SHORT HISTORICAL REVIEW

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One hundred years of tumor suppressor research: crucial achievements and unique perspectives

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Abstract

Tumor suppressors constitute the body's primary defense line against malignant transformation. Since Theodor Boveri's initial insight one century ago, a huge amount of knowledge on these molecules has been generated. However, the final step of application of this profound understanding in the clinical setting, *i.e.*, the treatment of cancer patients with tumor suppressors and their derivatives, is still ahead. Nevertheless, the important success achieved with similar biomimetic approaches in the therapy of other diseases suggests that tumor suppressor-based antineoplastic interventions should be accomplished soon as they may be equally rewarding.

Keywords: Theodor Boveri, tumor suppressor, retinoblastoma protein (RB), cancer therapy, biomimicry, review.

Introduction

It was in 1914 that the German physician and zoologist Theodor Boveri (1862–1915) published his landmark monograph [1], in which he predicted what then turned out to be one of the most important research fields of the 20th century. Therein, Boveri envisioned a set of chromosomes that protect our normal and healthy cells from turning cancerous [1, 2]. These chromosomes or, more precisely, distinct segments residing on them were later found to be so-called tumor suppressor genes.

The first such tumor suppressor gene was identified as the retinoblastoma gene on chromosome 13 in 1983 [3]. Subsequently, *i.e.*, in the second half of the 1980s, the exact structure of the human retinoblastoma gene was communicated [4, 5] and, as a result, the sequence of the corresponding retinoblastoma gene product (RB) could also be reported, this molecule being a protein encompassing 928 amino acids [5]. Shortly thereafter, an additional milestone study demonstrated that tumor viruses such as the human papilloma virus (HPV) 16 harbor specific oncoproteins, *e.g.*, the E7 protein, by means of which they bind and consequently inactivate RB, thereby decisively promoting neoplastic transformation [6].

Therefore, at the beginning of the 1990s, there was justified hope that further advances in the tumor suppressor field should yield the long-sought breakthrough in cancer treatment [7]. This hope was further strengthened by a seminal 1996 paper [8], in which data from numerous laboratories around the world were reviewed that collectively supported the notion that the so-called RB pathway – that essentially converges p53, p16 and p21 tumor suppressor signals towards RB activation – is defective in the majority of human tumors, thus providing a unique molecular basis for developing effective anti-neoplastic drugs.

Towards the clinical tumor suppressor therapy of cancer

Consistent with this pivotal insight, three major therapeutic approaches aiming to restore the anti-proliferative function of RB in human cancer cells by using the structure of RB as a template have been successful, this being specifically achieved through the administration of the RB gene [9, 10], the RB protein [11] and RB peptides [12–16] to these cells.

In the same framework of RB pathway-based therapeutics, it further appears worthwhile to (synergistically) combine several tumor suppressor-derived (peptide) compounds that affect this essential molecular circuitry, as previously suggested [14, 16] and shown [17]. In addition, more recently discovered tumor suppressors such as the (oxygen-binding) neuroglobin protein [18], the (autoimmunity-preventing) Fus1 gene product [19] and the SynCAM molecule [20] – the latter of which is also known as tumor suppressor in lung cancer 1 (TSCL1) – may offer additional templates for the development of promising treatment regimens that could be equally combined to yield additive and/or synergistic anti-cancer effects.

Thus, we have made tremendous progress since Boveri's initial insight. Yet, these strides still await their translation into the therapy of cancer patients. This final step still needs to be done and will predictably be successful as with a previous breakthrough in medical history, which has been the prevention and therapy of infectious diseases. This became possible because ingenious researchers were able to activate and, respectively, imitate the body's own defense mechanisms against microbes. Similar to the natural immune system, which is the main defense line against bacteria and viruses [21], and also in analogy to the causal and therefore particularly effective treatment strategies of active [22–27] and passive [28, 29] immunization against them, so might endogenous tumor suppressors serve as useful templates towards developing predictably efficient strategies against cancer in the clinical setting in this still incipient 21st century. This way, medical bionics [30] or, respectively, biomimicry [31] would be once again put into successful application for a crucial goal of mankind.

In this context, it should also be noted that, beyond the immunological treatment of infectious diseases, medical bionics has a long and successful tradition in the form of the so-called replacement therapies, *i.e.*, the substitution of a lacking natural, endogenous substance or, respectively, anatomical structure by identical or similar means. Major examples for this type of approach are the treatment of (type 1) diabetes mellitus with insulin, of hypo/avitaminoses with vitamins (*e.g.*, of pernicious anemia by means of vitamin B_{12}), of distinct electrolyte deficits through the administration of the deficient electrolyte (*e.g.*, the correction of hypokalemia with potassium), of Parkinson's disease with the dopamine precursor substance L-DOPA and, more recently, the application of cochlear implants for the compensation of inner ear deafness. Given this ample track record of efficient homeostatic strategies, tumor suppressor mimetic therapy for cancer should also be accomplished soon in the clinical setting since the rewards for humanity will predictably be high.

Acknowledgments

This work is a tribute to Theodor Boveri and his inspiring legacy as well as to those researchers that have intriguingly shown about two decades ago [Lee *et al.*, Nature, 1992, 359(6393):288–294] that RB is crucial not only for cancer prevention, but also for a normal development of the embryo, thus underscoring the unique role of tumor suppressors such as RB in preserving life.

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