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Characterization of NY-ESO-1 and SSX gene families

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Abstract

Among tumor antigens identified to date, cancer/testis (CT) antigens are recognized as a group of highly attractive targets for cancer vaccines. CT antigens have highly restricted expression in normal tissues, predominantly in testis, and yet they are found to be expressed in a significant proportion of various human cancers. More than a dozen CT antigen genes or gene families have been defined, including the NY-ESO-1 family and the SSX family.

NY-ESO-1 was initially discovered by autologous SEREX screening of an esophageal cancer cDNA library. It belongs to a gene family that has three distinct members, NY-ESO-1 (ESO1), LAGE-1 (ESO2), and ESO3. All three genes are within a 200 kb stretch on chromosome Xq28, and two exact copies of the ESO1 gene are present in tandem, but in reverse orientation. All three genes are consisted of three exons, and the exon-intron organization is conserved. NY-ESO-1 and LAGE-1 are highly homologous (84% amino acid, 94% nucleotide homology), whereas ESO3 is more distant, <50% identity to the other two genes. Another major difference is in the expression of these genes: NY-ESO-1 and LAGE-1 are CT antigens, whereas ESO3 is ubiquitously expressed in somatic tissues.

Both NY-ESO-1 and LAGE-1 have been shown to generate more than one protein product. For NY-ESO-1, the primary open reading frame encodes a 180 amino acid product, and a second ORF encodes a 58 amino acid polypeptide. For LAGE-1, in addition to the 180 amino acid product, two proteins have been shown, one derived from a second ORF, and the other from the first ORF, but from an alternative spliced transcript. Significantly, all variant protein products derived from NY-ESO-1 and LAGE-1 have been shown to contain peptide epitopes recognized by CD8+ T cells from cancer patients in an HLA-restricted fashion. In comparison, antibody responses have only been demonstrated against the 180-residue NY-ESO-1 and LAGE-1, but not the variant products.

In addition to NY-ESO-1, another CT antigen that has been shown to elicit spontaneous humoral and cell-mediated immune responses in cancer patients is SSX. The SSX gene family is also located on the X chromosome, Xp11. We have now characterized 9 structurally complete genes in this family, SSX1-SSX9, and exact duplicates of the SSX2 gene also exist. All SSX genes are highly homologous at both nucleotide and DNA levels. Although none of the genes shows ubiquitous expression, the expression profile of different SSX genes do differ significantly. Among normal adult tissues tested, testis expresses SSX1, 2, 3, 4, 5, and 7, but not SSX6, 8, and 9. In tumor tissues, SSX1, 2, and 4 are most frequently expressed (approx. 20-30% range); in contrast, SSX3, 5, 6, and 7 are rarely expressed (<1%), and SSX 8 and SSX9 expression have not been detected.