*Immunologic Research* 2006;36/1–3:247–254

# Human Tumor–Derived vs Dendritic Cell–Derived Exosomes Have Distinct Biologic Roles and Molecular Profiles

***Eva Wieckowski***
***Theresa L. Whiteside***

Departments of Pathology, Immunology and Otolaryngology
University of Pittsburgh School of Medicine

## Abstract

Microvesicles (MV) or exosomes are produced and secreted by tumor and normal cells. The molecular profile and functions of tumor-derived vs dendritic cell (DC)–derived MV are distinct. The former express death ligands and mediate apoptosis of activated T cells. The latter promote CD4+ T cell proliferation and may play a role in regulating T cell responses. Serving as intercellular communication networks, tumor-derived MV contribute to tumor escape, while DC-derived MV drive and regulate immune response.

## Key Words

Exosomes
Microvesicles
Human tumors
Dendritic cells
T cells
Apoptosis

## Introduction

Many different cells produce and release into their microenvironment membraneous microvesicles (MV) or exosomes. In humans, MV have been isolated from supernatants of cultured normal or malignant cells, sera, and other body fluids of patients with various diseases as well as placenta and cord blood *(1–4)*. The MV vary in size from 50 to 100 nM (the size of viruses), are bound by a double membrane and express a variety of known membrane-associated molecules *(5,6)*. The history of MV is quite long, but it is only recently that they have captured attention of the scientific community *(7)*. Johnstone first described vesicles shed by reticulocytes and named them "exosomes" in 1987 *(8)*. For many years thereafter, MV remained a relatively unknown and unappreciated biologic entity, until Zitvogel and colleagues, working in late 1990s with dendritic cells (DC), noted their ability to produce as well as internalize exosomes and characterized their molecular profile *(9)*. As

Theresa Whiteside
University of Pittsburgh Cancer Institute
Hillman Cancer Center
5117 Centre Avenue, Suite 1.27
Pittsburgh, PA 15213
E-mail: whitesidetl@upmc.edu


0257–277X/
(Online)1559-0755/06/
36/1–3:247–254/$30.00

exosomes derived from tumor antigen–pulsed DC elicited potent tumor-specific immune responses, Zitvogel et al. began using DC-derived exosomes as tumor vaccines first in mice and later in subjects with ovarian carcinoma *(10,11)*. In parallel, advances in cell biology allowed for elucidation of exosome cellular origin from endosomes and multivesicular bodies in the cytoplasm of most activated cells (Fig. 1). Our own interest in exosomes dates back to the controversy that emerged in the early 2000s indicating that exosomes released by various cell types may be either immunogenic or tolerogenic, and that MV and exosomes share the same or closely related characteristics *(12)*. It seemed that the same structures may have distinct biologic activities depending on their cellular origin, and we hypothesized that tumor-derived MV or exosomes were immunosuppressive *(13)*.

For many years, we have been engaged in evaluating antitumor responses of patients with cancer and reporting various degrees of dysfunction in their immune system *(14)*. Abnormalities that have been noted include depressed lymphocyte numbers, altered T cell distribution, functional deficiency, and premature apoptosis of immune cells, resulting in their rapid turnover. These abnormalities are especially evident in patients with advanced cancers. Mechanisms responsible for these abnormalities are varied, but most are ascribed to the ability of human tumors to subvert the host immune defense and thus escape immune recognition *(14)*. In cancer, immune cells are dysfunctional not only at the tumor site but also in the peripheral circulation *(15)*. To find an explanation for the demise of T effector cells distant from the tumor, we considered a possibility that tumor-derived MV found in the sera of patients with cancer were able to eliminate activated circulating effector T cells, especially those specific for the tumor. We recently reported that

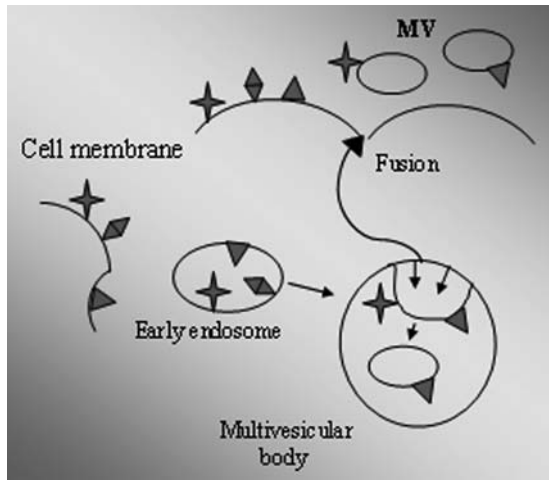


**Fig. 1.** A diagram showing the "inside out" mechanism of MV secretion. Upon fusion with the surface membrane, multivesicular bodies release MV into extracellular space.

MV isolated from sera of patients with head and neck cancer (HNC) had suppressive biologic activity and were able to induce apoptosis in Jurkat cells and in activated peripheral blood T cells *(16)*. Here, we extend these data to show that a variety of tumor cells produce and release MV and that tumor-derived MV have molecular and functional attributes that distinguish them from MV obtained from supernatants of normal cells such as DC.

## Molecular Profiles of MV in Tumor- vs DC-Derived Cell Supernatants

We have previously shown that PCI-13, an oral carcinoma cell line, which we had retrovirally transfected with the human FasL gene *(17)* produced biologically active MV expressing the membrane form (42 kDa) of FasL and HLA class I antigens. To investigate the presence of additional membrane markers on MV and to extend these observations to other tumor cell lines and to MV purified from supernatants of cultured monocyte-