Immunotherapy and Potential Molecular Targets for the Treatment of Pituitary Adenomas Resistant to Standard Therapy: A critical review of potential therapeutic targets and current developments

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BACKGROUND
Pituitary adenomas (PA) are primary CNS tumors, accounting for as much as 25% of intracranial neoplasms. Although existing remedies, including pharmaceutical, surgical, and radiologic interventions, show success in treating most PA, treatment of invasive PA (IPA) and non-functional PA (NFPA), in addition to functional PA refractory to standard therapy, remains challenging. Approximately one-third of patients with GH-secreting PA are resistant to somatostatin analogues, with many prolactinomas demonstrating similar resistance patterns. Additionally, 35% of patients who undergo surgical resection of PA exhibit subsequent gross invasion. More effective therapeutic strategies for IPA and NFPA are essential for amelioration of these pathologies. With the continually increasing understanding of biochemical pathways involved in tumorigenesis, immunotherapy and targeted therapies stand as promising alternatives for pituitary tumors that are resistant to standard therapy.

METHODS
A literature search of the PubMed database was conducted for immune and targeted therapies of PA. Keywords included: “immunotherapy”, “immunohistochemistry”, “immunotherapy” together with “pituitary adenomas” and “pituitary tumors”. Utilizing PRISMA guidelines, the search yielded a total of 2,621 articles, 26 of which were included in our discussion, which is demonstrated in Figure 1.

RESULTS
Clinically relevant immunotherapies and potentially targeted therapies for the amelioration of NFPA, IPA, and refractory FPA are documented in Table 1, which demonstrates the physiologic and pathologic role of each identified molecule in addition to the type and outcome of therapy. An overview of each of the 28 articles reviewed is documented in Table 2.

DISCUSSION
Several pathologically expressed molecules identified in this review could serve as promising current or future targets for a subset of PA which have shown to be classically challenging to manage. Programmed death ligand-1 (PD-1/PD-L1) is a well-known target for immunotherapies and recent studies demonstrate that upregulation of PD-L1 in pituitary neoplasms makes inhibition of this interaction a promising approach for therapy. Cancer-testis antigen MAGE-A3 has been targeted via a cancer vaccine in studies of NSCLC and melanoma; a similar vaccination could potentially be utilized in PAs to promote immune responses against MAGE-A3-positive tumors. Mitochondrial metalloproteinases (MMPs), EpCAM (Tropl) and Trop2, epidermal growth factor receptor (EGFR), and folate receptor alpha (FRa) have all been implicated as crucial factors involved with tumor invasion. Similarly, vascular endothelial growth factor (VEGF) and galectin-3 (Gal-3) have been identified as essential modulators of angiogenesis and invasion in PAs. Inhibition of these pathways, through interference of surface receptor signaling or by disruption of intracellular molecular pathways via targeted therapy, may prove efficacious in the management of invasive and treatment-resistant PAs.