The 548th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H22.10.6)

α-Synuclein in Parkinson's disease: pathogenetic culprit and therapeutic target

Maral Mouradian
(Professor, Department of Neurology,
UMDNJ-Robert Wood Johnson Medical School)

α-Synuclein (α-Syn) is a key protein in the pathogenesis of Parkinson's disease and other α-synucleinopathies including dementia with Lewy bodies and multiple system atrophy. This natively unfolded protein has the tendency to aggregate into oligomeric and eventually fibrillar forms under various conditions. Accumulating evidence suggests that the process of aggregation and particularly the early soluble oligomers are toxic to neurons. Among the factors that promote α-Syn aggregation that our laboratory has focused upon is its concentration. Human genetic studies have shown that individuals with multiplication of the α-Syn gene locus develop dominantly inherited Parkinson's disease with a symptom onset age that reflects a gene dosage effect. Additionally, over-expressing α-Syn in various animal models recapitulates many of the phenotypic features of the disease including protein aggregation and neuronal dysfunction. Thus, understanding the factors that regulate α-Syn expression in the human brain is critical in our efforts to keep the amount of this protein under control. To this end, we have found that α-Syn is down-regulated by a specific microRNA. miR-7, which is expressed by neurons, binds to the 3'-untranslated region of α-Syn mRNA and degrades it resulting in less protein production. Importantly, this is associated with protection of neuronal cells against the toxicity of α-Syn and oxidative stress. Another factor that promotes α-Syn aggregation is its cross-linking by transglutaminase 2. This enzyme interacts with α-Syn and results in its polymerization into high molecular weight aggregates *in vitro* and in cultured cells. We have found that this process leads to increased toxicity of α-Syn in yeast cells. We are beginning to test pharmacological inhibitors of this enzyme to block this process. And the third factor that enhances α-Syn aggregation is its phosphorylation. Postmortem human brain studies have shown that α-Syn is heavily phosphorylated at serine 129 in synucleinopathy lesions. Several kinases are known to carry out this post-translational modification making inhibition of a single kinase unlikely to be effective. In contrast, we have found that a single phosphatase variant appears to be the primary α-Syn phosphatase. We have also identified a small molecule (SIG1012) that promotes the activity of this phosphatase both *in vitro* and in mice. Treatment of α-Syn transgenic mice with this compound for 9 months was able to prevent many of the pathological features associated with α-Syn toxicity. The above findings highlight the complexity of the mechanisms by which α-Syn exerts its toxicity, but they also identify opportunities for therapeutic interventions.

The 556th Kitasato Medical Society Invitational Academic Lecture Series Abstract

(H23.2.9)

Angiogenesis inhibitors in cancer: lessons and surprises

Donald M. McDonald
(Professor, Department of Anatomy,
University of California, San Francisco)

Inhibitors that target vascular endothelial growth factor (VEGF) in tumors stop sprouting angiogenesis, prune VEGF-dependent tumor vessels, and transform tumor vessels that survive are more normal. These changes in the vasculature have complex effects on tumor cells. Pruning of tumor vessels can have multiple downstream effects including increased intratumoral hypoxia, which in turn can activate pathways that promote invasiveness and metastasis. The mechanisms underlying evasive resistance after inhibition of VEGE are not fully understood, but hypoxia-induced activation of HIF-1 α and pro-invasive pathways involving hepatocyte growth factor (HGF) and its receptor c-Met are likely factors. Tumors in RIP-Tag2 transgenic mice treated with function-blocking anti-VEGF antibody or the multi-targeted receptor tyrosine kinase (RTK) inhibitor sunitinib, which inhibits VEGF receptors but not c-Met, are smaller but more invasive and metastatic. The change in tumor phenotype is accompanied by increased expression of HIF-1 α and c-Met and evidence of epithelial-mesenchymal transition (EMT) in tumor ells. Increased invasiveness and metastasis associated with anti-VEGF therapy can be reduced by concurrent inhibition of c-Met. Similarly, treatment with RTK inhibitors that blocks both VEGFR and c-Met can reduce invasiveness and reduces metastases. Together, our findings indicate that evasive resistance that follows inhibition of VEGF signaling is accompanied by greater intratumoral hypoxia, activation of HIF-1 α, c-Met, and EMT, and can be reduced or blocked through the synergistic effects of inhibiting c-Met and VGEF signaling together. Inhibition of these two signaling pathways also causes a profound suppression of angiogenesis in tumors.