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Review

TAM receptor tyrosine kinases: Expression, disease and oncogenesis in the central nervous system

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ABSTRACT

Receptor tyrosine kinases (RTKs) are cell surface proteins that tightly regulate a variety of downstream intra-cellular processes; ligand-receptor interactions result in cascades of signaling events leading to growth, proliferation, differentiation and migration. There are 58 described RTKs, which are further categorized into 20 different RTK families. When dysregulated or overexpressed, these RTKs are implicated in disordered growth, development, and oncogenesis. The TAM family of RTKs, consisting of Tyro3, Axl, and MerTK, is prominently expressed during the development and function of the central nervous system (CNS). Aberrant expression and dysregulated activation of TAM family members has been demonstrated in a variety of CNS-related disorders and diseases, including the most common but least treatable brain cancer in children and adults: glioblastoma multiforme.

Contents

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1. Isolation and nomenclature of Tyro3, Axl, and MerTK

The prototypic TAM family member Axl was originally described as an unknown transforming gene present in the DNA of two patients with chronic myelogenous leukemia (Liu et al., 1988; O'Bryan et al., 1991). The authors subsequently cloned and characterized a receptor tyrosine kinase and named it Axl, from the Greek work anexelekto, or "uncontrolled" (O'Bryan et al., 1991). The DNA sequence predicted a protein of 894 amino acids and revealed for the first time the hallmark features of all TAM family members: an extracellular domain consisting of two fibronectin type III (FNIII) repeats and two immunoglobulin-like (Ig-like) repeats. These features immediately distinguished Axl from previously described protein tyrosine kinases. O'Bryan et al. prepared polyclonal anti-Axl antiserum and were able to detect 140- and 120-kDa proteins in Axl-transformed mammalian (3T3) cell lines, corresponding to fully and partially processed/glycosylated forms of the protein (O'Bryan et al., 1991).

Meanwhile, another group was exploring receptor tyrosine kinase genes in developing nervous system of the rat (Lai and Lemke, 1991). In 1991, Lai et al. published a report identifying partial sequences from 13 novel protein tyrosine kinase genes, three of which more closely resembled each other than any previously described kinase. The proteins encoded by the genes, originally designated Tyro3, Tyro-7, and Tyro-12, later came to be known as Tyro3, Axl and MerTK respectively, and comprise the TAM family of RTKs (Lai and Lemke, 1991). Interestingly, all were detected in the rat embryonic brain and, albeit with more restricted distribution, in the adult rat brain.

The same year, two additional groups independently isolated Axl. Rescigno et al. cloned a murine protein tyrosine kinase based on homology to the Bek FGF receptor and recognized two Ig-like domains and two FNIII domains; their find was dubbed Ark (adhesion-related kinase) (Rescigno and Mansukhani, 1991). Janssen et al. (1991) detected transforming activity derived from a patient with chronic myeloproliferative disorder and isolated the corresponding oncogene and named it UFO.

Soon after the description of Axl, Lai et al. published the isolation of Tyro3 in the mouse, and predicted, based on sequence analysis, the two Ig-like domains and two FNIII repeats in the extracellular region that later became recognized as hallmarks of this family (Lai et al., 1994). Tyro3 was independently described by a variety of labs and has been identified as Brt, recovered from fetal mouse brain (Fujimoto and Yamamoto, 1994); Sky, cloned from a human hepatoma cDNA library (Ohashi et al., 1994); Rse, from human and mouse brain (Mark et al., 1994); Etk2, from mice (Biesecker et al., 1993); and Dtk, from mice (Lewis et al., 1996).

Graham et al. isolated the last novel TAM family member in 1994 from a screen of a human B-lymphoblastoid expression library with anti-phosphotyrosine antibodies and designated it c-Mer, for its expression in *m*acrophages and tissues of *e*pithelial and reproductive origin (in the original report mononuclear cells were isolated from human peripheral blood based on their ability to adhere to plastic and found to express c-Mer; these cells are now defined to be macrophages) (Graham et al., 1994, 1995). c-Mer contained the now-characteristic two Ig and two FNIII coding regions in the extracellular portion of the protein. Sequence analysis suggested that c-Mer was the putative proto-oncogene corresponding to an oncogenic avian retrovirus (*v-eyk/v-ryk*) published in 1992 (Graham et al., 1995; Jia et al., 1992; Jia and Hanafusa, 1994) and associated with UFO/Axl/Ark by virtue of its structure (Jia and Hanafusa, 1994). Initial characterization demonstrated that c-Mer protein was found in prostate, testis, ovary, placenta, lung, liver, and kidney, but not in normal human brain (Graham et al., 1994). MerTK, as it came to be known (Weier et al., 1999), was also independently isolated from a cDNA clone derived from a human glioblastoma expression library and labeled Nyk (Ling and Kung, 1995b).

2. TAM protein structure, ligands, and tissue expression

2.1. *Structure*

The TAM family of RTKs has been amply reviewed (Binder and Kilpatrick, 2009; Lemke and Rothlin, 2008; Linger et al., 2008; Verma et al., 2011). As typical receptor tyrosine kinases, Tyro3, Axl, and MerTK contain an extracellular domain, a transmembrane domain, and a conserved intracellular kinase domain. Three features distinguish TAMs from other RTKs: a conserved KW(I/L)A(I/L)ES sequence (in the kinase domain); two Ig domains (near the N-terminal of the extracellular domain); and two FNIII domains (between the N-terminal of the extracellular domain and the trans-membrane region). The TAM extracellular domain is recognizable by antibodies on non-permeabilized cells in assays such as flow cytometry, indicative of cell surface expression; accordingly, Ig and FNIII domains are thought to be important in cell-to-cell contacts and adhesion to extracellular matrix. Both Ig domains are required for Gas6 binding to Axl in vitro and may facilitate other TAM receptor/ligand interactions (Sasaki et al., 2006). Recent studies have revealed that full-length TAMs contain putative nuclear localization and export signals and MerTK can be also found within the nucleus (Migdall-Wilson et al., 2012).

The observed molecular weights of Axl, Tyro3 and MerTK vary with tissue and cell type and may be considerably larger than their predicted weights due to posttranslational modifications including glycosylation, phosphorylation, and