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When there are two complimentary peptides on the class I major histocompatibility (MHC) complexes present on a cell's surface and the foreign peptide present on a virus binds to a complimentary peptide on the class I MHC of one of them this will produce both an adaptive, and an innate autoimmune response. The adaptive response will be to the foreign virus peptide exposed on the class I MHCs of the infected cells and the innate autoimmune response will be to the self-peptide exposed on the uninfected cells that are complimentary to the peptide the virus binds to. The cytotoxic T cells (CTLs) generated in adaptive immune responses will have peptides on their T cell receptors (TCRs) that are complimentary to the foreign peptide exposed on the class I MHC of the infected cells and to the identical self-peptides on the class I MHCs of uninfected cells.

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When there are two complimentary peptides on the class I major histocompatibility (MHC) complexes present on a cell's surface and the foreign peptide present on a virus binds to a complimentary peptide on the class I MHC of one of them and infects it this will produce both an adaptive immune response to those cells and complimentary peptides on the T cell receptors (TCRs) of the cytotoxic T cells (CTLs) generated there will bind to Stop 2/23/2023 to the, immune response to the and an innate autoimmune response.

The adaptive response will be to the foreign virus peptide exposed on the class I MHCs of the infected cells and the innate autoimmune response will be to the self-peptide exposed on the uninfected cells that are complimentary to the peptide the virus binds to. The cytotoxic T cells (CTLs) generated in adaptive immune responses will have peptides on their T cell receptors (TCRs) that are complimentary to the foreign peptide exposed on the class I MHC of the infected cells and to the identical self-peptides on the class I MHCs of uninfected cells.

Cells are damaged in all three immune responses resulting in phosphatidylserine (PS) on their surface where it.

I. INTRODUCTION

All biologic molecules are made of peptides and eukaryotic vertebrate cells expose their self-peptides on the class I major histocompatibility complexes (MHC) present on the surface of their membranes.

Viruses are protein molecules made by the eukaryotic cells of vertebrate species that apparently have no intracellular functions or extra cellular function such as proteins involved in blood coagulation and immune responses but if and when they gain access to the external surface of the epithelial pulmonary or gastrointestinal surface they may become infectious pathogens.

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For a virus to infect eukaryotic cells a foreign peptide or peptides on its surface must first be

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complimentary to a self-peptide on the class I MHC and then if it's successful in gaining entrance into it its RNA or DNA directs its replication.

A foreign peptide is one that isn't exposed on a class I MHC molecule but is complimentary to one that is.

When the virus infected cell replicates and it gains access to plasma in blood vessels the foreign peptides on its surface bind complimentary self-peptides on the toll like receptors of macrophages, dendritic cells and B cells and they phagocytize, disassemble them and expose the foreign peptide on the class II MHC of the dendritic and B cells to initiate the adaptive immune response.

The hypotheses proposed here are that autoimmune immune responses are initiated by virus infections when the foreign peptides on them bind to one of two complimentary peptides on the MHCs of a cell, that the phosphatidylserine (PS) molecule is exposed on the TMEM16 Fscramblase molecule in both the innate and adaptive immune responses where it generates physiologic checkpoint molecules (CPMs) that influence the outcomes of all three immune responses.

In the following we will very briefly examine inflammation, blood coagulation, the innate and adaptive immune responses and the presumptive generation of physiologic checkpoint molecules (CPMs) generated in innate immune responses that influence the generation of the innate, adaptive and autoimmune responses.

Phosphatidylserine (PS) molecules are present on the membranes of all eukaryotic cells where they are kept on their cytoplasmic surface in an energy dependent manner but when the eukaryotic cells of vertebrates are physically damaged and when pathogens breach the vertebrate's epithelial barriers PS moves to their surface.

When the vertebrate cells are physically damaged the PS moves to their surface by the TMEM16 F scramblase molecule where it activates inflammation, activates all immune cells in an innate immune response by binding to their TIM and TAM receptors and it becomes the platform upon which the coagulation cascade generates thrombin.

When pathogens infect vertebrates the foreign peptides on the pathogens bind to self-peptides on the toll like receptors on immune cells and generate an adaptive immune response that generate foreign peptide specific cytotoxic T cells (CTLs) and antibodies.

When cells die by programed cell death (PCD) and when they are lethally damaged caspase molecules direct PS exposure by the Xkr8 scramblase molecule where PS binds to TIM receptors on macrophages by the PS bridging molecule MFC-E8 and activates the phagocytosis of the PS+ cells.

Except for the macrophages that phagocytize the billions of cells that die by programmed cell death (PCD) each day the myelocytic and lymphocytic immune cells are predominantly dormant but when eukaryotic vertebrate cells are physically damaged and when pathogens with foreign peptides on their surface breach the vertebrates epithelial barriers they are activated.

Foreign peptides are those on the surface of pathogens that *aren't exposed* on class I MHC molecules but *are* complimentary to self-peptides exposed on class I MHC of eukaryotic vertebrate cells.

PS is present on the membranes of all eukaryotic cells where it's kept on their cytoplasmic surface in an energy dependent manner but it moves to their surface by the TMEM16F scramblase molecule when they are physically stressed or damaged and by the Xkr8 scramblase molecule when they die by PCD.

When cells are physically damaged calcium enters them and PS is exposed on TMEM16 F where it generates inflammation, activates *all* immune cells in innate immune responses by binding to their TIM and TAM receptors and becomes the platform upon which the coagulation cascade generates thrombin in blood coagulation.

Caspases activate PS exposure by the Xkr8 scramblase molecule on cells dying by PCD where

the PS on their surface binds to the PS bridging molecules MFG-E8 and they bind to TIM receptors on macrophages and activate them to phagocytize, disassemble and recycle their peptides.

When the foreign peptide on a virus bind to one of two or more complimentary peptides on a cell the cytotoxic T cells (CTLs) generated in the adaptive responses will have peptides on their T cell receptors (TCRs) that are complimentary to the foreign peptides on the class I MHC of the infected cells and to uninfected cells in the autoimmune response.

When the adaptive response has eliminated the virus the peptides on the TCRs of the CTLs will continue killing uninfected cells with peptides on their class I MHC that were complimentary to the peptide on the that the vi.

When the CTLs with peptides on their TCRs that are complimentary to the peptides on one of two peptides surface of the cells they infect they will.

In the CTLs generated when a virus binds to the foreign peptide on the class I MHC of a cell that has a complimentary peptide on another of its class I MHC molecules the peptide on the CTLs TCR will he peptides on the TCR of the CTLs.

The kind of cell the foreign peptide binds determines the kind of autoimmune response generated against uninfected cells as is demonstrated when it binds to a beta cell that secretes insulin.

It is also proposed that physiologic checkpoint molecules (CPMs) are generated whenever PS is exposed on TMEM16F and in autoimmune responses the

The hypotheses proposed are that autoimmune immune responses are initiated by virus infections when the foreign peptides on them bind to one of two complimentary peptides on the MHCs of a cell, that the phosphatidylserine (PS) molecule is exposed on the TMEM16Fscramblase molecule in both the innate and adaptive immune responses where it generates physiologic checkpoint molecules (CPMs) that influence the outcomes of all three immune responses.

In the following we will very briefly examine inflammation, blood coagulation, the innate and adaptive immune responses and the presumptive generation of physiologic checkpoint molecules (CPMs) generated in innate immune responses that influence the generation of the innate, adaptive and autoimmune responses.

Inflammation

Inflammation begins in adaptive immune responses when foreign peptides on pathogens bind to complimentary peptides on the toll like receptors of macrophages and dendritic cells and activate their secretion of inflammatory cytokines that stress somatic cells and expose PS on their surface by TMEM16F.

Inflammation begins in innate immune responses when PS is exposed on physically damaged cells by TMEM16F and peptides on its surface bind to TIM receptors on macrophages and dendritic cells. In both immune responses inflammation is generated when PS binds to the TIM-1 receptor on CD4 Th1 immune cells and activates their feedback secretion of inflammatory cytokines that stress somatic cells and expose PS on their surface. This was documented in 2017 when mice were infected with the Ebola virus and PS exposed on its surface produced a lethal cytokine storm. When TIM-1 knockout mice were infected by Ebola the mice survived and an inflammatory cytokine storm didn't develop. In that experiment the viral load was only minimally reduced proving that the PS on the virus, not the virus itself produces the inflammation. Inflammation is a physiologic action that amplifies adaptive immune response to respond to rapid pathogen generation but the Ebola virus is a long linear enveloped virus with PS exposed all over its surface and in the septicemia generated in an Ebola infection the PS numbers produce pathology. The same thing happens in other infections when PS exposure is excessive and also in massive trauma.

Blood coagulation

Blood coagulation begins whenever cells are stressed or damaged and tissue factor (TF) and PS are exposed with the TF initiating blood coagulation and PS amplifying it by being the

platform upon which the coagulation cascade generates thrombin [5,8]. TF activates factors IX and X and activated factor Xa changes prothrombin to thrombin and the thrombin activates PS exposure on platelets and initiates the cascade's feedback thrombin generation. The TF activated factor IX is essential for cascade function and as such is a rate limiting component of blood coagulation. Thrombin generated by the cascade binds to factor XI and activates it to bind to factor IX to maintain cascade thrombin generation and for maximum thrombin generation activated factor XIIa will bind to factor XI and activate its factor IX activation. However factor XII can't be activated intravascularly because it must bind to sulfatide exposed on the surface of activated platelets and activated platelets secrete a factor XII activation inhibitor.

When vascular walls are breached collagen is exposed and PS+ activated platelets with sulfatide on their surface bind to it and the factor XII activation inhibitor is washed away and maximal thrombin generation takes place at the breach.

Immune cell activation and autoimmunity

In an autoimmune response initiated by a virus there will be an adaptive immune response to the foreign peptide exposed on the class I MHC of an infected cell and an innate response to self-peptides on the class I MHCs of a cell when CTLs generated in the adaptive response bind to identical peptides on the MHC of non-infected cells and damage and kill them.

Adaptive immune response

In an adaptive response the foreign peptides on the surface of a virus bind to self-peptides on the surface of toll like receptors on macrophages, dendritic cells and B cells and activate them to secrete inflammatory cytokines and to phagocytize, disassemble and expose their peptides on their MHC molecules.

The inflammatory cytokines stress somatic cells and they expose PS on their surface that binds to TIM-1 receptors on Th1 immune cells and they secrete more inflammatory cytokines to amplify the innate response.

The viral self-peptides are exposed on those cells class I MHC and its foreign peptides are exposed on the class II MHC of dendritic cells and B cells.

The foreign peptides on the class II MHC of the dendritic cells bind to complimentary self-peptides on the class I MHC of CD4 and CD8 T cells and activate them.

The self-peptides on the activated CD4 cells bind to foreign peptides on the class II MHC of B cells and they secrete foreign peptide specific antibodies that cloak viruses generated by infected cell to prevent more cells from being infected.

They will also bind to pathogens and be joined there by compliment that enables their removal.

The activated cytotoxic CD8 T cells (CTLs) will have peptides on their T cell receptors that are complimentary to the foreign peptides on class I MHC of infected cells and kill them.

Innate immune responses

Innate immune responses repair physically damaged tissues and those innate responses are activated when PS is exposed by TMEM16F and it binds to complimentary peptides on the TIM and TAM receptors that are both present on the surface of each immune cell and they are activated to secrete cytokines that direct the repair.

Peptides on PS aren't complimentary to TAM receptors and must bind to complimentary peptides on the Gas6 and ProS bridging molecules and peptides on them bind to peptides on the Tyro3, AXL and Mer TAM receptors.

It proposed that TIM and TAM receptors are on/off switches that are activated by *some* PS peptides binding directly to TIM receptors on all immune cells and secreting cytokines to turn them on and *other* PS peptides binding indirectly to TAM receptors to secrete turn them off.

Other PS

It is also proposed the that individual peptides on PS bridging molecules determine which immune cells need to be turned off in innate immune

responses but that they all secrete the same off cytokine switch.

That cytokine switch has a peptide on it that is complimentary to the PS receptors on activated CTLs and macrophages and prevents them from recognizing and killing and phagocytizing physically damaged cells in innate immune responses.

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