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Targeting a heterogeneous tumor: the promise of the interleukin-13 receptor alpha2

I. Bodhinayake

M. Ottenhausen

J. A. Boockvar

Hofstra Northwell School of Medicine

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Targeting a Heterogeneous Tumor: The Promise of the Interleukin-13 Receptor α2

Molecular and histological heterogeneity presents a major challenge in the effective treatment of glioblastoma (GBM). Despite this tumor heterogeneity, there is a promise of a therapeutic target in an antigen that is selectively expressed in glioma compared with normal brain tissue, the interleukin-13 (IL-13) receptor α2 (IL-13Rα2). This receptor has been shown to bind with high affinity to IL-13 and to downregulate the expression of its usual receptor, the IL-13Rα1/IL-4Rα complex, to mediate transforming growth factor β production in tumor infiltrating monocytes and macrophages, and to promote tumor infiltration and proliferation. Notably, IL-13Rα2 expression has also been identified in stem-like malignant glioma cells. These selective expression patterns in glioma compel further investigation into therapeutic potential.

Further recognition of the exploitability of IL-13Rα2 as a therapeutic target comes through the work of Brown and colleagues.[1] They used a bioinformatics approach to characterize IL-13Rα2 expression across 8 large, publicly available gene expression profile data sets. Principal component analysis was used to determine the correlation between IL-13Rα2 expression and genes defining the molecular subtypes of GBM presented by Phillips et al[2] and Verhaak et al.[3] Cell surface markers of these molecular subtypes of glioma on IL-13Rα2–expressing vs –nonexpressing low-passage primary glioma cell lines were determined by flow cytometry, and gene expression profiles were established. The functional consequences of the resulting gene expression correlations were probed through ingenuity pathway analysis. Finally, they determined the survival significance of these expression profiles.

The authors found a significantly higher level of IL-13Rα2 expression in high-grade glioma compared with low-grade glioma ($P = 2.4 \times 10^{-4}$), with World Health Organization grade IV gliomas having a 2.5-fold increase in IL-13Rα2 expression level compared with grade III gliomas ($P = 2.9 \times 10^{-8}$). This strong association with glioma grade was independent of molecular subtype or recurrence. By modeling the bimodal expression of IL-13Rα2 seen in GBM as the sum of 2 normal distributions, the authors estimated a 58% IL-13Rα2 overexpression frequency in GBM. Importantly, principal component analysis revealed that IL-13Rα2 expression was closely associated with mesenchymal gene expression according to the subtypes defined by both Phillips et al[2] and Verhaak et al[3] that were independently defined in these 2 studies by patient survival and unsupervised clustering, respectively. Additionally, IL-13Rα2 expression correlates well with the expression profile for the proliferative subtype defined by Phillips et al.[2] Its expression is inconsistently correlated with the neural and classic subtypes defined by Verhaak et al.[3] These findings corroborate with flow cytometry data from patient-derived IL-13Rα2–positive glioma cell lines showing greater expression of mesenchymal adhesion markers such as CD44 and CD54/intercellular adhesion molecule-1 compared with IL-13Rα2–negative glioma cell lines.

The study further explores the functional and survival implications of IL-13Rα2 overexpression. Ingenuity pathway analysis for high IL-13Rα2 expression suggests the functional involvement of canonical pathways associated with mesenchymal genes and with immune-related pathways. Not surprisingly, mesenchymal gene signatures showed significant overlap with immune pathways. The survival analyses of GBM patients expressing high vs low levels of IL-13Rα2 showed decreased patient survival of 2.5 months with IL-13Rα2 overexpression ($P = .00012$; Figure). Median survival for patients with high IL-13Rα2 expression was 13.1 months compared with 15.6 months (95% confidence interval, 13.6-18.6; n = 357) for patients with low IL-13Rα2 expression, demonstrating the role of IL-13Rα2 as a prognostic marker of poor patient survival.

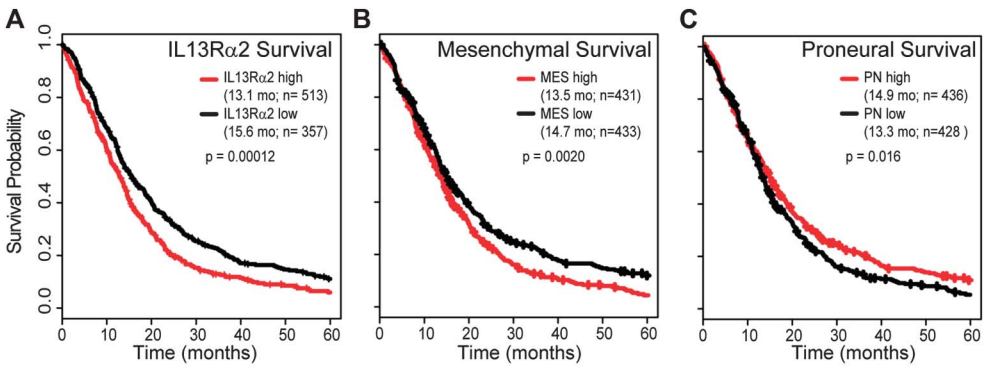

Figure. Overexpression of interleukin-13 receptor α2 (IL-13Rα2) is associated with decreased patient survival. **A**, *Kaplan-Meier survival plot for patients with glioblastoma segregated based on "high" vs "low" IL13Rα2 expression as determined with nonlinear least-squares regression (Table 1 in File S1 in the article by Brown and colleagues[1]). Kaplan-Meier plots for the same patient cohort evaluated in* **A** *are segregated on the basis of (***B***) mesenchymal (MES) signature gene expression or (***C***) proneural (PN) signature gene expression, with "high" and "low" expression determined by median expression level.*

These findings add molecular associations, functional implications, and prognostic value to the known selective expression of IL-13Rα2 in GBM tissue. The presence of this antigen on GBM tissue serves as an important target for both immune- and cytotoxic-based therapies. Immune system activation has been implicated in the resistance-promoting, epithelial-to-mesenchymal transition. The high degree of correlation between IL-13Rα2 and signature mesenchymal genes may be used to target the most resistant tumors. The predominant expression of this receptor in GBM and its association with poor patient prognosis present a promising opportunity for exploring the therapeutic potential of downstream signaling pathways and direct antigen targeting.

Imithri Bodhinayake, MD
Malte Ottenhausen, MD
John A. Boockvar, MD
Weill Cornell Medical College
New York, New York

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Let There Be Light and Muscle Contraction: Optogenetic Restoration of Muscle Function

Spinal cord injury is a devastating condition that greatly affects patients, their support system, and the entire healthcare system. The total economic burden to healthcare systems approaches $10 billion annually and stems from

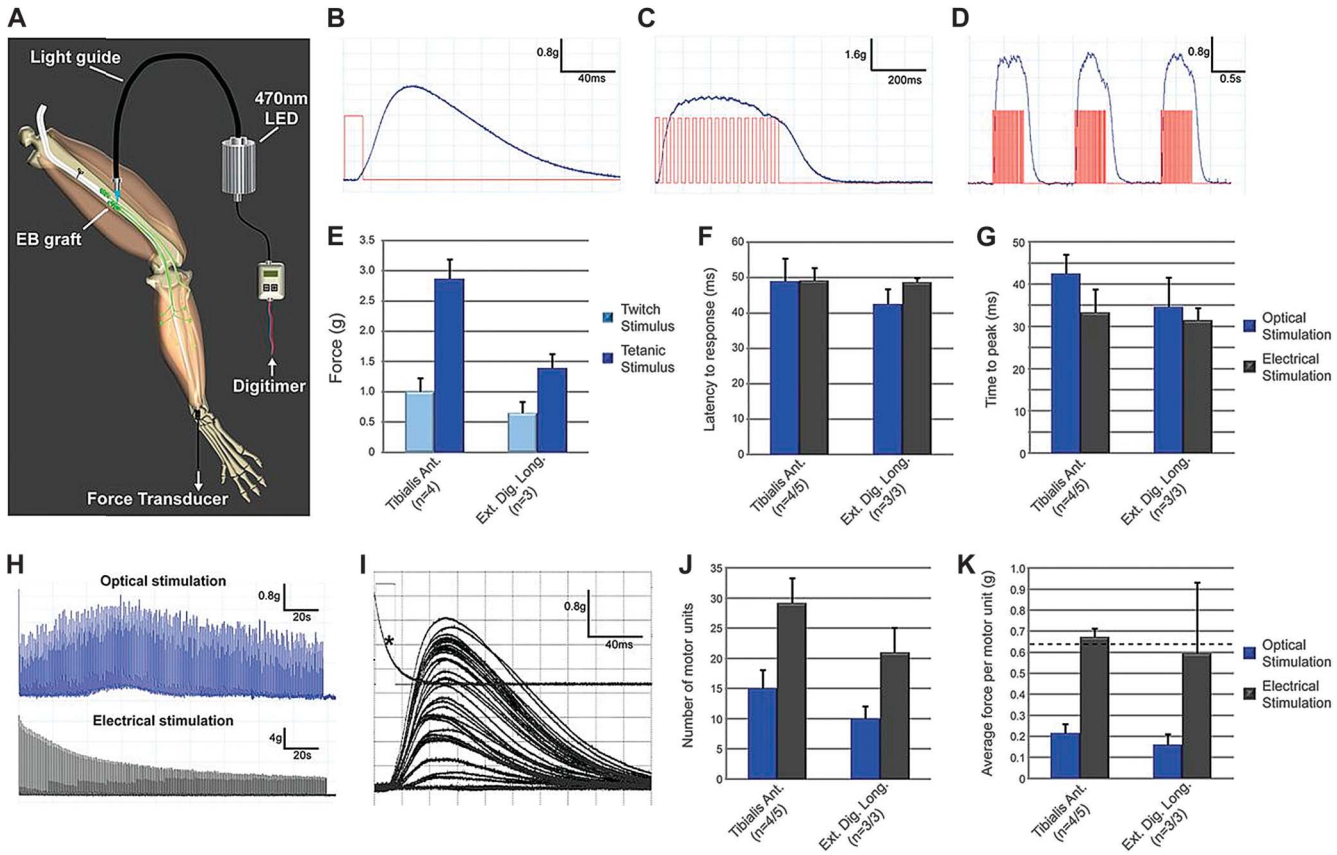

Figure. Restoration of muscle function in a controlled manner through the use of optical stimulation of engrafted channelrhodopsin-2 (ChR2) motor neurons in vivo.[1] **A**, *schematic of optical stimulation and isometric muscle tension recordings setup. Representative twitch (***B***), tetanic (***C***), and repetitive tetanic (***D***) contraction traces obtained from the transversus abdominis muscle, induced by optical stimulation. Blue shows muscle force; red, light-emitting diode (LED) light triggers.* **E**, *quantification of twitch and tetanic contraction of transversus abdominis and extensor digitorum longus muscles. Time to peak contractile force, from initiation of the electrical trigger to the LED unit (***F***) or from the initiation of muscle contraction (***G***), is shown alongside direct electric nerve stimulation.* **H**, *representative fatigue traces from transversus abdominis muscles produced by optical (top) or electrical (bottom) stimulation for 180 seconds.* **I**, *representative transversus abdominis muscle optical stimulation motor-unit number estimate trace. The asterisk indicates square-wave trigger voltage to the LED unit and oscilloscope trigger.* **J**, *motor-unit number quantification of transversus abdominis and extensor digitorum longus muscles after optical versus electrical stimulation.* **K**, *analysis of average motor-unit force. The dashed line indicates the normal extensor digitorum longus value. All error bars indicate SEM. Reprinted with permission from Bryson JB, Machado CB, Crossley M, et al. Optical control of muscle function by transplantation of stem-cell derived motor neurons in mice. Science. 2014;344(6179):94-97.*