Turning a tumour into its own worst enemy

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A personalized, essentially side-effect-free cancer immunotherapy is now in FDA-fast-tracked Phase III clinical trials for two separate indications. This therapy has applications across a broad range of cancer indications and a mechanism-of-action whose explanation has only recently achieved broad scientific consensus.

Results of Phase II trials of this vaccine in metastatic melanoma patients, reported in the *Journal of Clinical Oncology* in autumn 2002 [1], included two complete responses that persisted for more than two years. 'Anything that causes complete remission in metastatic melanoma is something that needs to be investigated,' says Walter Urba, Chief of Cancer Research at Earle A. Chiles Research Institute (http://www.providence.org/Oregon/Programs_and_Services/research/e05chiles.htm), who became familiar with the then-ongoing trial during an American Society of Clinical Oncology (ASCO; http://www.asco.org) panel discussion on cancer vaccines in 2001.

Shared versus self

Cancer immunotherapy has traditionally focused on so-called 'shared antigens' – bits of cell-surface proteins that are frequently overexpressed in particular tumour types – because (at least in theory) such antigens can be characterized, mass produced and administered in precise amounts, offering the promise of a widely applicable, inexpensive vaccine. However, shared antigens have been identified in only a fraction of tumour types, and appear only on a subset of those tumours. Moreover, with few exceptions, they are 'self antigens': abundant in tumours but also expressed on normal tissues. Thus, the immune system has already been rendered tolerant to them – and were immunotherapy to break that tolerance, the result could be autoimmunity, with all its repercussions.

By contrast, the cancer immunotherapy under development by Antigenics (http://www.antigenics.com) targets antigens that are unique to each patient's tumour. Because the immune system has developed no tolerance to them, these antigens – products of random mutations inevitably created in the course of cancer cell replication – can be highly immunogenic. However, their uniqueness presents a challenge: because they differ from patient to patient, how can they be cost-effectively identified, characterized, evaluated for their immunogenic potential, and formulated into a vaccine? Antigenics's approach skirts the first three issues by formulating the vaccine and letting the patient's own immune system solve the problem of selecting the best antigens by itself.

The key players in this self-help program are intracellular molecules called heat-shock proteins (HSPs), which are expressed at extremely high levels in every living cell placed under stresses ranging from heat or cold to oxygen or glucose deprivation. Indeed, HSPs are among the most abundant proteins, even in an unstressed cell.

An intracellular protein's secret extracellular life

The crucial immunological role of HSPs was first hinted at just over two decades ago in experiments by Pramod Srivastava, who showed that HSPs extracted from a rodent's tumour could confer resistance to that tumour – and only that tumour – when it was implanted into a syngeneic mouse [2]. Srivastava went on to co-found Antigenics in 1993 and has served as Chief Scientific Officer ever since.

Paradoxically, the HSP moiety that Srivastava initially isolated has only a single allele for all human beings – HSP sequences in general are more carefully conserved within and among species than even ribosomal proteins – so HSPs alone can not possibly convey any antigen-specific immunological information. Rather, their immunological capability hinges on the more standard but crucial intracellular function of HSPs: they chaperone other proteins, whose 3D structures they help to maintain throughout the life cycle of these proteins. This normal function renders HSPs capable of forming non-covalent complexes with a vast variety of peptide sequences.

Collectively, the HSPs extracted from a cell carry a virtually complete library of all the peptide sequences that cell has been generating. Thus, 'even though the HSP itself does not differ from tumour to tumour, the peptide profile that it carries differs markedly, and that is what provides the specificity,' says Urba. 'Not only do HSPs carry peptides but when you use them as a vaccine, they actually target

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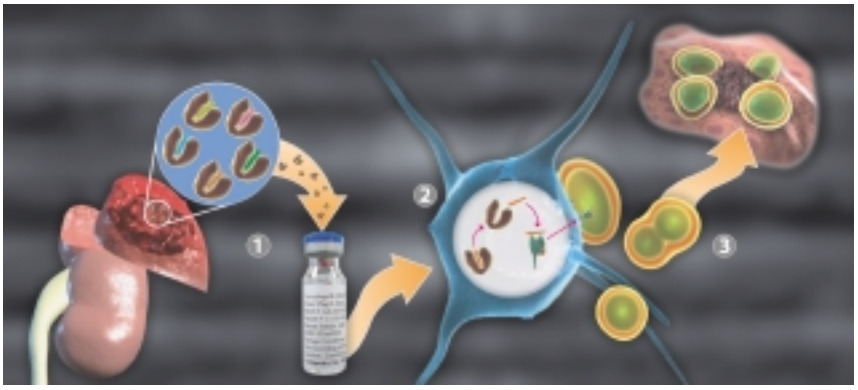

Figure 1. Antigenics' (http://www.antigenics.com) cancer vaccines Oncophage and AG858 are produced from the cancerous tissue or cells of the patient (1) and consist of purified heat shock proteins (HSPs) complexed to peptides that are specific to each individual cancer. The purified HSPs are vialed as sterile, injectable vaccine, to be administered on an outpatient basis over the course of several weeks. At the site of injection, there are dendritic cells (antigen presenting cells) that recognize and take in the HSP-peptide complexes (2). The peptides are then transferred onto molecules that can present the abnormal peptides on the cell surface, where they are made visible to the immune system (3). The immune system's T cells (yellow) recognize the displayed peptides, become specifically activated, then divide and travel throughout the body to identify and kill cancer cells bearing these specific peptides (purple). Figure courtesy of Alex Yildiz of Antigenics (http://www.antigenics.com).

the most-important antigen-presenting cell in the body: the dendritic cell.'

Ordinarily, HSPs are found only within cells. But upon necrosis, the cell contents – including HSPs – are released into the surrounding medium. Srivastava (Director of the Center for Immunotherapy of Cancer and Infectious Diseases, University of Connecticut; http://www.uconn.edu) and colleagues have identified high-affinity receptors for HSPs on dendritic cells (DCs) [3], professional antigen-presenting cells that are crucial in raising a cellular immune response. When an HSP docks in a DC's receptor, whatever peptide it might be holding is preferentially processed and re-presented on the DC's surface in a context that maximizes the prospect of T-cell activation. Most of these peptides (even from a tumour cell) are normal and thus non-immunogenic, but the few that are products of mitosis-driven mutations elicit a strong T-cell response.

Industrialized production of personalized vaccines

Some personalized immunotherapeutic approaches involving incubation of interesting antigens with DCs, which are then reintroduced into the patient's body, are in early stages of development [4]. But, in addition to potential FDA quality-control concerns regarding any cell-based therapy, a big hurdle for DC therapy is cost [5].

By contrast, Antigenics's vaccine is acellular and more amenable to industrial production methods. Resected tumours are frozen and their antigen-laden HSPs are extracted. They are then administered to patients in series of weekly injections for four weeks, and then biweekly as long as supplies last (Fig. 1). (The bigger the tumour, the more material that can be obtained.) Each vaccine carries a gamut of potentially immunogenic, patient-specific tumour antigens. The impractical task of identifying, selecting and packaging large numbers of these antigens to launch strong, broad-spectrum attacks on individual patients' tumours is delegated to the immune system.

Any tumour that is large enough to provide sufficient material is, theoretically, a candidate for this approach. In several early trials of Antigenics's vaccine, adverse events have been essentially nonexistent. Antigenics's HSP-based vaccine is now undergoing two large multicenter Phase III trials as a front-line, stand-alone treatment in renal-cell carcinoma and metastatic melanoma. Two further Phase II trials, in breast cancer and non-small cell lung cancer, have entered the planning stage. Encouraged by results of a pilot study, Antigenics is initiating a large Phase II trial of a related HSP-based vaccine administered to chronic myelogenous leukemia patients in combination with Gleevec. Furthermore, HSP-based vaccines are adaptable to chronic viral disease, which leaves telltale antigenic traces on infected cell surfaces. A Phase I trial of such a vaccine for HSV2 is under way at the University of Washington (http://www.washington.edu).

References

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