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EDITORIAL 2

Changing Paradigms in Understanding Pain: The Role of Networks, Genomics and Proteomics

When we are posed with a clinical problem in pain medicine, as in most other branches of medicine, we follow a set of time-tested techniques. This involves understanding the anatomic substrate, which, in pain medicine is the 'pain generator'. We further probe into the etiopathophysiology underlying the problem. This also leads us to understand the possible array of neurotransmitters and other chemicals involved in generation and propagation of pain. This is the current state of clinical pain medicine.

With the advancement in neurosciences, it is now possible to postulate the various networks involved in maintenance of pain. For example, the frontal-subcortical networks are important in the cognitive and behavioral aspects of pain. Unless we understand these networks we will not be able to address the issue of pain fully. This is, because, we often target our approach to only a part of the network and this leads to suboptimal levels of pharmacological and nonpharmacological approaches in treatment.

Understanding pain at a molecular level increases the effectiveness of already established electrophysiological and network level knowledge. Genomics and proteomics are relatively new and rapidly expanding research areas in the 21st century that advances the conventional research tools.

Genomics is the study of all the nucleotide sequences and coding/noncoding sequences of DNA (transcriptomics). The vulnerability to certain degenerative and pain syndromes and responses to various pharmacotherapy is dependent on genes. It is important to study genomics to understand traits, in particular diseases, as some inherited diseases results from the change of 1 base in a DNA sequence. This is called single-nucleotide polymorphism (SNP). The effect of any particular SNP, i.e. the resulting phenotype, will depend on the impact of the resulting substitution of the encrypted amino acid on the respective protein. Having detected a SNP, it is possible using gene-association studies to link the abnormal gene with either a disease process or an abnormal response to a drug.[1] Functional genomics is the search for a physiological role of the gene, when only its primary sequence is known. Technological developments in microarray and microchip have now made it possible to assess the contribution of genes in pain treatment. This has been enhanced by mathematical tools like normalization, hierarchical clustering, heat maps and pathway analysis.

Proteomics is the global analysis of the complete complement of proteins that make up a cell, tissue or body fluid. It is important to study proteomics because the genome/transcriptome is not sufficient to model and predict biological systems. Post-transcriptional modifications, such as phosphorylation, proteolytic cleavage, etc. often regulate protein activities. The quantity of protein in a cell, tissue or organism is not always regulated by mRNA. Instead, translation and degradation play critical roles in determining the abundance of protein. Major applications of proteomics include proteome profiling (large scale identification of proteins, comparative proteomics (quantitative proteomics) for target identification and biomarker discovery and functional proteomics-antibody arrays to monitor proteins involved in various functions, e.g. the immune system.[2]

It is now possible to rapidly obtain the amino acid sequence of neuropeptide precursors, either by cloning and sequencing the cDNA that encodes the precursor, or by reconstructing the arrangement of introns and axons in a neuropeptide coding gene.[1] The databases generated from these methods have been used to design probes to identify cells that express the gene and also assess the rate of expression of the gene, and even to predict the post-translational modifications that can generate functional neuropeptides from a biologically inert precursor.[3] Parallel studies on the receptors and molecules that bind such neuropeptides as well as how the signalling cascades are affected before and after a noxious stimulus, are also milestones in the last couple of decades.[2]

Proteomic studies have generated databases which have diagnostic, therapeutic and prognostic significance in human cancer studies. A proteomic study looked at the spinal protein expression in rats exposed to repeated injection of intrathecal morphine, with a primary objective to investigate the neuroadaptive changes in the spinal cord that are thought to underlie molecular mechanisms in the development of morphine tolerance and dependendance.[2] They found eight proteins that were upregulated or downregulated in the spinal cord after morphine tolerance development, including those involved in targeting and trafficking of glutamate receptors and opioid receptors, proteins involved in oxidative

stress, and cytoskeletal proteins. These may serve as potential targets for the prevention of morphine tolerance.[3]

The mechanisms underlying pain signal transduction, transmission, and spinal and central processing are subject to variations between individuals owing to their genetic codes. Different phenotypes are potentially produced when genes undergo variations (or mutations) from the normal (or wild-type) form. Whether a specific polymorphism is responsible for an associated phenotype, is difficult to determine. This is because some genetic variants do not produce a change in phenotype. For example, it has been calculated that there are more than 20 candidate genes whose SNPs could influence points on the pain pathways. These include SNPs of genes that encode cytokines, kinins, ion channels and opioid receptors. Genetic factors regulating pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction), contribute to variability in drug responses.

The future of pain may lie in the applications of genomics and proteomics in neuroimmunomodulation, especially psychoimmunopharmacology design and development. As clinician-scientists who are interested in promoting milestones to the young discipline of pain medicine, it is our combined responsibility to contribute in developing, understanding and applying this knowledge from bench to bedside.

Abnormal accumulations of misfolded proteins, such as tau, alpha-synuclein and beta amyloid are identified in several neurodegenerative disorders. We are not far away from definitively identifying proteins involved in chronic pain disorders. After identifying the clinical syndrome, we should try to go beyond gross anatomy and pathology to the levels of neural networks, genomic and proteomic substrates involved in generation and/or propagation of pain. This dual approach at holism and reductionism should be taught at undergraduate programs and this will enhance the accuracy of diagnosis as well as prognosis. It also opens vistas to modulate a more precise target like the genes during pre-pathogenesis and thereby change the evolution of the disease.

We, at the editorial team, sincerely hope to build and carry forward evidence and credibility to this interdisciplinary approach in traversing the final frontiers of understanding pain. No doubt, there are murky waters and unchartered territories, but we dream a smooth sail and will soon hit an enviable impact factor. It is a great honor and responsibility which our Editor-in-Chief has bestowed on us, and we start off with prolific enthusiasm and on a war footing.

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Pravin Thomas
Lead Consultant and Director
Department of Neurology
Pain Services, Believers Church Medical College Hospital
Thiruvalla, Kerala, India