Epigenetics

The Epicenter for Future Anesthesia Research?

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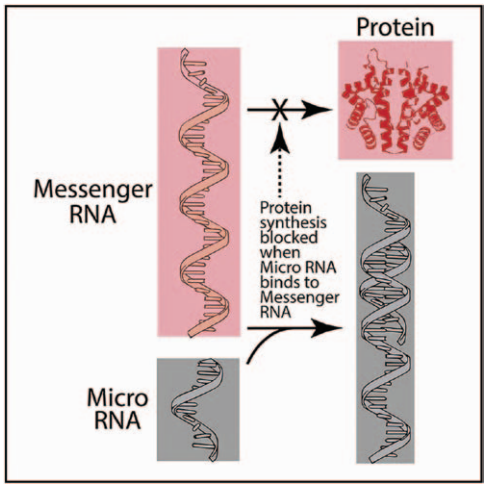
CONRAD Hal Waddington (1905–1975), a British embryologist, geneticist, and philosopher, proposed the concept of *epigenetics*, defined broadly as the bridge between an organism's inheritable genome and the observable traits of that organism, such as morphology, physiological properties, and behavior.[1] For example, although a majority of a given organism's cells share an identical set of chromosomes, embryological development results in a wide diversity of cell types, each with individualized gene expression patterns and functions. In this light, epigenetics is generally now defined as the study of gene expression processes that are impacted by the external environment and can be passed to successive generations, independently of changes in Watson-Crick DNA base pairing.[2] In this issue of Anesthesiology, Qiao *et al.*[3] explore for the first time *in vivo* the epigenetic regulation of cardiac anesthetic preconditioning by microRNAs (miRs). Their findings provide insight into upstream regulatory control of prosurvival protein expression in the heart by a "noncoding" species of RNA.



"miRs are small (19 to 22 nucleotides), highly conserved across species, and.... [Their binding to target genes] results in gene silencing or degradation."

Our knowledge of the cellular processes that determine whether a particular sequence of DNA becomes a functional protein has grown substantially in recent years. The results of the Human Genome Project provided a new layer of complexity in our understanding gene regulation: sequencing data suggested that the approximately 20,000 genes that code for proteins only represent approximately 1.5% of DNA. Since 2003, determining the function of the remainder of our genome has been the intent of the U.S. National Human Genome Research Institute Encyclopedia of DNA Elements (ENCODE) project. A major accomplishment of the ENCODE project has been the determination that approximately 80% of the human genome is indeed associated with at least one biochemical function: regulation of the expression of coding genes.[4] These results in part explain the observation that the majority of RNA species that are generated are not subsequently translated to protein[5] and demonstrate that gene regulation is far more complex than has been traditionally believed.

The list of noncoding RNAs has grown from transfer RNAs and ribosomal RNAs to include the discovery of small nucleolar RNAs, long noncoding RNAs, and, the topic of the current study by Qiao *et al.*, miRs. miRs are important posttranscriptional regulators that interact with multiple target mRNAs to coordinately regulate protein expression. miRs are small (19 to 22 nucleotides), highly conserved across species, and function *via* base pairing with complementary sequences within target mRNA molecules. Complementary binding of a given miR to its target gene results in gene silencing or degradation. A short (5 to 7 nucleotides) sequence in the mature miR determines the specificity of binding to mRNAs, so miRs can bind multiple mRNAs and a given mRNA can be bound by multiple miRs, creating a new and complex layer of posttranscriptional control. In the current study, Qiao *et al.* examine the contribution of miR-21 in isoflurane-mediated cardioprotection from ischemia–reperfusion injury by using *in vivo* and *ex vivo* models of ischemia–reperfusion injury in miR-21 knockout and wild-type mice. Their results suggest that miR-21 is a critical regulator of isoflurane preconditioning, mediated by downstream effects on several known cardioprotective molecules. As Qiao *et al.* indicate, miR-21 is "highly expressed in cardiomyocytes, cardiac fibroblasts, vascular

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endothelial cells, and vascular smooth muscle cells,"[3] and given that endogenous miRs in tissue can be easily increased or decreased with chemical mimics and inhibitors, their findings may hold clinical relevance for future therapeutic strategies that would serve to effectively modulate cardiac gene regulation.

In 1957, 4 yr after Watson and Crick's groundbreaking theory of DNA structure and function, Waddington proposed the concept of a multidimensional *epigenetic landscape* using images to represent the process of cellular decision-making.[1] His images reflect an understanding that human diversity is likely a result of the myriad of complex cellular and environmental interactions and not simply one-to-one protein coding of the genome. Today, we are just beginning to realize the magnitude of this complexity: in addition to controlling protein expression within their own cell of origin, miRs have more recently been shown to exist extracellularly in the circulation secreted in exosomes and to originate from the external environment from sources such as plants[6] and viruses.[7] This suggests an additional dimension of gene regulation *via* intercellular, interorgan, and interspecies epigenetic communication. Continuing to explore and map the terrain of Waddington's epigenetic landscape may provide answers to some of the long-standing questions in anesthesia research, and several we have not yet considered.

Competing Interests

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References

1. Baedke J: The epigenetic landscape in the course of time: Conrad Hal Waddington's methodological impact on the life sciences. Stud Hist Philos Biol Biomed Sci 2013; 44(4 Pt B): 756–73
2. Penny D: Epigenetics, Darwin, and Lamarck. Genome Biol Evol 2015; 7:1758–60
3. Qiao S, Olson JM, Paterson M, Yan Y, Zaja I, Liu Y, Riess ML, Kersten JR, Liang M, Warltier DC, Bosnjak ZJ, Ge Z-D: MicroRNA-21 mediates isoflurane-induced cardioprotection against ischemia-reperfusion injury *via* Akt/nitric oxide synthase/mitochondrial permeability transition pore pathway. Anesthesiology 2015; 123:786–98
4. Consortium ENCODEP: An integrated encyclopedia of DNA elements in the human genome. Nature 2012; 489:57–74
5. Thum T, Condorelli G: Long noncoding RNAs and microRNAs in cardiovascular pathophysiology. Circ Res 2015; 116:751–62
6. Vaucheret H, Chupeau Y: Ingested plant miRNAs regulate gene expression in animals. Cell Res 2012; 22:3–5
7. Dhuruvasan K, Sivasubramanian G, Pellett PE: Roles of host and viral microRNAs in human cytomegalovirus biology. Virus Res 2011; 157:180–92