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One gene, two proteins: alternative splicing in human CD157/Bst1 unmasked

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Until now, CD157 (alias Bst1) has lived a double life: one as a receptor, expressed in human neutrophils and monocytes, that regulates leukocyte diapedesis through interactions with the extracellular matrix, and one as an ectoenzyme of the ADP-ribosyl cyclase family of NAD-cleaving enzymes that generates nucleotide derivatives that somehow trigger endocellular Ca2+ mobilization. For decades, we have known but one form of human CD157: a 318 amino acid protein generated from one transcript (BST1-001) encoded by the 9-exon BST1 gene on chromosome 4(p15). However, RT-PCR experiments revealed the existance of a second BST1 transcript. Database mining, molecular cloning and sequence analysis of this transcript, designated BST1-002, revealed that it contained a previously undescribed exon. Located between canonical exons 1 and 2, this exon was named exon 1b. Exclusion of exon 1b by alternative splicing yields canonical CD157, whereas inclusion of the exon 1b-encoded sequence in frame yields CD157-002, a novel proteoform of 333 amino acids. Neutrophils express both canonical and CD157-002 proteins, although the canonical transcript is the dominant form. Both forms are also co-expressed in other tissues. By comparative functional assays, the proteoforms show overlapping properties in mAb (anti-CD157 SY/11B5) binding, subcellular localization and migration. However, NAD glycohydrolase activity was found in canonical CD157 alone, CD157-002 appearing to be catalytically inert in our experimental conditions. As the 10-exon organization of human BST1 is a departure from the 9-exon organization found in other mammals, we performed phylogenetic analyses to trace the origins of the novel exon, identifying the exon 1b sequence as dynamically evolving and conserved in BST1 in primate evolution. We believe that it is important to bear in mind its quadruple life forms when dealing with human CD157 in basic molecular and biomedical studies.