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Editorial Open Access

Epigenetics: Understanding Molecular Roots of Autoimmunity

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Editorial

Why do some individuals encounter autoimmune diseases while others don't?

An outstanding challenge in Rheumatology practice! The answer is autoimmune diseases represent a set of disorders of indefinite etiology in which the immune system experiences a potential trigger mostly environmental that leads to significant deterioration in immunologic self-tolerance promoting an immune response directed to self-antigens.

If this is the case then, why do individuals who experience similar environmental triggers don't display the same pattern of autoimmune diseases. It has been well recognized that the clinical interpretation of such self-immune attack encompasses a vast array of autoimmune diseases with multi-organ affection and variable outcomes that might be devastating. An obvious explanation for this would be an individual based factor meaning that each individual has a unique genetic profile which might define the interpretation of autoimmunity into a specific disease category following exposure to an environmental trigger.

What are the molecular theories behind the evolution of an autoimmune disease or favor the existence of one autoimmune disease over the other?

In the last two decades researchers have been exerting a lot of efforts in attempt to find the answer coming up with a new term in the field of autoimmunity known as epigenetics. Epigenetics are defined as the mechanisms that contribute to stable changes of gene expression without a change in the primary nucleotide sequence. Epigenetic modifications might lead to over expression of some nucleotides with suppression of others and that's why they are the reason why an identical gene set within human bodies might display highly specific lineages and phenotypes despite being identical.

Research experts were able to identify three distinct forms of epigenetic modifications: DNA methylation, histone modifications and RNA interference. The understanding of each has effectively defined their relevance to gene expression in autoimmune disorders. Methylation means the addition of a methyl group (CH_3) to DNA nucleotides from the methyl donor S-adenosyl methionine (SAM) by a family of enzymes called the DNA transferases. Such DNA alteration becomes relevant if it takes place within clusters of cytosine nucleotides called CpG islands or the high CpG density region of promoters. DNA methylation affects gene transcription in two ways: first, DNA methylation physically hinders binding of transcriptional proteins to the gene and second, methylated DNA recruits proteins known as methyl-CpG-binding domain proteins that facilitate formation of compact inactive chromatin or the silent chromatin. In such case it would be expected that the more the methylation of a specific gene nucleotide the lesser the expression of its respective gene [1-9].

Then comes another form of epigenetic alteration which involves the histones. Histones are a special group of proteins found in the nuclei of eukaryotic cells. They provide the anchor structure around which the DNA strands get spun to form chromatin. An eukaryotic chromatin structure consists of building units known as nucleosomes which are repeating units resembling beads on a string with connecting sequences of linker DNA. Each nucleosome is formed of DNA sections wrapped around a core octamer of eight histones. The core proteins can be grouped into H2A, H2B, H3, and H4, while the linker histones into H1 and H5. This core is subject to several post-translational modifications including methylation, citrullination, acetylation, phosphorylation, SUMOylation, ubiquitination, and deimination which are responsible for another form of epigenetic modifications that has been well recognized to affect gene transcription. It was generally considered that the lesser the bound histones the higher the transcriptional activity of a particular gene, subsequently inactive genes were expected to be highly bound to histones. Later, profound research disclosed a more precise hypothesis; it's the modification of specific set of histones that alter the binding status of histones and consequently might alter gene transcription either by decreasing or increasing this gene transcription. The detection of such 'histone marks' or signatures in specific gene loci allows for assessment of the transcriptional status of this specific gene [6-11].

Another hot topic that was recently tackled in the field of epigenetics and autoimmune diseases is the 'RNA interference'. In the early 1990s, a number of scientists observed that RNA was independently capable of inhibiting protein expression in plants and fungi with the first evidence that dsRNA could achieve such efficient gene 'knock down' coming from studies on the nematode Caenorhabditis elegans in 1998 by Fire and Mello (2006 Nobel prize winners). This process was later described as RNA interference or post-transcriptional gene silencing. RNA interference (RNAi) is a post-transcriptional process triggered by the introduction of double-stranded RNA (dsRNA) which leads to gene 'Knock down' or 'silencing' in a sequence-specific manner. For some time the use of RNAi as a tool was limited to lower organisms because delivering long dsRNA for RNAi was nonspecifically inhibitory in mammalian cells. In depth studies demonstrated that the actual molecules that led to RNAi were short dsRNA oligonucleotides processed internally by an enzyme called "Dicer". Such Dicer cleavage products are now defined as the "short interfering RNA, siRNA". Recently in 2001 and with more engaged researches it was demonstrated that siRNA could directly trigger RNAi in mammalian cells. In mammalian cells, short pieces of dsRNA, short interfering RNA (siRNA), initiate the specific degradation of a targeted cellular mRNA, during this process the

antisense strand of the siRNA duplex becomes part of a multi-protein complex the RNA-induced silencing complex (RISC). RISC is capable of identifying its' corresponding mRNA and cleaves it at a specific site. This cleaved mRNA is in fact targeted for degradation that ultimately results in the potential loss of protein expression, translational repression and gene silencing. The translational repression and target degradation of mRNAs is highly dependent on the level of complementarity between miRNA strands and the site in the 3′ UTR targets to achieve effective gene knock down [12-15].

Approaching molecular origins of autoimmune diseases is becoming a point of major interest with the evolution of advanced treatment strategies. Epigenetics represent a rich investigational field in the recent era that is increasingly establishing its' importance in cancers and autoimmune diseases and can effectively widen the spectrum for targeted therapeutic strategies in the field of autoimmune disorders.

Are we done yet? In fact such achievements in the field of epigenetics represent a striking advent. However, we still believe that the influence of each of the above mentioned alterations on a specific set of genes and their actual contribution to the development of a specific subset of autoimmune diseases needs a lot of effort. Rheumatologists need to define the exact role of each of these modifications in each disease category separately and to what extent they might influence the clinical presentations and response to therapy.

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