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Phosphatidylserine's Exposure on Tumor Cells Determines a Tumor's Microenvironment and Checkpoint Molecule Exposure, a Hypothesis

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Abstract

One constant in all malignant tumors is their continuous growth and there appear to be only two kinds of cell mutations that can cause this. One causes continuous mitotic cell division at a rate that exceeds the one required for their replacement when they physiologically die by programed cell death (PCD). In the other PCD is eliminated and the cells continuously divide at their normal rate until they finally die a senescent death. Phosphatidylserine (PS) is present on the inner leaflets of cell membranes but it moves to their surface when they are stressed and damaged and when they die by PCD. The hypothesis proposed is that when mutations delete PCD in a cell the PS will move to the surface of the damaged senescent cells where it will produce a tumor with an inflammatory and procoagulant microenvironment where checkpoint (CPMs) are generated by an innate immune response that prevents the immunologic removal of the tumor cells.

Keywords: Cancer; Checkpoint; Inflammation; Immune; Phosphatidylserine; TMEM16F

Introduction

Innate immune responses repair cell damage and they begin when the damage exposes PS on the damaged cell's surface and it binds to the TIM and TAM receptors that are both present on each immune cell [1]. Peptides on PS's surface are complimentary to those on TIM receptors but they aren't to the TAM receptors and they must bind to them by PS bridging molecules [2]. It is hypothesized that TIM activated immune cells secrete cytokines that activate *all* immune cells to repair cell damage and TAM activated immune cells secrete cytokines to prevent the activation of immune cells that will increase cell damage. It is also proposed that cytokines secreted by TAM activated immune cells are physiologic checkpoint molecules (CPMs) that prevent the removal of somatic cells that are continuously being damaged by reactive oxygen species (ROS), minor daily traumas and the exposure to environmental pollution and toxins. In the following we will very briefly examine phosphatidylserine, inflammation, blood coagulation, the complimentary peptide interactions between PS exposed on damaged cells and TIM and TAM receptors in innate immune responses and the interaction between foreign peptides on pathogens and self-peptides on immune cells in adaptive responses. We will also examine immune checkpoint inhibitors (ICIs) and how their administration blocks the generation of CPMs in malignant tumors.

Phosphatidylserine

PS is present in the membranes of all eukaryotic cells where it is kept on

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their inner leaflet in an energy dependent manner but it moves to their surface by the TMEM16F scramblase molecule when they are damaged [3] and it move their surface by the Xkr8 scramblase molecule when they die by PCD and when they are *lethally* damaged [4]. When PS is exposed on TMEM16F it signals for the phagocytic removal of damaged cells, becomes the platform upon which the coagulation cascade generates thrombin and activates all immune cells in innate immune responses [5]. When cells die by PCD they bind to class II macrophages by the PS bridging molecule MPG- E8 and they are rapidly phagocytized. Billions of cells die by PCD each day and their removal is so efficient that PS+ cells aren't normally detected [6].

Inflammation

The physiologic role of inflammation is the amplification of immune responses in adaptive immune responses where pathogens are rapidly replicating and virus infected cells are generating viruses. Inflammation is generated in adaptive immune responses when foreign peptides on pathogens bind to macrophages and dendritic cells and activate the secretion of inflammatory cytokines. The inflammatory cytokines stress somatic cells and expose PS on their surface where it binds to the TIM-1 receptors on T helper one (Th1) immune cells and activates their feedback secretion of inflammatory cytokines [7]. This was documented in 2017 when mice were infected with the Ebola virus and this produced a lethal inflammatory storm but when it was repeated using TIM-1 knockout mice they survived and the inflammatory storm was prevented [7]. In the study the viral load was only minimally reduced proving that that PS was the pathologic inflammatory agent, not the virus.

Blood Coagulation

Blood coagulation begins whenever cells are stressed or damaged and tissue factor (TF) and PS are exposed with the TF initiating coagulation and PS amplifying it [5,8]. TF activates factor IX and X and activated factor Xa changes prothrombin to thrombin and it activates the cascade's feedback thrombin generation and the exposure of PS on platelets. Activated factor IXa is required for cascade function and as such it is a rate limiting component of blood coagulation. Factor IX's activation is initiated by TF exposure, is continued in the cascade when the thrombin it generates activates factor XI and it activates factor IX and is maximally activated by factor XII activating factor XI. For factor XII to be activated it must bind to sulfatide on activated platelets [9] but those activated platelets secrete a factor XII activation inhibitor [10]. This fortunately prevents factor XII from amplifying intravascular blood coagulation but when a vascular wall is breached and collagen is exposed PS+ platelets with sulfatide on their surface will bind to the collagen and thrombin will be generated because the factor XII activation inhibitor will be washed away. This enables maximum thrombin generation exclusively at the vascular breach. Unfortunately collagen and PS are exposed and TF is released in coronary arteries when an atherosclerotic plaque ruptures.

Immune Cell Activation

The hypothesis proposed is that the TIM and TAM receptors on immune cells are the on/off switches for immune cells in innate immune response. It is hypothesized that when cells are physically damaged the PS exposed on them binds directly to TIM receptors on all immune cells_and activates their secretion of cytokines that direct the innate response and it binds indirectly to TAM receptors to turn off immune cells that damage cells and the cytokine secretion by cells not involved in an innate response. This is analogous to electrifying a home with one switch to connect the power from the grid to it where the thermostats, rheostats and occupants act like cytokines to turn off and on its appliances. PS doesn't actually bind to TIM and TAM receptors, complimentary peptides on their surface provide the connection. *Some* peptides on PS bind to complimentary peptides on the *TIM* receptors of immune cells and activate the secretion of cytokines that turn on *all* immune cells but PS peptides aren't complimentary to TAM receptors and *other* PS peptides bind to them by PS bridging molecules and turn off individual or groups of *specific* immune cells. The *other* PS peptides bind to complimentary peptides on the PS bridging molecules Gas6 and ProS and peptides present on them bind to complimentary peptides on the three TAM receptors Tyro3, AXL and MER on *TAM* receptors of immune cells and activate cytokine secretions that then bind to specific immune cells and/or immune cell groups and turn them off. A single peptide in the bridging sequence can activate the secretion of one or more cytokines. In innate responses all immune cells are activated when PS on damaged cells binds to their TIM receptors including cytotoxic T cells (CTLs), class I macrophages and immune cells not involved in innate responses. The CTLs, macrophages and the cytokines secreted by immune cells that aren't involved in innate responses can kill, phagocytize and damage somatic cells but they are turned off by cytokines secreted by TAM activated immune cells. It is hypothesized that the cytokines the TAM activated immune cells secrete each have a specific *bridging molecule peptide* on their surface that bind to and cloak the complimentary peptides on specific *TIM activated immune cell* and prevent them from recognizing PS exposed on physically damaged cells and removing them. It also proposed that those cytokines are physiologic checkpoint molecules (CPMs). Those cytokine CPMs are *physiologic* because they cloak PS exposed on cells continuously being damaged by reactive oxygen species (ROS), minor daily traumas, radiation and the exposure to environmental pollution and ingested toxins and prevent their removal. They also cloak PS on *senescent tumor cells* created

when mutation delete PCD in a cell and it keeps on dividing and growing until all the tumors cells eventually become senescent and expose PS on their surface by TMEM16F. Adaptive immune responses begin when foreign peptides on pathogens bind to complimentary *self-peptides* on the toll like receptors (TLRs) of class I macrophages, dendritic cells and B cells. Foreign peptides are peptides unlike the self-peptides exposed on the class I MHC molecules of eukaryotic cells but *are complimentary to them*. The macrophages, dendritic cells and B cells activated by foreign peptides secrete inflammatory cytokines that expose PS to amplify the adaptive response and they phagocytize and disassemble the pathogens and expose their peptides on their MHC. The foreign peptides are exposed on the class II MHC of dendritic cells and B cells and the self-peptides are exposed on their class I MHC. The foreign peptides exposed on the class II MHC of dendritic cells bind to *self-peptides* on the class I MHC of CD4 and CD8 T cells and activate them. The foreign peptides on the class I MHC of the activated CD4 cells bind to foreign peptides on the class II MHC of B cells and activate their secretion of antibodies and the CD8 T cells activated by the dendritic cells expose peptides on their T cell receptors that are complimentary to foreign peptides on virus infected somatic cells and on pathogens and they kill them. PS isn't exposed on physically damaged cells in adaptive immune responses unless the pathogens damage them and then innate and adaptive responses will coexist. CPMs generated when innate and adaptive responses coexist won't eliminate PS+ stressed somatic cells that amplify the adaptive response because they are generated by immune cells, not by PS on damaged cells.

Checkpoint Molecules and Immune Checkpoint Inhibitors

It is proposed that the CPMs generated in innate immune responses to prevent the removal of damaged cells are physiologic molecules that do this for us each day and also prevent the removal of senescent tumor cells generated when mutations delete PCD. ICIs are exogenously generated antibodies that are administered intravenously to treat cancers by making it possible for the CTLs and macrophages activated in certain malignant tumors to access, kill and phagocytize PS+ tumor cells. It is proposed that the ICI antibodies have peptides on their Fab segments that bind to and cloak complimentary peptides on *PS bridging molecules* and prevent them from binding to TAM receptors on immune cells and activating their secretion of CPM cytokines. The specific bridging peptide the ICI binds to in the bridging sequence will determine whether single or multiple CPM cytokines will be generated. The ones that generate multiple CPMs will be more effective in removing tumor cells but may also increase the side effects associated with ICI administration because ICIs also block the physiologic protection of damaged cells [11,12]. The administration of ICIs has been successful in prolonging the survival of cancer patients but it is only rarely successful in producing a cure. This would appear to be due to the fact that CTLs only kill PS+ damaged tumor cells and when mutations delete PCD the tumor cells don't become PS+ until they become senescent. Unfortunately the administration of ICIs eliminates the CPMs physiologic role of preventing the removal of damaged somatic cells and their cumulative loss while ICIs are continuously present may interfere with organ function. Bridging molecule peptides involved in CPM generation may have other physiologic functions when they are on the surface of undamaged somatic cells and if ICIs cloak them this may be responsible for some of their pathologic side effects [11,12].

In conclusion

Until and if the hypotheses presented here are tested and found invalid it would seem prudent to very carefully examine the microenvironments of newly discovered tumors in patients before administering ICIs and to be especially thorough in the evaluation of newly developed ICIs before their approval for general therapeutic use.

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