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The Usual Suspects in Melanoma Pathogenesis and the Role of Tissue Microarrays Analysis in Melanoma Research

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Editorial

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Abstract

Hippocrates of Cos being the first one ever to describe it also gave it its name: melas meaning dark and oma meaning tumor. Malignant melanoma is a neoplasm rising from the melanocyte. Although the cell is programmed to die when aged, in cancer including melanomas apoptosis seems to have been canceled. This paper focuses on the deregulation of apoptosis in malignant melanomas, the role of telomerase and the contribution of Tissue Microarrays Analysis in researching this specific type of cancer.

Keywords: Melanoma; Microarrays; Skin cancer; Pathogenesis

Abbreviations: CISH: Chromogenic in Situ Hybridization; TMA: Tissue Microarray Analysis

Introduction

Hippocrates named it melanoma deriving from melas (dark) and oma (tumor). Malignant melanomas are known to doctors for more than two thousand years, however diagnosing and treating them remains a challenge for modern medicine. In late 90s the use of interferon and interleukin [1] and later on discovery of BRAF mutations (2002) [2] brought optimism for evolution in melanoma treatment and though medicine did greatly evolved in the rise of the new millennium malignant melanoma did still hold many of its secrets undiscovered.

Pathogenetic Mechanisms in Melanoma

In understanding malignant melanoma development from a healthy melanocyte this paper will focus in the deregulation of apoptosis and especially in the role bcl2 and caspases play in the process. Then we will examine the role telomerase plays in uncontrolled proliferation in this specific type of cancer.

The Role of BCL2 Gene

BCL 2 (B-cell lymphoma gene 2) gene located in chromosome 18 was soon after its discovery linked with apoptosis: its over-expression connected to higher apoptosis resistance [3]. Soon more similar genes were discovered in viruses, invertebrates, vertebrates and humans and this led to the discovery that some members of the BCL 2 family actually have pro-apoptotic action. Under normal circumstances, expression of pro- and counter- apoptotic genes is well regulated and the products form dimmers so that the mitochondrial membrane remains intact. When under apoptotic stress pro-apoptotic genes over-express leading in release of cytochrome c out of the mitochondrion; cytochrome c forms the apoptosome, activating Caspase induced cell apoptosis [4]. BCL 2 research from 1984 [5] has shown

evidence of the role this protein plays in various types of cancer such as CLL [6] and AML [7], prostate [8], breast [9] and lung cancer [10], and in skin malignances [11]. BCL 2 family products have been suggested in the literature as therapeutic targets [12] and experiments are being contacted [13] at the present time.

Role of Caspases – Apoptotic Proteins

Caspases are a family of proteins members of which involve in programmed cell death. Caspases 3 and 8 are considered to be pro-apoptotic (effector and initiator respectively). Knockout mice experiments have demonstrated the role of caspases 3 and 8 in wound healing [14] while Caspase 3 was also found to play a great role in embryogenesis. Evidence published showed that inhibition of Caspase 4 (which is activated by Caspase 8) partially blocks Caspase 3 and TRAIL (TNF-related apoptosis-inducing ligand) induced apoptosis in melanoma cells [15]. However, in 2011 researchers found that although Caspase 3 facilitates death of cancer cells during radiotherapy it may be responsible for cancer regrowth [16] and in 2014 that this also happens during cytotoxic therapy [17]. Recent studies in the field also focus in the role of Caspase cascade in cancer and recently the use of Caspase 3 as a marker for response in cancer treatment was suggested [18]. Ongoing research will show if Caspase 3 will be part of everyday practice in clinical oncology.

Telomeres and Telomerase

Suggestive of the significance of the discovery, the 2009 Nobel Prize was awarded to Elizabeth Blackburn, Jack Szostak, and Carol Greider for their work in the discovery of telomeres and telomerase [19]. Shrinking of the telomeres located in the end of linear chromosomes is linked with cell death. Telomerase activity prevents shrinking and enables cancerous cells to surpass the Hayflick limit. Telomeres and telomerase were found to be connected with aging and cancer and were also targeted in hopes of new therapeutic approaches [20].

In melanomas: Increased telomerase activity was linked to melanomas already in 1999 [21] and soon more researchers [22,23] published on the role of telomerase in melanomas in early 2000. The evolution of TRAP (Telomerase Repeated Amplification Protocol) methodology contributed in research in this field [24]. In 2005 in vitro experiments [25] already targeted telomerase. Although telomerase activity gave us a deeper understanding of this type of cancer in specific, more research is needed in order to watch a real breakthrough based on the telomerase activity in melanomas in the ward.

Tissue Microarray Analysis (TMA) – a Tool in Cancer Research

With the increase of the volume of tissue data the need for a novel analysis system was obvious; cost-effective, quick and able to process many tissues samples at once tissue microarrays analysis was developed to cover for this need. First announcement on the methodology as we know it today in 1998 [26] and since then, the numerous papers regarding TMA published testify for the impact of the method in cancer research [27-29].

Quick description of the method: In tissue microarray analysis tissue embedded in paraffin is used after special processing. A hollow needle is used to extract core from the donor and insert it in the recipient block. As suggested in the literature [30] ideal core size for microarrays range from 0.6mm to 2mm. Modern trend is to prefer smaller sizes. The recipient block is then micro-sectioned and each section can be used in separate tests. Immunohistochemical stains are then used and can be combined with hybridization techniques such as fluorescence in situ hybridization-FISH or Chromogenic in situ hybridization (CISH).

Use in melanoma research: In the first 20 years of TMA use in science many studies investigated its possible applications in melanoma research. In early 2000, TMA was used in evaluating different possible biomarkers for melanoma [31-33]. In 2009 same technology was used to purpose a prognostic model for melanoma [34]. During the last decade, ongoing recent research on the field [35-37] remains focused in using TMA methodology in hopes of discovering a melanoma biomarker for broad clinical use.

Conclusion

Bcl2, caspases and telomerase activity seem to explain some questions about melanomas that previous knowledge could not. TMA is a relatively new methodology enabling the scientists to examine multiple tissue samples at once and could still have much to offer in melanoma treatment. Light shed in the apoptosis mechanism may reveal novel therapeutic approaches that will improve the quality and the life span of melanoma patients. As new treatments were approved in the last decade and antibodies are yet another promising new field in pharmacology we are moderately optimistic that

knowledge gained in the lab will find new applications in the clinical practice.

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