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Evolution of the concept of tumor marker: A historical overview

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Abstract. Tumor markers are biochemical entities potentially related to the presence of neoplastic diseases in humans. The history of the discovery and development of tumor markers (TuMa) goes back to the last hundred years, yet the first to be described dates back to 1848, when H. Bence Jones reported a protein associated with the presence of multiple myeloma. In the twentieth century between the twenties and thirties a number of TuMa were identified, among others ectopic hormones (1928), human chorionic gonadotropin (1930), and prostatic acid phosphatase (1933). In the sixties the first immunometric dosages became available and the study of tumor markers became more organic, while in the seventies the first monoclonal antibodies were developed. In the eighties mucinic markers (e.g., cancer antigen 125 in 1981 and cancer antigen 15-3 in 1984) appeared and the idea gained ground that tumor markers were minimally invasive, as well as relatively low-cost tools to monitor neoplastic diseases. In the nineties there was an ulterior diffusion of tumor markers, due to increased public sensitivity regarding neoplastic diseases, though, at the end of the twentieth century the overall low specificity of TuMa in the diagnostic phase of neoplastic diseases emerged. The recent comprehension of the variety of non-oncologic causes capable of modifying the quantitative level of tumor markers has led to the current views on TuMa, indicating that they should not be used as stand-alone parameters in the diagnosis of malignancy, but rather that they should be considered complementary tools in the entire management of cancer. (www.actabiomedica.it)

Key words: tumor markers, history of medicine, cancer, epistemology, physiology, medical humanities

Tumor markers are biochemical entities potentially related to the presence of neoplastic diseases in humans. The history of the discovery and development of tumor markers (TuMa) substantially goes back to the last hundred years, yet the first one, and a particularly famous one, dates 1848, when the English chemist and physician H. Bence Jones (1813-1873) described "a new substance occurring in the urine of a patient with mollities ossium", a protein associated with the presence of multiple myeloma (1). Bence Jones paved the way to the tracing of a series of biochemical compounds detectable in the presence of malignancies (and also in other conditions), and between the twenties and the thirties of the twentieth century a number of TuMa were identified and described. Many distinguished scientists in different countries have in the course of time furnished a valuable contribution to this historical development, among others W.H. Brown, who detected ectopic hormones in 1928, and B. Zondek, who reported human chorionic gonadotropin (HCG) in 1930. Two years later, in 1932, the American surgeon H.W. Cushing described the adrenocorticotropic hormone and in 1933 the US professor of medicine A.B. Gutman defined the isoenzyme prostatic acid phosphatase (PAP) (2). It was however after World War II, and more precisely in the sixties that the first immunometric dosages became available and that the study of tumor markers became more organic,

on the one hand allowing for a distinction between tumor derived substances and tumor associated ones, and on the other identifying other aspects related to malignancies, such as chromosomal alterations (the case of P.C. Newell and of the Philadelphia chromosoma is paradigmatic in this regard). In 1963 the Russian researcher G.I. Abelev described alpha-fetoprotein in liver carcinoma and in 1965 the Canadian scientists P. Gold and S.O. Freedman demonstrated the presence of tumor specific antigens in human colonic carcinomata (today known as carcinoembryonic antigen - CEA). In this period the expression of estrogen receptors in breast cancer became the first extensively adopted marker in the clinical setting to predict the response of this neoplastic disease to therapeutic measures. The tumor derived substances mentioned above came to include, in the course of time, isoenzymes, specific proteins, hormones, oncofetal antigens and mucins, while tumor associated elements comprised immune complexes, ferritin and neopterin (3). In the seventies, precisely in 1975, the German biologist G.J.F. Kohler and the British biochemist C. Milstein first developed monoclonal antibodies, thus adding a new important chapter to the history of TuMa. These two scientists were later (1984) awarded with the Nobel Prize in Physiology or Medicine, together with N.K. Jerne, "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies" (4). At the end of the seventies a fundamental tumor marker still used today, the prostatic specific antigen (PSA), appeared in the clinical scenario. In the eighties mucinic markers (among others cancer antigen 125 in 1981 and cancer antigen 15-3 in 1984) appeared and tumor markers attained diffusion as minimally invasive, relatively low-cost and quantitative tools for following neoplastic diseases. The awareness in that period that TuMA could be used to anticipate the proportion of malignant cells actively growing in solid cancers reinforced the idea that tumor markers had potential prognostic significance, given the greater aggressiveness of neoplastic diseases with a high cellular division rate. Meanwhile, the diffusion of monoclonal antibodies gave boost to a wider use of TuMa in clinical practice (5). In the nineties, tumor markers had further diffusion, due to an increased public sensitivity regarding neoplastic diseases and also to the increasing acceptability of these tools on the part of patients (6). They were progressively put in a clinical perspective and so, not by chance, in 1996 the first guidelines relative to the use of tumor markers in breast and colon cancers were released by the American Society of Clinical Oncology (ASCO), opening the way to the current tailored consideration of the role of TuMa in the context of tumoral pathologies (7). On the basis of the individual characteristics of specific tumor markers, from the nineties onwards the scientific community undertook a methodological effort to define not only for which individual malignancies TuMa were more appropriate, but also for what clinical-pathological stage of the disease single markers (or their possible combinations) were more useful. From this derived the evaluation of their eventual specific role in prevention, screening, initial evaluation, stadiation, identification of (micro-)metastases, post-surgical period and therapeutic follow-up (8). In this decade the diagnostic role of tumor markers was nonetheless reduced in comparison to their previous past, because the understanding of their overall low specificity in the diagnostic phase of neoplastic diseases emerged, as also the knowledge that clinically meaningful quantities of tumor markers were not generally released by early-stage malignancies. In effect, it became clear that the relationship between hematic concentrations of TuMa and the extension of neoplastic tissue was direct (9). In the last twenty years a deeper insight into the cellular biology of tumors has led to major progress in clinical science such as the measurement of the activity of telomerase and the search for mRNA, and this in the scenario of the markers for cancer as a social disease and as a major cause of mortality in humans (10). Furthermore, technical-scientific development in the area of tumor markers has also been accompanied by biological-epistemological progress, involving a more complete comprehension of the variety of non-oncologic causes capable of modifying the quantitative level of these markers. These causes include non-neoplastic diseases, factors related to lifestyle and, last but not least, iatrogenic causes (such as surgery, drugs and chemotherapy) (8). The more recent methodological international indications point therefore, and in conclusion, to "appropriateness" and "integration" as the key words

to apply correctly the role of tumor markers in clinical practice. Current views suggest that TuMa should not be used as stand-alone parameters in the diagnostic phase of neoplastic diseases and should not be considered the unique decision-making criteria in the therapeutic segment of such pathologies (5). Their function in the clinical panorama of neoplastic diseases may more meaningfully be that of a useful complementary tool to adopt in a frame of cooperation and synergy with other instruments currently available in the field of cancer management: a global endeavor so challenging as to require at the clinical-scientific level the full and harmonic inclusion of every resource available.

Ethic Approval: Historical article, not needed.

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