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Mini-review

Role of the tumor microenvironment in regulating apoptosis and cancer progression

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ABSTRACT

Apoptosis is a gene-directed program that is engaged to efficiently eliminate dysfunctional cells. Evasion of apoptosis may be an important gate to tumor initiation and therapy resistance. Like any other developmental program, apoptosis can be disrupted by several genetic aberrations driving malignant cells into an uncontrolled progression and survival. For its sustained growth, cancer develops in a complex environment, which provides survival signals and rescues malignant cells from apoptosis. Recent studies have clearly shown a wide interaction between tumor cells and their microenvironment, confirming the influence of the surrounding cells on tumor expansion and invasion. These non-malignant cells not only intensify tumor cells growth but also upgrade the process of metastasis. The strong crosstalk between malignant cells and a reactive microenvironment is mediated by soluble chemokines and cytokines, which act on tumor cells through surface receptors. Disturbing the microenvironment signaling might be an encouraging approach for patient's treatment. Therefore, the ultimate knowledge of "tumor–microenvironment" interactions facilitates the identification of novel therapeutic procedures that mobilize cancer cells from their supportive cells. This review focuses on cancer progression mediated by the dysfunction of apoptosis and by the fundamental relationship between tumor and reactive cells. New insights and valuable targets for cancer prevention and therapy are also presented.

Introduction

In 1842, the notion of cell death, known now as apoptosis, was introduced by Carl Vogt after his work on developmental cell death in toads. Later, in 1885, Walther Flemming was the first to propose a morphological description of apoptosis showing the deformation of the cell, DNA degradation and apoptotic body formation [1]. In 2002, Sydney Brenner, Robert Horvitz and John E. Suston deciphered the genetic regulation of programmed cell death and provided "*Caenorhabditis elegans*" as a biological model to study apoptosis [2].

The process of apoptosis, a tightly regulated programmed cell death, occurs normally to maintain the development and homeostasis in normal cell populations. Inappropriate apoptosis is a major factor in many human diseases. Defects in apoptosis cause autoimmune diseases or cancers, whereas enhanced cell death may cause degenerative diseases and immunodeficiency [3].

The apoptotic mechanism is triggered by two distinguished pathways: (i) the "extrinsic pathway" which is initiated by a variety of death receptors – members of TNF receptor superfamily – such as TNFα receptor, Fas-L receptor, TRAIL receptors and (ii) the "intrinsic pathway" mediated by the mitochondria which releases apoptogenic factors from its inter-membrane space. In both pathways, most of the changes depend on a group of cysteine proteases described as "caspases", which were revealed as the central executioners of the apoptotic pathway because of their role in the cleavage of major cellular substrates such as nuclear lamins, cytoskeletal proteins (Fodrin, gelsolin) and the caspases themselves [4,5]. Additional studies have demonstrated a novel apoptotic pathway mediated by the activation of caspase-12 in response to the endoplasmic reticulum stress (ER-stress). Caspase-12 is responsible for the induction of ER-stress specific caspases cascade, such as caspase-9 in a cytochrome-C independent manner, confirming the central role of caspase-12 in ER stress-mediated apoptosis [6].

Each disruption or defect in apoptosis can allow pre-neoplastic and neoplastic cells to survive and enhance tumor pathogenesis via activation of proto-oncogenes. One of the mechanisms that provides apoptotic resistance to tumor cells is the overexpression of anti-apoptotic proteins (e.g. Bcl2) or the downregulation of pro-apoptotic proteins (e.g. BAX) [3]; and the overexpression of anti-apoptotic proteins such as Bcl-2 will contribute with other proteins like c-myc to tumorigenesis [4]. Once the tumor is formed, it ini-

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tiates an inflammatory response and modifies the texture of the surrounding environment to convert it into a pathological entity. In contrast, the tumor microenvironment provides inappropriate signals that lead to the maintenance of tumorigenesis and resistance to cancer therapies [7]. In numerous situations, tumor cells can become fully resistant to apoptosis, so they can escape from the immune system and resist subsequently to any therapeutic strategy targeting the apoptotic pathways.

The aims of this review are (i) to present the correlations between defects in apoptosis and cancers, and (ii) to clarify the crosstalk between tumor cells and their microenvironment interfering with these mechanisms of apoptosis. We finally highlight the novel therapeutic issues that target common pathways of stroma and tumor cells.

Apoptosis

Apoptosis: vital component of cell turnover

The mechanism of apoptosis, or programmed cell death (PCD), is a vital factor of different processes including cell renewal, embryonic development, and immune system activity. Many morphological changes occur during apoptosis: cell shrinkage, formation of cytoplasmic blebs, mitochondrial breakdown, chromatin condensation, and eventually disturbance of cytoplasmic membranes and release of apoptotic bodies. Two main apoptotic pathways have been extensively described, which include the extrinsic pathway and the intrinsic pathway. Each of them requires the implication and activation of caspases – *cysteinyl aspartate proteases* – to allow a proteolytic cascade which promotes the apoptotic signaling pathways.

(a) *The extrinsic pathway*, or death receptor pathway, is initiated by the activation of transmembrane death receptors (DRs) such as Fas/CD95, TRAIL receptors and all members of the TNF (tumor necrosis factor) receptor superfamily, following the binding of their suitable ligands. Then, the activated receptors are able to recruit the adaptor protein FADD which associates with procaspase-8 and form the death-inducing signaling complex (DISC). This complex is responsible for caspase-8 activation and the induction of a downstream cascade of effectors such as caspase-3, -6, and -7, leading finally to an irreversible cell death.

(b) *The intrinsic pathway*, also called mitochondrial pathway, is triggered by intracellular signals, such as DNA damage, oxidative stress and irradiations. These multiple forms of stresses induce the release of pro-apoptotic proteins from the mitochondria: Cytochrome c, Smac/Diablo, AIF, and EndoG. Then, Cytochrome c will bind to APAF1 (apoptotic protease activating factor-1) to form a large complex – the apoptosome – which in turn recruits pro-caspase-9 leading to caspase-9 activation. Activated caspase-9 will induce additional caspases such as caspase-3. While Smac/DIABLO plays an essential role in blocking the activity of IAPs (inhibitors of apoptosis proteins) allowing apoptosis to occur. These two major apoptotic pathways end by the execution phase which is characterized by the degradation of the nuclear material and cytoskeletal proteins, contributing to cell death. In most cells, a "cross-talk" between the extrinsic and intrinsic pathways occurs through the cleavage of BID in t-BID by activated caspase-8. Truncated BID (t-BID) permeabilizes the mitochondria and promotes the activation of additional caspase molecules (caspase-9, -3, -6 and -7) amplifying the apoptotic signal [8–10] (Fig. 1).

(c) *A third apoptotic pathway* has been more recently described which highly underscores the role of the ER stress. This pathway initiates cell death through caspases activation, primarily caspase-4 in humans and caspase-12 in mice. Once triggered and activated by the ER stress, caspase-12 induces the activation of downstream caspases like caspase-9 and -3, responsible for ER stress–induced apoptosis [6]. Several models of caspase-4 activation have been proposed, one of them brings out the role of IRE1α, an ER-transmembrane protein which transduces the stress signals initiated by the accumulation of misfolded proteins, from the ER to the cytoplasm and nucleus. In response to ER stress, procaspase-4 localized into the ER and interacts with IRE1α through TRAF2 (tumor necrosis factor receptor-associated factor 2), leading to the auto-processing and activation of caspase-4. The mechanisms of caspase-4 activation by ER apoptotic signals or how TRAF2 transmits ER signals from IRE1α to its downstream effector caspase-4 are still unknown [11]. In contrast, the overexpression of Calreticulin, an ER luminal protein, resulted in an increased release of cytochrome c from the mitochondria and an enhancement of caspase activity during apoptosis. These findings suggest that ER and mitochondria pathways are tightly linked, and this correlation involves Ca^{2+} which is released from the ER and accumulates into the mitochondria [12].

Defects of apoptosis and tumorigenesis

Several forms of mutations contribute to apoptosis resistance, facilitating the uncontrolled cell growth of tumor cells, invasiveness and metastatic ability. The anti-apoptotic gene "Bcl2" is activated by a chromosomal translocation, contributing to lymphomagenesis. The p53, tumor suppressor gene, is considered as a central regulator of apoptosis. It recognizes DNA damage and thereafter arrests the cell cycle and triggers the DNA repair mechanisms. Due to its rescuer role, the downregulation of p53 enhances tumorigenesis in many cancer types. In addition, any loss or defect in the function of one factor of the intrinsic or extrinsic pathways can enhance tumor progression. For example, deficient function of APAF1 contributes to oncogenesis in ovarian and melanoma cancer cell lines, when perturbation of the FAS pathway, such as Fas gene mutation, contributes to non-Hodgkin's lymphomas and other cancer types [13]. Moreover, the amplified resistance to apoptotic cell death is a hallmark of quickly proliferating cancer cells. Then, the inhibition of this anti-apoptotic defense could improve cancer therapies [14]. Indeed, the overexpression of anti-apoptotic proteins such as Bcl-2, survivin and Mcl-1, which act as negative regulators of the mitochondrial pathway, leads to cell death resistance in follicular lymphomas. Quercetin, a natural flavonoid, restores TRAIL-mediated cell death by induction of the proteasomal degradation of Mcl-1 and by suppressing survivin mRNA expression [15]. The absence of caspases also promotes cell survival and clonogenic growth. Downregulation of caspase-2 or -8 in murine embryonic fibroblasts (MEFs) enhances cell proliferation and tumorigenesis. Besides, there is a correlation between the absence of autophagy and carcinogenesis. Mutations of autophagic genes contribute deeply to tumorigenesis. For example, Atg5 mutation has been observed in gastric cancer [16]. In addition, reduced expression of Beclin 1, an autophagy inducer, is observed in breast and ovarian carcinomas due to a significant deletion of the corresponding gene. Hence, resistance to autophagy and apoptosis greatly contributes to cancer drugs' resistance. Then, proteins involved in the autophagic and the apoptotic pathways might be important targets of cancer therapies [17].

Resistant tumor cells

Drug resistance is considered as an essential mechanism for inhibiting chemotherapy efficiency. Resistance to chemical drugs could