerative diseases such as Alzheimer (AD) suggests that miRNAs could have a crucial regulatory role in age-related neurodegenerative diseases. The retinal diseases that have been most commonly compared to AD are age-related macular degeneration (AMD) and glaucoma. This presentation focuses on the miRNA expression profiles in age-related neurodegenerative diseases such as AD, AMD and glaucoma.

**Commercial Relationships:** Claudio Bucolo, None

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