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REVIEW

Human embryo immune escape mechanisms rediscovered by the tumor

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Abstract

Towards the end of the 1990s, the two opposing theories on immunosurveillance and immunostimulation were extensively studied by researchers in an attempt to understand the complex mechanisms that regulate the relation between tumors and the host's immune system. Both theories probably have elements that would help us to comprehend how the host can induce anti-tumor clinical responses through stimulation of the immune system and which could also give us a deeper insight into the mechanisms of tumor immunosuppression. The model that most resembles the behavior of tumor cells in terms of growth, infiltration and suppression of the immune system of the environment in which they live is undoubtedly that of the embryonic cell. The fetus behaves like an allogenic transplant within the mother's body, using every means it has to escape from and defend itself against the mother's immune system. The majority of these mechanisms are the same as those found in tumor cells: antigenic loss, lack of expression of classic HLA-I molecules, production of immunosuppressive cytokines, induction of lack of expression of co-stimulatory molecules in antigen presenting cells, and induction of apoptosis in infiltrating lymphocytes, with activation of a type Th2 regulatory lymphocyte response. A careful and comparative study of key mechanisms capable of triggering tolerance or cytotoxicity in both embryonic and tumor cells could prove immensely valuable in designing new strategies for anti-tumor immunotherapy.

Keywords: Embryo immune escape; Tumor immune escape; Tumor immunosuppression

Contents

Abbreviations: DC, dendritic cell; HLA, human leukocyte antigen; KIR, killer cell Ig-like inhibitory receptor; MHC, major histocompatibility complex; NK, natural killer; Th1, helper-1 T lymphocyte; Th2, helper-2 T lymphocyte; TRAIL, TNF-related apoptosis-inducing ligand; uNK, uterine NK; VEGF, vascular endothelial growth factor.

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Introduction

Immunosurveillance and immunostimulation

Over the past 20 years a great deal has been learnt about the capacity of the immune system to recognize and destroy tumor cells, at least *in vitro*, and about the ability of tumor cells to escape recognition and attack by the immune system (Marincola et al., 2000; Shiozaki et al., 2003).

During the course of the last century, two theories were put forward by researchers: the theory of immunosurveillance, which sustains that an immune system exists in mammals capable of preventing the onset and development of tumors within our organism, and the theory of immunostimulation, which maintains that chronic or indolent diseases create a favorable immunological habitat for the development and growth of the tumor, which, in turn, enhances the chronicity of the condition, thus creating a vicious circle. Evidence for and against either theory can be found and, as often happens, elements of truth are present in both (Ichim, 2005).

The relation between the immune system and the tumor is undoubtedly a complex one. Experimental evidence of the capacity of the immune system to discriminate between self and non-self, which forms the basis of the recognition and elimination of emerging tumors, in accordance with the theory of immunosurveillance, has proven to be of fundamental importance. Indeed, this key ability to distinguish between self and non-self is essential for an adequate response to external pathogens and growing tumor cells (Pardoll, 2003).

Starting from the fact that tumor cells derive from cells of the host, anti-tumor response resembles a sort of autoimmune response. Nonetheless, important differences exist between tumor cells and healthy tissue, and such diversity is constituted by molecules recognized as antigenic by the immune system (Bennink et al., 1993).

The mutation-derived antigens that are present in tumor cells can be classified as *unique tumor antigens* specific for the tumor or *shared tumor antigens*, that is, antigens common to a large number of individuals and tumors (Perez-Diez and Marincola, 2002). However, the theoretically simple interaction that occurs between tumor and immune system is strongly influenced by the environment. Tumors generally develop in tissues that have been chronically altered by endogenous or exogenous causes in which the immune system tends to tolerate a pathological situation that it cannot eliminate.

Like exogenous agents, cancer cells have the ability to invade and destroy natural tissue barriers; however the immune system, which theoretically should recognize and attack tumor cells, adopts an *attitude* of tolerance, which supports the theory of immunostimulation (Campoli et al., 2005). The consequences are, of course, well known: the tumor escapes recognition and launches it own counter-attack against the immune system; in doing so, it is able to grow, invade, and metastasize to normal tissues (Carbone and Ohm, 2002).

Evidence in support of the two theories prompted the development of the cancer immunoediting hypothesis to more broadly encompass the potential host-protective and tumor-sculpting functions of the immune system throughout tumor development (Dunn et al., 2002, 2004). Cancer immunoediting is a dynamic process composed of three phases; *elimination*, representing the classical concept of cancer immunosurveillance; *equilibrium*, describing a period of latency; and *escape*, referring to the final outgrowth of tumors. Although no clear analogies can be drawn between the embryo–maternal relationship and the *elimination* and *equilibrium* phases, there seems to be no doubt of a similarity in terms of the mechanisms described in the *escape* phase.

A comparison of the immunoescape mechanisms used by the embryo and tumor could provide useful information for the development of new integrated anticancer therapeutic strategies.