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mTOR/p70S6K in Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

To the Editor:

We read with interest the review article by Nassar and coworkers (1) on diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). As correctly reported by the authors, this uncommon, possibly underrated, and often indolent disease may lead to severe respiratory obstructive symptoms and finally to death. In symptomatic patients, therapeutic options are limited to steroids, surgical lung resections, and lung transplantation.

Whatever the pathogenesis underlying the occurrence of DIPNECH, respiratory functions were deteriorated by a diffuse constrictive bronchiolitis secondary to fibrogenic peptides produced by the proliferating neuroendocrine cells (2, 3).

Pulmonary and extrapulmonary neuroendocrine cell proliferations are characterized by a consistent expression of somatostatin receptors (SSR) (mainly types 2 and 5) and of mammalian target of rapamycin (mTOR) (4). These findings represent a solid scientific rationale in explaining the good clinical results recently reported with selective somatostatin analogs and mTOR inhibitors in neuroendocrine tumors (5). Little is known about the expression of SSR and mTOR in DIPNECH. Gorshtein and colleagues (6) recently highlighted the important role of SSR in DIPNECH showing a high uptake in all 11 cases tested by ^{111}In-pentetreotide scintigraphy (Octreoscan) or gallium-68 (^{68}Ga) 1,4,7,10-tetra-azacyclododecane-*N*,*N*′,*N*′′,*N*′′′-tetraacetic acid-Tyr3-octreotide/Na3-octreotide ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*,*N*′-tetraacetic acid positron emission/computed tomography imaging. In addition, six patients with progressive respiratory symptoms treated with somatostatin analogs experienced disease stabilization with consistent improvement of respiratory functions in four cases.

To our knowledge, there are no data about mTOR-related molecule expression in DIPNECH. By immunohistochemistry, we tested phosphorylated-mTOR (p-mTOR) and its major target, namely the ribosomal p70S6-kinase (p70S6K), in four cases of DIPNECH collected from our archival files. All these cases were characterized by the presence of a typical carcinoid and foci of neuroendocrine hyperplasia as well as tumorlets. On immunohistochemistry, a robust and diffuse expression of p-mTOR and p70S6K was observed in all neuroendocrine lesions. Thus, the activation of mTOR pathway in DIPNECH seems to be entirely similar to what has been observed in sporadic carcinoid tumors (4).

Although preliminary, these results seem to support a scientific rationale in adopting mTOR inhibitors in DIPNECH and then to widen the spectrum of therapeutic tools in this intriguing disease.

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From the Authors:

We appreciate the interest and comments by Dr. Rossi and colleagues regarding our article (1). As with many diseases, awareness and recognition encourage progress in treatment. Recent publications and discussions within the past year have brought to the forefront treatment strategies in extrapulmonary neuroendocrine tumors that may be relevant to pulmonary proliferations expressing somatostatin receptors (SSR) (2, 3). Although little is known about the expression of SSR and mammalian target of rapamycin (mTOR) in DIPNECH, the information highlighted by Gorshtein, Righi, and colleagues (4, 5) complements our clinical paper and illustrates the need to better understand the important role of somatostatin analogs (SSA) and their potential for treatment in DIPNECH. Neuroendocrine cell proliferation with somatostatin receptor expression is the fundamental pathologic response to probable injury, so it makes teleological sense that SSA may be beneficial in the therapeutic paradigm.

The discussion of immunohistochemistry evidence, including the activation of the mTOR pathway in DIPNECH, is an

excellent example of the progress that can be made with recognition and international collaboration on this disease. These leads may result in successful treatment strategies utilizing mTOR inhibitors in DIPNECH.

Another point of importance is the role of octreotide analog radio-labeled nuclear scintigraphy with positron emission/computed tomography imaging (6) in perhaps guiding treatment where the density of SSR in DIPNECH patients may predict therapeutic success with SSA.

As with most uncommon and often unrecognized diseases, collaboration may be the only way to obtain the volume of patients required to properly strategize and assess treatments. True progress and treatment algorithms would be best served with the establishment of an international registry for patients, a tissue repository, and the synergy of knowledge and experience between institutions.

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Camphor, an Old Cough Remedy with a New Mechanism

To the Editor:

In an interesting correspondence, Patberg and colleagues (1) have commented on a recent proposal by Birring (2) on unexplained chronic cough (UCC). The hypothesis regards the role of the transient receptor potential vanilloid (TRPV)1 channel as a common final pathway underlying the heightened cough sensitivity of individuals with UCC. The presence of TRPV1 in vagal afferents, the successful use of the selective TRPV1 stimulant, capsaicin, as a protussive agent in experimental animals and humans, and the lower threshold to capsaicin-induced cough in patients with UCC have suggested (and Dr. Birring has reconsidered this hypothesis) a central role for TRPV1 hyperexpression and hyperfunction in chronic cough. Patberg and coworkers (1) further supported this hypothesis with the observation that an old cough remedy, camphorated oil, contains camphor, which initially stimulates but then strongly desensitizes TRPV1. Clinical evidence for the antitussive action of camphor has been also reported in their comment (1). We agree with the proposed hypothesis and with the implied therapeutic perspectives for TRPV1 desensitizers/antagonists. However, camphor can no longer be regarded as a selective agent for TRPV1. Rather, camphor has been identified as a TRPA1 ("A" stands for ankyrin) channel antagonist. TRPA1 is coexpressed with TRPV1 in nociceptive neurons, including vagal afferents; various TRPA1 agonists, including cinnamaldehyde and acrolein, cause cough by TRPA1 stimulation in guinea pigs (3) and humans (4); and camphor reduces TRPA1-mediated cough (3). Also, menthol (mentioned in the comment by Patberg and colleagues) (1), an agonist of the cold receptor TRPM8 (and via this mechanism responsible for the fresh sensation associated with mint), and traditionally used as a cough remedy, has been found to inhibit TRPA1 (5). Thus, while we recognize the possible role of TRPV1 in the mechanism of UCC, we recommend that the emerging role of TRPA1 not be disregarded. This is of particular relevance when considering the peculiar chemical features of TRPA1, which are responsible for the unique ability of this channel to sense a series of irritant and reactive endogenous (associated with inflammation and tissue injury) and exogenous (associated with environmental pollution) molecules, derived from oxidative and nitrative stress (6). Following the advice of the children's song "John Brown's baby had a cough," the future challenge in drug discovery for the treatment of chronic cough would be better suited by a compound that more efficiently and safely combines the blocking property of camphor at both TRPV1 and TRPA1.

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