Viral Disease, Tissue Injury, Repair and Regeneration

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Abstract

Adult stem cells present in various tissues play key roles in tissue repair and regeneration upon injury. The inflammatory responses associated with tissue damage that are caused by physical, chemical, infectious, nutritional and genetic factors activate stem cells to proliferate and differentiate. The severity and duration of the injury influence the outcome of tissue repair. Viral diseases are major public health problems and over 500 million people worldwide are affected with viral hepatitis. Virus infection of acute or chronic nature could disrupt the tissue homeostasis by altering cell function and architecture. Little is known about the effect of viral diseases on resident stem or progenitor cell population during tissue repair and the regeneration process. This review summarizes the liver-specific inflammatory and healing responses to injury and provides a detailed overview of the cellular and molecular basis of tissue regeneration following viral diseases. Understanding the behavior of resident stem or progenitor cells in response to tissue injury caused by infectious agents such as viruses can allow for the development of small molecule and cell-based therapy for tissue regeneration.

Keywords: Viral disease; Tissue injury; Adult stem cells; inflammatory responses.

Introduction

Living organisms evolved to repair or regenerate the injured tissues in order to enhance the rate of survival and fitness. Tissue injury is caused by physical, chemical, nutritional, genetic and infectious etiologies and, depending on their nature and severity, can lead to various healing responses at the cellular level. The scourge of viral disease outbreaks at pandemic and epidemic proportions shaped our evolution. Currently, over 500 million people are affected with viral hepatitis and an estimated 35.3 million are infected with human immunodeficiency virus (HIV) [1-4]. Besides, morbidity and mortality associated with seasonal influenza exert huge burden on the healthcare system and have tremendous impact on the economy [5]. Understanding host-pathogen interaction is crucial for counteracting viral diseases by development of vaccines and direct acting antiviral agents. Viral pathogens can be transmitted by person-to-person contact (aerosols, touch, contaminated blood and bodily fluids), food, water, arthropod vectors and inanimate objects. Upon entry to the host organism, viruses reach the target organs and establish localized or generalized infection.

Viral tissue tropism is determined by the cellular expression of viral entry receptors and host factors critical for completing the viral growth cycle. The liver-specific pathogen, hepatitis C virus (HCV) envelope proteins (E1, E2) have been shown to directly or indirectly interact with hepatocyte surface receptors including CD81, LDL receptors (LDL-R), scavenger receptor - B1 (SR-BI), and claudin1 [6]. The influenza virus hemagglutinin (HA) glycoprotein binds to cell membrane sialic acid for entry into upper respiratory tract cells [7]. Non-enveloped viruses, coxsackievirus B (CVB) and adenovirus-2/5 enter through the coxsackievirus and adenovirus receptor (CAR) [8,9]. Viral entry occurs through pH-dependent or pH-independent endocytosis pathway [10]. Cellular innate immune factors, such as toll-like receptors (TLRs), and retinoic acid inducible gene I (RIG-I) sense the viral pathogen associated molecular pattern (PAMP), which results in activation of IFN-alpha/beta pathways [11,12]. Inflammatory response and innate immune factors are key drivers for eliciting specific T- and B- cell mediated immune response.

Inflammation is the general response that occurs in many different organ systems in response to tissue/cell injury. It encompasses the combined effects of vascular changes and cellular reactions that have the collective purpose of removing the injurious stimuli and initiating the healing process [13]. Viral-mediated cell injury elicits acute and/or chronic inflammatory responses. Acute inflammation refers to inflammation of relatively short duration primarily characterized by the excretion of fluids and plasma proteins and the emigration of neutrophils to the site of injury by chemotraction, which engulf necrotic tissue and pathogenic microorganisms [14-17]. Hepatitis A virus and influenza virus can cause acute infection, resulting in an acute inflammatory response [18,19]. Chronic inflammation, on the other hand, refers to inflammation of relatively long duration, and is characterized by the presence of macrophages and lymphocytes, and the extensive proliferation of blood vessels, tissue necrosis, and fibrosis/scar tissue formation [13]. Chronic disease can result from infection with hepatitis B virus, HCV, and herpes viruses (Epstein-Barr virus and cytomegalovirus). Depending on the nature of the viral pathogens, the infected cell’s fate can be non-lytic, lytic, or cancerous transformation. Viral infection may cause tissue injury by triggering auto-immune responses. Pathogenesis of auto-immune diseases such as multiple sclerosis and type 1 diabetes mellitus has been linked to Epstein-Barr virus and enterovirus infections, respectively [20,21].
After inflammation, the healing process occurs either by regeneration, repair or a combination of both. Complete regeneration occurs in labile tissues that continuously divide such as the epithelia of the skin, gastrointestinal tract, and the hematopoietic system [22-24]. Viral enteritis caused by rotavirus, astrovirus and norovirus can be self-limiting and recovery of intestinal villus epithelial cells can occur [25-27]. Recovery and regeneration of upper respiratory tract lining epithelium takes place following common cold caused by rhinoviral infection [28]. Full functional regeneration can also occur in minor, non-chronic injuries to quiescent tissues such as that of the liver. Regeneration entails the proliferation of cells and tissues to functionally replace lost/damaged structures, and requires that the basement membranes of the extracellular matrix are intact. In cases in which permanent damage to the extracellular matrix is sustained, the repair process is initiated through the compensatory formation of nonfunctional scar tissue via collagen deposition. This occurs in chronic liver inflammation resulting in liver fibrosis/cirrhosis and in deep skin wounds [23,29]. As with many other processes in the body, our capacity for cellular regeneration declines with age. Understanding the complex interactions of viral infection and various host cells (inflammatory, immune and stem cells) at the systems biology level can provide new avenues to combat viral pathogens. Figure 1 presents the cell and molecular players involved in host-pathogen interaction. Though viral diseases affect various organs, we limit the scope of this review to the liver. The following sections focus on the stem cell niche, viral-mediated cell injury, and the repair and regeneration processes of the liver.

**Hepatic Cellular Composition and Stem Cell Niche**

The liver, the largest metabolic organ, carries out both exocrine and endocrine functions. The functional compartments of the liver encompass the hepatic lobule and portal triad. The portal triad consists of the portal vein, hepatic artery and bile duct. From the portal triad, blood flows through the liver sinusoidal spaces where the nutrients, metabolites and waste products are transferred to the hepatic plates across the endothelial fenestrue (Figure 2). Sinusoidal blood drains into the central vein present in the hepatic lobule. Periportal and pericentral hepatocytes execute different but complementary metabolic roles depending on oxygen zonation. The parenchymal cells which make up approximately 70% of the whole liver are the hepatocytes which along with biliary epithelial cells, originate from embryonic endoderm. Moreover, the stromal cells, hepatic stellate cells (HSCs; Ito cells), Kupffer cells (resident macrophages) and sinusoidal endothelial cells that constitute the liver have a mesodermal - embryonic origin. Hepatic stellate cells reside in the space of Disse (space between hepatocytes and sinusoidal endothelium) in adult liver and are identified by the expression of desmin and glial fibrillary acidic protein in the quiescent state [30-32].

![Figure 1: Schematic illustration of cell and molecular components involved in host-pathogen interaction. Viral-mediated injury to target cells elicits inflammatory response. Inflammatory cytokines and cells (neutrophils and macrophages) orchestrate the events of clearing dead cells, removal of pathogen and tissue remodeling which pave the way for healing by repair or regeneration. Tissue-specific stem and progenitor cells receive activation signals for proliferation and differentiation to become functional parenchymatous cells. Viral-specific immune response is mediated by antigen presenting cells, T- and B–lymphocytes.](image1)

![Figure 2: Cartoon showing the cell and molecular basis of liver injury, regeneration and repair during acute and chronic hepatitis.](image2)
In the adult liver, bipotential progenitor/stem cells called oval cells have also been reported [33]. The oval cell population was first observed in the rat liver and has been shown to have originated in biliary ductules called the canals of Hering, which are known to compose the principal stem cell niche in adult livers [34–36]. Oval cells express cytokeratin 19, CD90/Thy-1, CD34, CD133 and c-kit markers which some are shared among the hematopoietic progenitor cell population [33,37]. Self-renewing liver stem cells marked by Wnt target gene Lgr5 have been described in murine liver [38]. Using the human embryonic stem cell (hESC) differentiation system, a novel hepatic progenitor cell population expressing the KDR (VEGFR2/FLK-1) receptor was identified and subsequently verified in both human and mouse livers [39].

Liver Injury, Repair and Regeneration Processes

Throughout history, the liver has been known as the regenerative organ which dates back to Greek mythology with the well versed Blood of Prometheus. Nonetheless, its remarkable capacity for regeneration is best illustrated by recovery after partial hepatectomy. Restoration of the resected lobules has been attributed to the proliferative capacity of adult hepatocytes, which restore liver mass and function in a process called compensatory growth [40–42]. In these acute phases of injury, the hepatocytes are able to enter the cell cycle through a combined-paracrine cascade of induced cytokines and growth factors such as HGF, EGF, TGF-α, TNF-α, u-PA (plasminogen activator, urokinase) and IL-6, which are mainly generated by the surrounding non-parenchymal cells that constitute the liver [40,43–47]. Higher levels of HGF, CXCL12/SDF-1, and IGF-1 were present within the first 6 hours in the plasma of patients who underwent partial hepatectomy [48]. HGF and its receptor cMET are involved in embryonic liver development, hepatocyte differentiation and liver regeneration [49–52]. Beta-catenin signaling pathway has been shown to be critical for liver regeneration [53]. Recent evidence suggests that IL-22 and IL-17 secreting γδT lymphocytes promote regeneration of liver [54].

The growth factors stimulate hepatocytes into a primed state of cell dormancy, quiescent state and proliferate. In mild injuries, replicating hepatocytes, biliary ductule cells and stromal cells regenerate the liver [36,37]. Upon exposure, HCV replicates mainly in hepatocytes and a small proportion in mononuclear cells, biliary epithelial cells and sinusoidal lining cells [65]. The body’s immune response in the majority of patients (around 80%) is ineffective in eliminating the virus, which leads to chronic inflammation of the liver. The inefficiency of the immune response to HCV has been linked to a weak CD4+ and CD8+ T-cell response during the acute phase likely due to the immuno-suppressive effects of hepatitis C viral factors such as core, NS3 and NS5A [32,34].

Viral Hepatitis

The hepatitis C (HCV) virus is a member of the Flaviviridae virus family, and is a small (about 50 nm in diameter), positive sense, enveloped, single-stranded RNA virus. HCV is transmitted by exposure to infected blood via sharing contaminated needle and blood transfusions. In around 80% of cases, HCV infection becomes chronic [36,37]. Upon exposure, HCV replicates mainly in hepatocytes and a small proportion in mononuclear cells, biliary epithelial cells and sinusoidal lining cells [65]. The body’s immune response in the majority of patients (around 80%) is ineffective in eliminating the virus, which leads to chronic inflammation of the liver. The inefficiency of the immune response to HCV has been linked to a weak CD4+ and CD8+ T-cell response during the acute phase likely due to the immuno-suppressive effects of hepatitis C viral factors such as core, NS3 and NS5A [32,34].

Hepatitis B Virus (HBV), a member of the Orthohepadnavirus genus of the virus family Hepadnaviridae, is an icosahedral, lipid-enveloped virus containing a circular, partially double-stranded DNA genome (full-length negative strand and shortened positive strand) with a length of about 3,200 base pairs [34,38]. There are 8-9 distinct HBV genotypes that have been identified and labeled as genotypes A-I [38]. HBV is transmitted through contact with blood, semen, and other bodily fluids of an infected individual. The most common routes of infection are intravenous drug use, sexual contact, and perinatal transmission [38–41]. HBV, which targets hepatocytes, is known to be non-cytopathic. The main source of hepatocyte/liver tissue damage is the host immune response and the inflammation that results [34]. HBV infection can cause both acute and chronic infections. HBV infection in adults usually results in only acute hepatitis; while, perinatal HBV infection almost always results in chronic hepatitis. As with most other viruses, immunocompromised individuals are at higher risk for developing chronic hepatitis B [38–41].

Hepatitis A virus (HAV), a RNA virus (genus: Hepatovirus, Family: Picornaviridae), causes acute hepatitis and the infection is mostly self-limiting [66,67]. Hepatitis D virus (HDV) is a viroid-like agent consisting of a circular RNA genome. HDV replication takes place in
cells already infected with HBV since HDV uses hepatitis B surface envelope proteins to package its RNA genome. Co-infection may result in fulminant hepatitis. In hepatitis B and C, ducular reactions indicating proliferation of hepatic progenitor cells in the portal area have been reported [55,68,69]. In hepatitis C, cytokeratin 7 expressing progenitor cells in ducular reactions were correlated with fibrosis [68]. The viral-mediated biological effect on the progenitor cell population is unknown.

Perspectives

This review provides an in depth analysis of the key cell and molecular basis of the viral infection, inflammation, repair and regenerative processes of liver. New tools and technologies developed in the recent years usher an exciting era of investigation on stem cells and infectious diseases. Adult stem cells and progenitor cells are a very minor population in a tissue or organ, which poses the challenge of studying the pathophysiological effect of viral infection on stem cells. Recent discovery of induced pluripotent stem cells (iPSCs) provides an unlimited supply of defined organ-specific progenitor and mature cells which can be a very useful tool for modeling viral infections. Lineage tracing studies in animal models following viral infection can allow tracking of progenitor cell population in action during inflammatory and healing processes.

Upon injury activation of innate immune factors, DNA repair machinery, and inflammation pathways orchestrate the cell fate decision of apoptosis, cell survival, proliferation and differentiation to limit tissue or organ damage. Tissue remodeling and regenerative processes are greatly influenced by the severity and duration of exposure to the injurious stimuli. Massive tissue necrosis observed in diseases like fulminant hepatitis C/B and influenza pneumonia can lead to organ failure without having sufficient time for the regenerative process to start. On the other end of the disease spectrum, chronic or repeated long-term exposure of tissues to injurious agents in conditions such as chronic hepatitis C can provide ample chances for tissue regeneration to take place. However, in chronic conditions, exhaustion of stem cells and loss of functional parenchymatous cells lead to fibrous scar tissue formation. In order to facilitate tissue repair or regeneration through stem cell therapy or allow body's natural ability to heal, the disease causing agent has to be removed. Combinatorial therapies consisting of direct acting anti-viral agents and organ-specific stem cells have the potential to greatly improve the clinical outcomes. Further investigation can help assess the stem cell role in degenerative viral diseases and identify a therapeutic window for cell therapy interventions.

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