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# Mini Review From the Molecular Base to the Diagnostic Value of Adenosine Deaminase

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Adenosine deaminase (ADA) or adenosine aminohydrolase (EC 3.5.4.4) is an important enzyme in purine metabolism. It is involved in the breakdown of dietary adenosine as well as those produced from the turnover of nucleic acids in tissues. Although several enzymes including 5′-nucleotidase, ADA and adenosine kinase are involved in the metabolism of adenosine (1), its concentration is mainly regulated by the hydrolytic activity of ADA, which converts adenosine and deoxyadenosine nucleosides in an irreversible manner into inosine and deoxyinosine, respectively (2). This ubiquitous enzyme has been found in a wide variety of microorganisms, bacteria, plants, invertebrates and vertebrates with a highly conserved amino acid sequence (3). In addition, it is present in all mammalian cells and its primary function in humans is development, differentiation, and maturation of the lymphoid system (4). ADA association has also been observed with epithelial cell differentiation, neurotransmission, and gestation maintenance. However, the full physiological role of ADA is not yet completely understood. The ADA gene is located on the long arm of chromosome 20 at the position of 20q13.12, consisting of 12 exons and 11 introns distributed over 32 kb of the genomic DNA. The sequence of the human ADA promoter region is extremely G/C-rich (82%) and reveals no classical TATA box characteristic for eukaryotic promoters (5). The exons range from 62 to 325 base pairs (bp), while the introns are 76-15166 bp (6). The ADA gene encodes a 1.5-kb mRNA, leading to production of a 363-amino acid protein (7). ADA exists in both small monomer- and large dimmer-complex forms (3). Based on the information from the Protein Data Bank (http://www.pdb.org), the enzyme in the monomer form is a polypeptide chain, folded into eight central β barrels and eight peripheral α helices, which surround the active site. ADA also contains three additional helices located between the β1 and α1 folds and two helices located across the amino-terminal of the β-barrel (7). The ADA active site contains a zinc ion as a necessary cofactor for the enzyme activity. Human ADA in the small form is a catalytically active protein with a relative molecular mass (Mr) of 36-38 kDa, whereas the large form (Mr = 298 kDa) is a complex of the small form and a nonenzymatic binding protein. ADA binding protein may function to regulate the clearance of ADA from serum and may further anchor the enzyme to the external surface of the cell membrane where it can regulate plasma adenosine concentrations and/or purine nucleoside transportation (7).

Two major isoforms of ADA are isolated with different characteristics. ADA1 exists in all human tissues and accounts for the main ADA activity in most of the tissues. ADA1 is present in cytosol as well as on cell membrane in the ecto- form, attached to dipeptidyl peptidase 4 (8). ADA1 is involved mostly in intracellular activity and exists both in small monomer and large dimmer forms (3). ADA2 on the other hand is the main ADA isoenzyme in serum, originated mainly from the monocyte-macrophage system and exists solely as a homodimer (9). In addition to ADA that regulates the ratio of free adenosine to deoxyadenosine, there are at least two other ADA enzymes which act on adenosine in RNA strands. ADAR is a double-stranded RNA-specific ADA which is responsible for RNA editing by site-specific deamination of adenosines. This enzyme destabilizes double-stranded RNA through conversion of adenosine to inosine (10). Likewise, ADAT is a tRNA-specific ADA, changing tRNA to allow for a wobble base pairing (11). The total plasma ADA can be determined by measurement of the ammonia liberated from adenosine. Ammonia reacts with Berthelot reagent and forms a blue-colored complex, proportional to the amount of enzyme activity. To determine the ADA2 isoenzyme activity, the serum ADA1 activity can be selectively inhibited by the addition of erythro-9-(2-

hydroxy-3-nonyl) adenine (EHNA) into serum samples (12). Alteration in the serum ADA activity has been reported in a wide array of diseases such as schizophrenia (13), HIV infection (14), HIV-HBV co-infection (15), chronic obstructive pulmonary disease (16), chronic heart failure (17), tuberculosis (18), autism (19), and rheumatoid arthritis (20). Some mutations in the ADA gene cause ADA deficiency, as observed in severe combined immunodeficiency (21). Conversely, mutations causing overexpression of ADA enzyme have also been reported in hemolytic anemia (22). Over 894 single nucleotide polymorphisms on the ADA gene (http://www.genecards.org/) have been identified. However, the most common functional polymorphism of the ADA gene has been reported as G22A polymorphism (rs73598374). Transition of G to A on nucleotide 22 of exon 1 leads to the substitution of asparagine for aspartic acid at the 80th codon of the gene (23). This functional polymorphism leads to a 30% reduction in ADA enzyme activity and may cause an increase in tissue concentrations of adenosine as a physiologic substrate for ADA. Adenosine is a signaling molecule that promotes processes such as angiogenesis, matrix production and regulation of inflammation. Engagement of adenosine to its cell surface receptors leads to changes in intracellular cAMP and $Ca^{2+}$ levels (24). Under physiologic conditions, concentrations of adenosine in extracellular fluid vary from 40-600 nM and downstream effects of ADA signaling include regulation of a variety of homeostatic and adaptive functions (25). However, under some pathologic conditions adenosine levels are elevated, since ADA activity varies in many diseases, particularly in those associated with the immune system such as rheumatoid arthritis (20), cancers (26), diabetes (27), fertility (28), coronary artery disease (29), autism (19), and obesity (30). In conclusion, recent investigations suggest that ADA could play a role in initiation or progression of some diseases. Its G22A polymorphism is also a candidate polymorphism associated with pathologic complications present in different diseases.

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