Ad-ISF35

National Cancer Institute

Source

National Cancer Institute. Ad-ISF35. NCI Thesaurus. Code C127154.

A replication-defective adenovirus vector (Ad-ISF35), which encodes a membrane-stabilized, chimeric human-mouse CD40 binding protein (CD40 ligand; CD40L; CD154), with potential immunomodulatory and antineoplastic activities. Upon intratumoral administration, Ad-ISF135 preferentially transduces tumor cells and immunoregulatory cells in the tumor microenvironment. This increases the expression of CD154 in tumor cells, activates CD40 and stimulates signaling and immunoactivation, which are both mediated by CD40. This increases the expression of co-stimulatory molecules on these cells, which enhances their ability to function as antigen presenting cells (APCs) and increases their apoptotic potential. This leads to an increase in the infiltration of macrophages and neutrophils, which promote direct cytotoxicity, enhances the production of pro-inflammatory cytokines in the tumor microenvironment, and induces a specific cytotoxic T-lymphocyte (CTL) response against the tumor cells. In addition, transduction with Ad-ISF35 induces direct tumor cell death, probably through an anti-viral immune response. Ad-ISF35 also exerts a strong bystander effect in non-transduced cells thereby further inducing tumor cell death. Altogether, this will eradicate tumor cells. CD154, the main ligand for CD40, plays a key role in the activation of APCs, promotes immunoactivation, and increases apoptotic potential. The protein encoded by Ad-ISF35 does not contain the mouse antibody binding domains and does not induce human neutralizing antibodies. The metalloprotease cleavage site is deleted in this chimeric CD154 and thus it resists cleavage; the encoded protein also contains amino acid substitutions within the carboxy-terminal. Both sets of engineered mutations promote cell surface expression.