LncRNAs in Age-Related Macular Degeneration

Subjects: Cell Biology

Contributor: Janusz Blasiak

lncRNAs are a novel class of functional RNA; the landscape of their mutations and variations is small as compared with other ncRNAs, not to mention mRNAs. However, the variability of lncRNA-encoding genes in the pathogenesis of human diseases, especially in cancer, is emerging (reviewed in the work of), but we have not found any association of lncRNA we described in this review with AMD. On the other hand, AMD is reported to associate with mutations in hundreds of genes, often in the form of polymorphisms, which should be considered in experimental studies and projection of therapeutic interventions (reviewed in the work of).

Keywords: age-related macular degeneration ; AMD ; long non-coding RNA ; epigenetic regulation ; oxidative stress-induced dedifferentiation ; micro RNA

1. Introduction

Does everything lie in genes? In a way, yes, as the genetic constitution of an organism determined by the sequence of its genome is a blueprint for an individual, but it represents the only potential for its development in normal conditions. The final phenotype is determined by the pattern of gene expression, which is underlined by both the genome sequence and its epigenetic modifications, as well as the environment/lifestyle that may also influence phenotype by non-genetic mechanisms. Changes in the epigenetic pattern are associated with many pathological states, and they are an essential step in cancer transformation. The epigenetic pattern is established by DNA methylation/demethylation, histone modifications, and the action of regulatory non-coding RNAs, which can be broadly divided into short and long non-coding RNAs (sncRNAs and lncRNAs, respectively).

Age-related macular degeneration (AMD) is a common cause of vision loss in the elderly. It is a complex, multifactorial eye disease with an interplay between genetic and environmental/lifestyle factors in its pathogenesis. AMD epigenetics is relatively recently subjected to AMD research but exploding during the last 10 years. The first paper related to AMD epigenetics from Salminen's and Kaarniranta's lab appeared in 2007, but in 2011 Hjelmeland still called epigenetics in AMD as a "dark matter" [1][2]. Today (22 July 2021), searching PubMed, even with a simple syntax "epigenetic AMD or epigenetic retina degeneration", returns 181 results with a significant portion published in the last three years. There are several recent excellent reviews on epigenetics in AMD, but lncRNAs are likely the least frequently addressed subject due to a low number of experimental works on lncRNAs in AMD. In this review, we update information on the involvement of lncRNAs in AMD pathogenesis and present the potential of lncRNAs in AMD diagnosis and therapy. In some cases, the results of works on other retinal diseases, especially diabetic retinopathy (DR), are presented as they contain information on retinal changes that can also contribute to AMD pathogenesis, e.g., retinal neovascularization. Many studies are allocated as "diabetic retinopathy" on the basis of oxidative stress induced by glucose at high concentrations, but this stress can also contribute to AMD pathogenesis [3].

2. Age-Related Macular Degeneration (AMD)—A Complex Eye Disease with the Involvement of Genetic/Epigenetic Factors in Its Pathogenesis

Age-related macular degeneration, a neurodegenerative disease of the eye, is the commonest reason for legal blindness and vision loss in the elderly. Its worldwide estimated prevalence in 2040 is about 300 million [4]. It is associated with physical and mental problems for affected individuals as well as it is a serious burden for societies. AMD affects the macula, a small functional structure in the central retina responsible for fine and color vision. The disease affects vision through progressive damage and loss of photoreceptors and the underlying retinal pigment epithelium (RPE). The RPE plays an important role in the maintenance of the balance in the retinal microenvironment through phagocytosis of the used photoreceptor outer segments (POSs), involvement in the visual cycle, and the blood-retina barrier as well as secreting growth factors needed for endothelial cells (reviewed in the work of [5]). Due to this and other effects, RPE cells are a main player in AMD pathogenesis.

Age is, per definition, the most serious factor of AMD pathogenesis, and several other reported or putative factors may play a role. These include modifiable factors, such as tobacco smoking, improper diet, high body-mass index, increased blood lipid, and cholesterol levels, female sex, exposure to the sunlight, especially its blue component, and others (reviewed in the work of [6]). Almost all these factors may contribute to the production of reactive oxygen species (ROS) and oxidative stress, which is frequently presented as the main factor of AMD pathogenesis.

Positive family history is, apart from aging, the strongest AMD risk factor. Family segregation and twin studies performed by Seddon JM et al. suggest that genetic components may play a role in AMD and age-related maculopathy, and up to 71% of AMD cases may be underlined by genetic factors [7]. Early association and genetic linkage studies identified the complement factor H (CFH) gene and the age-related maculopathy susceptibility 2/HtrA serine peptidase (ARMS2/HTRA1) genes to be associated with AMD [8]. Subsequent studies with high-throughput techniques, first of all, GWAS (genome-wide association studies), confirmed these conclusions and revealed a genome-wide set of other common variants of complement-related genes associated with AMD occurrence, including C2/CFB, C3, C7, CFI, and SERPING (reviewed in the work of [9]). However, the results of GWAS published in 2013 by the AMD Gene Consortium identified 19 loci showing enrichment in genes involved in the regulation of complement activity, collagen synthesis, lipid metabolism/cholesterol transport, receptor-mediated endocytosis, endodermal cell differentiation, angiogenesis, and extracellular matrix organization were associated with AMD, but only up to 15–65% of all AMD cases might be attributed to those variants [10]. The discrepancy between that and earlier studies was attempted to be explained by the interplay with environment, rare variants, gene-gene interaction, and epigenetics.

If the genetic profile is important in AMD, the same concerns its epigenetic counterpart, as any phenotype is not determined by gene sequence per se, but the gene expression regulated by epigenetic marks and events. However, the epigenetic profile may play a role in AMD pathogenesis as it may influence the expression of genes whose sequence is not changed, but their alternate products are important in AMD. As the DNA sequence of an individual is difficult to modify, the epigenetic profile can be alternated by many drugs and environmental factors and even with the lifestyle, especially diet [11]. This creates an opportunity to consider modifications of the epigenetic profile not only in experimental research on AMD pathogenesis but also in AMD prevention and therapy [12][13].

3. Long Non-Coding RNAs in AMD

The myocardial infarction-associated transcript (MIAT, also known as retinal non-coding RNA2, RNCR2) is an abundant lncRNA with a punctuate distribution in the nucleoplasm [14]. In the neural retina, MIAT is expressed in differentiating progenitor cells with no expression in the adult retina [15]. MIAT knockdown resulted in an increase in the number of amacrine interneurons and Müller glial cells, suggesting that it might be important for type-specification of retinal cells [16].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is expressed in all retinal layers, and its expression is increased in stress conditions in Müller cells and retinal ganglion cells [17]. Another lncRNA counteracting stress condition in the retina is MEG3 (maternally expressed gene 3) [18].

Clusterin (apoliprotein J) is a major protein present in drusen observed in the retinas of AMD patients [19]. It was shown that clusterin decreased ROS production in ARPE-19 cells exposed to hydrogen peroxide and defended them from apoptosis [20]. These protective effects were associated with AKT phosphorylation and suppressed by a PI3K/AKT inhibitor, and the authors concluded that clusterin might play a protective role against the consequences of oxidative stress in human RPE cells via the PI3K/AKT pathway. Suuronen et al. showed that clusterin expression on the mRNA and protein levels was epigenetically regulated in ARPE-19 cells, but the exact mechanism of this regulation was not completely clear [2]. Using a bioinformatic approach, Ye et al. showed a differential expression of 386 lncRNAs and a clusterin-associated ceRNA (competitive endogenous RNA) network with 75 lncRNAs and 32 miRNAs in ARPE-19 cells treated with clusterin the work of [21]. Some of these ncRNAs were previously associated with AMD. Therefore, clusterin may induce lncRNAs and ceRNA network, which may play a role in AMD pathogenesis.

miR-125b was reported to inhibit neovascularization through translational suppression of VE (vascular endothelial)-cadherin in endothelial cells [22]. Liu et al. showed an upregulation of MALAT1 and VE-cadherin and downregulation of miR-125b in human retinal microvascular endothelial cells (hRMECs) treated with glucose at high concentration [23]. The authors concluded that MALAT1 could compete with VE-cadherin to bind to miR-125b. Binding of this miRNA in the 3′-untranslated region (3′-UTR) of VE-cadherin resulted in its upregulation. They also observed that knockdown of MALAT1 inhibited proliferation, migration, and angiogenesis of hRMECs cells. Although the authors performed their research to explore mechanisms of DR, their results are important for retinal neovascularization in general and indicate MALAT1 as a potential target in retinal neovascularization-related diseases, including AMD.

4. Conclusions and Perspectives

Long non-coding RNAs are an emerging issue in molecular biology and clinical sciences, reflecting an emerging interest in the epigenetic regulation of gene expression as a main mechanism determining normal and disease phenotypes. Many new lncRNAs are identified with potentially important functions in physiology and pathology.

As presented above, in many cases, the mechanism of the involvement of a lncRNA in AMD pathogenesis included its action as a sponge for miRNAs. Therefore, studies on lncRNAs in AMD may bring important information on the involvement of miRNAs in this disease, which is also an emerging issue in research on AMD pathogenesis [24][25].

lncRNA dynamics is another subject that should be addressed in studies on lncRNA in AMD as lncRNAs undergo post-translational surveillance and only a small subset of the transcripts attain sufficient stability to persist in the cellular environment and perform their functions (reviewed in the work of [26])

Several works on the involvement of lncRNA in AMD pathogenesis are mostly association studies with the identification of a single lncRNA or lncRNA set supported by advanced bioinformatics analysis to identify a network of lncRNA-mRNA interaction to draw a conclusion on the role the identified lncRNAs might play in AMD pathogenesis. No mechanistic and clinical studies are performed to validate these assumptions. Such investigations are conducted in silico, and therefore they predict candidate lncRNAs, some of which may not be confirmed in biological studies. Therefore, mechanistic and clinical studies are needed to validate the biological functions of already identified and new lncRNAs. In addition, there are critical demands for well demographically characterized clinical material to perform a longitude analysis to better understand the role of lncRNA in AMD progression.

References

1. Hjelmeland, L.M. Dark matters in AMD genetics: Epigenetics and stochasticity. Investig. Opthalmol. Vis. Sci. 2011, 52, 1622–1631.
2. Suuronen, T.; Nuutinen, T.; Ryhänen, T.; Kaarniranta, K.; Salminen, A. Epigenetic regulation of clusterin/apolipoprotein J expression in retinal pigment epithelial cells. Biochem. Biophys. Res. Commun. 2007, 357, 397–401.
3. Gregory-Evans, K. A review of diseases of the retina for neurologists. Handb. Clin. Neurol. 2021, 178, 1–11.
4. Wong, W.L.; Su, X.; Li, X.; Cheung, C.M.G.; Klein, R.; Cheng, C.-Y.; Wong, T.Y. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob. Health 2014, 2, e106–e116.
5. Strauss, O. The retinal pigment Epithelium in visual function. Physiol. Rev. 2005, 85, 845–881.
6. Pennington, K.L.; DeAngelis, M.M. Epidemiology of age-related macular degeneration (AMD): Associations with cardiovascular disease phenotypes and lipid factors. Eye Vis. 2016, 3, 1–20.
7. Seddon, J.M.; Cote, J.; Page, W.F.; Aggen, S.H.; Neale, M.C. The US Twin Study of age-related macular degeneration. Arch. Ophthalmol. 2005, 123, 321–327.
8. Huang, L.; Meng, Q.; Zhang, C.; Sun, Y.; Bai, Y.; Li, S.; Deng, X.; Wang, B.; Yu, W.; Zhao, M.; et al. Gene–gene interaction of CFH, ARMS2, and ARMS2/HTRA1 on the risk of neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in Chinese population. Eye 2015, 29, 691–698.
9. Warwick, A.; Lotery, A. Genetics and genetic testing for age-related macular degeneration. Eye 2017, 32, 849–857.
10. The AMD Gene Consortium. Seven new loci associated with age-related macular degeneration. Nat. Genet. 2013, 45, 433–439.
11. Tiffon, C. The impact of nutrition and environmental epigenetics on human health and disease. Int. J. Mol. Sci. 2018, 19, 3425.
12. Kiel, C.; Weber, B.H.F.; Grassmann, F. Pleiotropic effects of risk factors in age-related macular degeneration and seemingly unrelated complex diseases. Adv. Exp. Med. Biol. 2018, 247–255.
13. Luu, J.; Kallestad, L.; Hoang, T.; Lewandowski, D.; Dong, Z.; Blackshaw, S.; Palczewski, K. Epigenetic hallmarks of age-related macular degeneration are recapitulated in a photosensitive mouse model. Hum. Mol. Genet. 2020, 29, 2611–2624.
14. Sone, M.; Hayashi, T.; Tarui, H.; Agata, K.; Takeichi, M.; Nakagawa, S. The mRNA-like noncoding RNA Gomafu constitutes a novel nuclear domain in a subset of neurons. J. Cell Sci. 2007, 120, 2498–2506.

15. Blackshaw, S.; Harpavat, S.; Trimarchi, J.; Cai, L.; Huang, H.; Kuo, W.P.; Weber, G.; Lee, K.; Fraioli, R.E.; Cho, S.-H.; et al. Genomic analysis of mouse retinal development. PLoS Biol. 2004, 2, e247.
16. Rapicavoli, N.A.; Poth, E.M.; Blackshaw, S. The long noncoding RNA RNCR2 directs mouse retinal cell specification. BMC Dev. Biol. 2010, 10, 49.
17. Yao, J.; Wang, X.; Li, Y.; Shan, K.; Yang, H.; Wang, Y.; Yao, M.; Liu, C.; Li, X.; Shen, Y.; et al. Long non-coding RNA MALAT 1 regulates retinal neurodegeneration through CREB signaling. EMBO Mol. Med. 2016, 8, 346–362.
18. Zhu, Y.-X.; Yao, J.; Liu, C.; Hu, H.-T.; Li, X.-M.; Ge, H.-M.; Zhou, Y.-F.; Shan, K.; Jiang, Q.; Yan, B. Long non-coding RNA MEG3 silencing protects against light-induced retinal degeneration. Biochem. Biophys. Res. Commun. 2018, 496, 1236–1242.
19. Baek, J.-H.; Lim, D.; Park, K.H.; Chae, J.-B.; Jang, H.; Lee, J.; Chung, H. Quantitative proteomic analysis of aqueous humor from patients with drusen and reticular pseudodrusen in age-related macular degeneration. BMC Ophthalmol. 2018, 18, 289.
20. Kim, J.H.; Kim, J.H.; Jun, H.O.; Yu, Y.S.; Min, B.H.; Park, K.H.; Kim, K.-W. Protective effect of clusterin from oxidative stress–induced apoptosis in human retinal pigment epithelial cells. Investig. Opthalmol. Vis. Sci. 2010, 51, 561–566.
21. Ye, Z.; Li, Z.; He, S. Long non-coding RNA associated-competing endogenous RNAs are induced by clusterin in retinal pigment epithelial cells. Mol. Med. Rep. 2017, 16, 8399–8405.
22. Muramatsu, F.; Kidoya, H.; Naito, H.; Sakimoto, S.; Takakura, N. microRNA-125b inhibits tube formation of blood vessels through translational suppression of VE-cadherin. Oncogene 2013, 32, 414–421.
23. Liu, P.; Jia, S.-B.; Shi, J.-M.; Li, W.-J.; Tang, L.-S.; Zhu, X.-H.; Tong, P. LncRNA-MALAT1 promotes neovascularization in diabetic retinopathy through regulating miR-125b/VE-cadherin axis. Biosci. Rep. 2019, 39.
24. Hyttinen, J.M.; Blasiak, J.; Felszeghy, S.; Kaarniranta, K. MicroRNAs in the regulation of autophagy and their possible use in age-related macular degeneration therapy. Ageing Res. Rev. 2021, 67, 101260.
25. Blasiak, J.; Watala, C.; Tuuminen, R.; Kivinen, N.; Koskela, A.; Uusitalo-Järvinen, H.; Tuulonen, A.; Winiarczyk, M.; Mackiewicz, J.; Zmorzyński, S.; et al. Expression of VEGFA-regulating miRNAs and mortality in wet AMD. J. Cell. Mol. Med. 2019, 23, 8464–8471.
26. Nair, L.; Chung, H.; Basu, U. Regulation of long non-coding RNAs and genome dynamics by the RNA surveillance machinery. Nat. Rev. Mol. Cell Biol. 2020, 21, 123–136.
