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Short Communication Open Access

Chaperones and Glioma Immunotherapy

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Short Communication

Molecular chaperones, also known as heat-shock proteins or HSPs, are a functionally conserved class of proteins whose primary function is to keep cellular proteins in their native conformation, under both physiological and stress conditions. In most cases these chaperones do not participate in the final mature structures that their 'clients' form. Apart from folding, chaperones play vital roles in cellular localization, transport, secretion and assembly of proteins in multiprotein complexes [1-4].

Chaperones have also emerged as an important class of proteins in the context of anti-cancer therapy. Brain cancers, like all other cancers, are highly dependent on chaperones for their elevated protein folding needs. Further, chaperones in tumorigenic cells provide impetus for malignant growth by acting as phenotypic capacitors of mutant proteins allowing accumulation of genetic variations [5].

Currently approved therapy for GBM patients include surgical resection followed by radio and/or chemotherapy. As complete surgical removal of GBM tissue is almost impossible, adjuvant treatments are often administered upon recurrence. However, such adjuvant treatment options are limited and invariably have side-effects such as neurological disorders and cognitive dysfunction [6,7]. Thus there is a strong need for a highly specific and non-toxic adjuvant therapy for GBM patients.

Immunotherapy is amongst the most promising options in an era of personalized medicine because of its appeal to deliver specific, adaptable, antitumor activity with minimal toxicity. Two properties of HSPs make them particularly suitable for eliciting anti-tumour immune response, (1) they bind to misfolded antigenic peptides with high-affinity thus providing a snapshot or fingerprint of a tissue/cell and (2) antigen presenting cells have evolved to see HSPs as danger signals and have unique receptors that make them readily internalizable and induce a strong cytotoxic T cell response [8,9]. Not surprisingly, the concept of HSP-based anti-cancer vaccination has engaged researchers in this area.

In glioma, initial studies on chaperones as therapeutic targets focussed on the differential content of several HSPs (e.g., HSP27, Alpha-B crystallin, Mortalin) in tumour versus normal tissue and attempted to derive their prognostic significance. As tumour cells were shown to be completely reliant on chaperones for their survival, attempts to inhibit chaperones, particularly HSP90, using pharmacologic (e.g., geldanamycin and its derivatives) and non-pharmacologic (e.g., gene therapy, hyperthermia) means were made with encouraging results. Early experiments also demonstrated that purified members of HSP70 and HSP90 family could be used as tumour specific vaccine which can elicit tumour rejection, a property largely dependent on the tumour cells 'peptidome' binding ability of these chaperones. Surprisingly, chaperones themselves were shown to provide a strong pro-inflammatory stimulus spurring activation of macrophages, dendritic cells (DCs) and microglia [10]. Providing further support for this immunotherapeutic promise of chaperones in glioma, three relatively recent articles took advantage of the two unique properties of chaperones, namely (1) antigen-binding and (2) specific interaction with antigen presenting cells, to establish that chaperone-driven induction of tumor-specific immunogenicity has encouraging potential for glioma management.

To explore the immunization potential of HSPs and the subsequent clinical benefit to glioma patients, Crane et al. immunized 12 patients with recurrent GBM with an autologous HSPPC-96 preparation derived from surgically resected non-necrotic tumour mass. HSPPC-96 is a heat shock protein peptide complex consisting of the HSP gp-96 and chaperoned substrates. They observed that 11 out of 12 patients immunologically responded to the vaccination as indicated by; for example, increased IFNγ production by NK cells and cytotoxic T cells (CD3+/CD4+/CD8+) together with diminished regulatory T cells (CD4+/CD25+/FoxP3+) indicating an effective pro-inflammatory response against the tumour. Consequently, the responders had a median survival of 47 weeks compared to 16 weeks for the non-responder [11].

Super paramagnetic iron oxide nanoparticles (SPIONs) are becoming increasingly attractive as Nano vaccines because of their ability to enhance dendritic cell (DC) activation and promote vaccine delivery to immune cells. In a related and interesting study Shevtsov et al. explored a novel approach to induce anti-cancer immune responses against orthotopic C6 glioma model in rats. The authors coated SPIONs with a recombinant heat shock protein 70 (Hsp70) followed by incubation with C6 tumour derived cell lysates to capture antigenic peptides. These antigenic peptide loaded Hsp70-SPION conjugate were then pulsed onto DCs which are professional antigen presenting cells to activate them towards a tumour-specific, CD8+ cytotoxic T cell response. For immunization animals received three subcutaneous injections of the vaccine on days 4, 5 and 6 after injection of C6 tumour cells. Animals which received peptide-HSP70-SPION vaccine had a median survival of about 2-fold higher than the control group (55.2 ± 11.0 days vs 29.0 ± 5.3 days) and marginally higher than peptide-HSP70 group (45.6 ± 10.1 days). Similar to the previous study, the authors observed higher IFNγ secretion in serum and an enhanced infiltration of NK cells and CD8+ T cells in peptide-HSP70-SPION group [12].

Taking a different approach, Bu et al. demonstrated that DCs loaded with exosomes isolated from DCs stimulated by glioma cell (GL261)-derived chaperone-rich cell lysates (CRCLs) exhibited potent

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anti-tumor activity against intracranial mouse glioma by activating cytotoxic T cells with significant survival benefits [13].

Therefore, taking quite different approaches all the above studies report a significant elicitation of anti-tumour immunity and considerable improvement in overall survival. Considerations for devising an effective immunotherapy include selection of relevant antigens and maximizing presentation of these antigens by APCs to mount a strong tumour specific immune reaction. Chaperones not only have broad anti-glioma immunogenic potential in terms of ´antigen-selection` but also have the natural ability to effectively stimulating DCs. These observations significantly advance our appreciation of the potential of chaperones for anti-glioma personalized immunotherapy. However, a major limitation in case of tumour-derived chaperone preparations is that it is time-consuming (about 6-8 weeks) and requires an adequate amount of tumour tissue from patient (usually 1-10 grams) to generate sufficient quantities of vaccine [14]. Thus, a more viable alternative approach may be to use recombinant chaperone and load it with tumour protein extracts. On the flip side, it has been encouraging to see that in patients and mouse models immunized with autologous chaperone vaccines, overall toxicity has been consistently minimal with almost no signs of autoimmunity; providing a strong reason to pursue further explorations.

As is unfortunately true for most anti-cancer therapies at present, each of the above studies is far from an ideal situation where the disease is cured. In the context of immunotherapy the failure has been explained by tumour heterogeneity, immune editing and antigen-loss where the surviving tumour variants following immunotherapy acquire insensitivity to immunologic elimination through genetic or epigenetic changes. In conclusion, devising novel strategies, for example, by combining multiple therapies for overcoming these confounding hurdles for clinical success are desperately needed [15,16]. An account of the possible options for such combinations with chaperone vaccines has been enlisted by Graner and Bigner [10].

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