miRNAs in Neurodegeneration

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might work, consider three privacy-affecting systems: surveillance cameras, wireless networks, and radio-frequency identification (RFID) tags for patients.

Video surveillance cameras have become a commonplace component of security systems in public places. High-resolution images over a wide field of view can be digitally stored indefinitely to identify and track persons. Mindful of visual privacy, researchers have developed an approach to perturb all facial features so that each face matches a number of others (*8*). However, major practical problems remain in implementing such procedures, in say a football stadium, underlining the need for further research; the existing techniques are too expensive and slow to be used in general video surveillance.

The rich connectivity of wireless networks involves a spectrum shared by a wide variety of devices, such as laptops, Bluetooth headsets, and mobile phones. Because any device can be identified, tracked over time, and profiled by anyone with sufficient technical capability, this congestion raises concerns that the usual encryption procedures cannot protect an individual's locational privacy. Greenstein has identified various research challenges in designing wireless systems that are privacy-aware (*9*). The challenges include, for example, cryptographic schemes to prevent the necessary device addresses from being identified without burdensome changes to existing protocols for media access, and ways for a device to discover and bind to resources without revealing to an eavesdropper that it is doing so.

Wrong-site surgery is estimated to occur between 1300 and 2700 times per year in the United States (*10*). With an RFID tag attached to a patient, a physician in the operating room can reduce the number of such errors by verifying the correct patient, procedure, and site. The U.K. health minister Lord Hunt recently supported recommendations for such strategies (*11*). Because privacy is affected, the U.S. National Institute of Standards has recommended stringent practices in designing an RFID system (*12*, *13*). For example, only the surgeon and others with a need to know would have access. Only as much personal data are captured as is necessary; thus, the tags would not contain personal financial information. Last year, Birmingham Heartlands Hospital, UK, began to expand the use of RFID bracelets to all patients on five wards, linking them to a digital photograph and the electronic medical records for their visit.

To ensure clarity and accountability (*14*), privacy-aware systems must implement a definition of privacy that users find meaningful, reasonable, and transparent. A privacy risk assessment must be performed to identify the potential for disclosure of personal information. Disclosures must be revealed, and measures must be in place to deal with privacy failures. Access by individuals to their personal data should be easy, and mechanisms must be in place to ensure that personal data are accurate.

To ensure effectiveness, systems must make a trade-off between privacy risk and utility, but reasonable expectations for privacy must always be met. For example, a subject need not be identified by name if just authentication of the subject's role in the system is required. Achieving "adequate" privacy will require engineering innovation, managerial commitment, informed cooperation of data subjects, and social controls (legislation, regulation, codes of conduct by professional associations, and response to reactions of the public).

References and Notes

1. www.oracle.com/corporate/press/2007_feb/oracledataintegrator.html
2. G. Gilder, *Telecosm: How Infinite Bandwidth Will Revolutionize the World* (Free Press, New York, 2000).
3. G. T. Duncan, In P. Shane, J. Podesta, R. Leone, Eds., *A Little Knowledge: Privacy, Security, and Public Information After September 11* (Century Foundation Press, New York, 2004), pp. 71–88.
4. National Research Council, *Engaging Privacy and Information Technology in a Digital Age* (National Academies Press, Washington, DC, 2007).
5. The Royal Academy of Engineering, *Dilemmas of Privacy and Surveillance: Challenges of Technological Change* (London, 2007).
6. www.verispan.com/index.php
7. A. Greenspan, at *Conference on Privacy in the Information Age* (Salt Lake City, 7 April 1997); see www.federalreserve.gov/boardDocs/speeches/1997/19970307.htm.
8. E. M. Newton, L. Sweeney, B. Malin, *IEEE Transactions on Knowledge and Data Engineering* **17**, 232 (2005).
9. B. Greenstein, at *11th Workshop on Hot Topics in Operating Systems (HotOS XI)*, San Diego, CA, 7 to 9 May 2007.
10. S. C. Seiden, P. Barach, *Archives of Surgery* **141**, 931 (2006).
11. www.gnn.gov.uk/environment/fullDetail.asp?ReleaseID=264567&NewsAreaID=2&NavigatedFromDepartment=False
12. T. Karygiannis *et al.*, *Guidelines for Securing Radio Frequency Identification (RFID) Systems* (National Institute of Standards and Technology, Washington, DC, 2007).
13. The guidelines include firewalls that separate RFID databases from other databases, signal encryption, authentication of users, prevention of unauthorized access, and tag disposal to destroy sensitive data.
14. M. Langheinrich, in *Proceedings Third International Conference on Ubiquitous Computing*, G. Abowd, B. Brumitt, S. Shafer, Eds. (Springer, Atlanta, 2001), pp. 273–291.

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MOLECULAR BIOLOGY

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Noncoding microRNAs are necessary for the survival of postmitotic cells such as neurons that die in Parkinson's and other brain diseases.

The human genome sequencing effort has taught us that it takes relatively few genes to build a human being. Complexity arises from the combination of these building blocks into genetic programs that are finely tuned in space and time during cell and tissue differentiation. A major part of this regulation is performed by microRNAs (miRNAs), small RNA molecules encoded by the genome that are not translated into proteins; rather, they control the expression of genes. Deregulation of miRNA function has been implicated in human diseases including cancer and heart disease (*1*, *2*). On page 1220 of this issue, Kim *et al.* (*3*) suggest that miRNAs are essential for maintaining dopaminergic neurons in the brain, and thus could play a role in the pathogenesis of Parkinson's disease.

Similar to classical genes, regions of the genome that encode miRNAs are transcribed in the cell nucleus. Nascent miRNA transcripts are initially processed into long (up to several kilobases in length) precursor miRNAs that are then sequentially cleaved by two enzymes, Drosha and Dicer, into small functional RNAs (~22 nucleotides). These miRNAs are subsequently incorporated into an RNA-induced silencing complex (RISC), which suppresses the translation and/or promotes the degradation of target messenger RNAs (mRNAs)—RNA molecules that encode proteins—by binding to their 3′-untranslated regions (3′-UTRs) (*4*). miRNAs are abundant in the brain and are essential for efficient brain function. In this regard, expression of a brain-specific miRNA (miR-124a) in nonneuronal cells

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converts the overall gene-expression pattern to a neuronal one (*5*, *6*). Another brain-specific miRNA, miR-134, modulates the development of dendritic spines—neuronal protrusions that connect with other neurons—and therefore probably controls neuronal transmission and plasticity (*7*).

Recent evidence suggests that miRNAs and transcription factors work in close concert. For instance, the RE1 silencing transcription factor can inhibit transcription of miR-124a, thereby suppressing cell differentiation into neurons (*8*). Kim *et al.* observe a similar relationship between miR-133b and the transcription factor Pitx3. The pair forms a negative-feedback loop that regulates dopaminergic neuron differentiation (see the figure). Pitx3 transcribes miR-133b, which in turn suppresses Pitx3 expression.

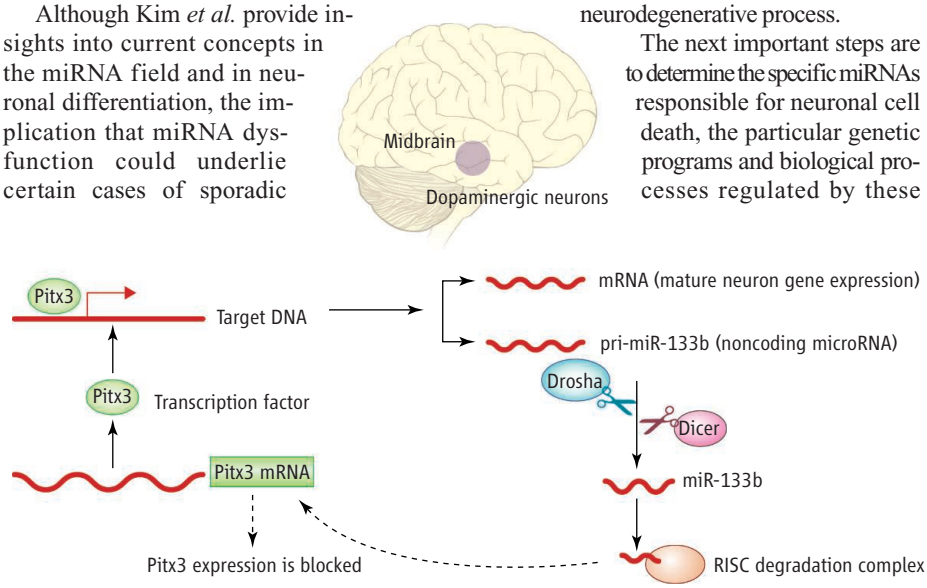
Although Kim *et al.* provide insights into current concepts in the miRNA field and in neuronal differentiation, the implication that miRNA dysfunction could underlie certain cases of sporadic Parkinson's disease is profound given that after Alzheimer's disease, Parkinson's disease is the second most prevalent age-associated neurodegenerative disorder. The gradual loss of dopaminergic (and eventually other) neurons results in severe mobility problems and occasionally evolves into full-blown dementia. As with Alzheimer's disease, gene mutations can result in inherited forms of Parkinson's disease (*9*). Although the study of these rare familial forms has helped enormously in understanding their molecular pathogenesis, the real challenge for future research in the field is the vast number of nonfamilial cases.

The hypothesis that alterations in miRNA networks in the brain contribute to neurodegenerative disease is appealing and has been tested to a certain extent by Kim *et al.* along with previous work in mice (*3*, *10*), flies (*11*), and cultured neurons (*3*), in which the enzyme Dicer was genetically inactivated. Loss of Dicer leads to the complete absence of miRNAs and is lethal (*12*). However, Kim *et al.* show that mice lacking Dicer in specific dopamine neurons are born alive but develop a progressive loss of neurons later in life, displaying a Parkinson's disease–like phenotype. Thus, Dicer is essential for neuronal survival and loss of miRNAs may be involved in the development and/or progression of Parkinson's disease (*3*, *10*). Given that the transfer of cellular-derived small RNAs (including miRNAs) partially preserved the dopaminergic phenotype in cell culture (*3*), it is likely that the absence of miRNAs, and not the lack of other potential Dicer-related functions, is involved in the neurodegenerative process.

The next important steps are to determine the specific miRNAs responsible for neuronal cell death, the particular genetic programs and biological processes regulated by these miRNAs, and the extent to which these miRNAs play a relevant role in the neurodegenerative phenotype. The evidence presented by Kim *et al.* is somewhat ambiguous as far as relevance to neurodegeneration. Screening the expression of 224 different miRNAs obtained from brain samples of patients with Parkinson's disease and control subjects revealed notable changes in a small number of miRNAs, including miR-133b. Normally, miR-133b is enriched in the midbrain; however, it was surprisingly deficient in the brains of patients with Parkinson's disease. The relative number of patients investigated in this study is too small to draw definite conclusions about the clinical relevance of this observation. The finding that miR-133b suppresses the full differentiation of dopaminergic neurons in cell culture, whereas its expression is down-regulated in the brain of Parkinson's disease patients, is, however, puzzling. This observation suggests that miR-133b might have additional functions in dopaminergic neuronal differentiation beyond suppressing Pitx3 expression. Further work is necessary, not only to elaborate the clinical importance of these findings, but also to elucidate the full genetic program that miR-133b modulates.

Apart from the possibility that an overall loss of miRNA function could be associated with aging and could contribute to the age-related increased risk for Parkinson's and Alzheimer's disease, very specific molecular mechanisms should also be envisaged. Thus, polymorphisms in the genetic regions encoding specific miRNAs and alterations in molecular machinery (such as miRNA-processing enzymes) should be investigated. In particular, the 3′-UTR of the mRNAs encoding proteins such as α-synuclein or amyloid precursor protein should be scrutinized. Because dosage effects of these proteins are sufficient to induce Parkinson's disease (*13*) and Alzheimer's disease (*14*), respectively, further alterations that control their expression might also contribute to pathogenesis. Indeed, the neurological disorder Tourette's syndrome is associated with a variation in the binding site for a specific miRNA in the 3′-UTR of mRNAs encoding the neuronal proteins Slit and Trk-like 1 (SLITRK1) (*15*).

The work by Kim *et al*. and other recent studies (*7*, *11*) herald a new area of exciting research in the field of neurodegenerative diseases. Clinical studies will rapidly determine the extent to which miRNAs contribute to the pathogenesis of sporadic Parkinson's and Alzheimer's disease; however, the role of miRNAs as a potential therapeutic target remains a challenging question.



Neuronal survival in the brain. An autoregulatory feedback loop composed of the transcription factor Pitx3 and miR-133b is implicated in dopaminergic neuron maturation and survival in the brain. miR-133b is deficient in the midbrain of Parkinson's disease patients and in mouse models of dopamine neuron deficiency.

References

1. G. A. Calin, C. M. Croce, *Nat. Rev. Cancer* **6**, 857 (2006).
2. B. Yang *et al.*, *Nat. Med.* **13**, 486 (2007).
3. J. Kim *et al.*, *Science* **317**, 1220 (2007).
4. K. S. Kosik, *Nat. Rev. Neurosci.* **7**, 911 (2006).
5. L. P. Lim *et al.*, *Nature* **433**, 769 (2005).
6. E. V. Makeyev, J. Zhang, M. A. Carrasco, T. Maniatis, *Mol. Cell* **27**, 435 (2007).
7. G. M. Schratt *et al.*, *Nature* **439**, 283 (2006).
8. C. Conaco, S. Otto, J. J. Han, G. Mandel, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 2422 (2006).
9. W. Mandemakers, V. A. Morais, B. De Strooper, *J. Cell Sci.* **120**, 1707 (2007).
10. A. Schaefer *et al.*, *J. Exp. Med.* **204**, 1553 2007).
11. J. Bilen, N. Liu, B. G. Burnett, R. N. Pittman, N. M. Bonini, *Mol. Cell* **24**, 157 (2006).
12. E. Bernstein *et al.*, *Nat. Genet.* **35**, 215 (2003).
13. A. B. Singleton *et al.*, *Science* **302**, 841 (2003).
14. A. Rovelet-Lecrux *et al.*, *Nat. Genet.* **38**, 24 (2006).
15. J. F. Abelson *et al.*, *Science* **310**, 317 (2005).

10.1126/science.1148530