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Role of Bone Marrow in Pathogenesis of Viral Infections

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Bone marrow suppression is a well-recognized clinical observation documented in virus-induced human diseases [1,2]. Despite the exquisite details that have been uncovered about viruses and illness, it is unknown how the bone marrow becomes engaged and contributes to pathogenesis. It is pertinent that we understand the role of this compartment during infection because it is the root of all hematopoietic cells circulating in the peripheral blood [3]. Historically, the importance of the bone marrow in orchestrating immune cell production has been well-documented and fully-established [4]. But due to its difficulty to access, isolate and culture, peripheral blood components have overtaken the stage of investigations on the causative development of diseases. Even though peripheral hematopoietic cells and their activities are resultant of the compartment from which they derive, investigating these cells cannot tell us what is happening in the bone marrow. The interaction between the pathogen and the bone marrow compartment and how this contributes to patient symptoms is still an enigma. In the advent of escalating success in treating conditions, such as sickle cell anemia, with cells originating from the bone marrow [5], we should feel prompted to pay extra attention to the physiology of the bone marrow cells. Questions, such as, does bone marrow play a role in the pathogenic causes of viral disease? If yes, to what extent? Furthermore, how is it involved in the process? Investigating these topics will allow us to begin to dissect the role of the bone marrow in the physiological maintenance during infection and the manifestation of disease.

Bone marrow is the major hematopoietic organ, being the principal site for blood cell formation, and accounts for approximately 5% of the body weight in humans [6]. It consists of hematopoietic tissue islands and adipose cells surrounded by vascular sinuses interspersed within a meshwork of trabecular bone [7]. It has been well-established that the cellular compositions in these organs change with age [8-10]. The bone marrow compartment is composed of two cell populations: the red marrow (which is hematopoietically active) and the yellow marrow (or fatty cells). The frequencies of these two constituents can vary at any given time, depending on the age and health of the person in question [3,8,11-13]. Although at birth red marrow is dominant, it converts from hematopoietic to fatty marrow as the child ages. The red marrow begins to decrease in frequency starting at about the age of 5 years, and by the age of 20 to 25 years, marrow conversion is usually complete [3,12]. The bone marrow compartment is a highly delicate and dynamic environment; even small changes can lead to a very significant modification in the cellular constituents in the corresponding peripheral blood and tissues.

How the bone marrow contributes to cancerous cell formation has been more thoroughly investigated than other diseases. Interestingly, the incidence of most cancers peak at advanced ages, after the marrow has converted to mostly yellow, indicating that increasing apoptosis and cell senescence of the hematopoietically active cells with age likely contributes to disease development [14]. In contrast, viral infections are common among people of all ages but often seem to be concentrated in infants and children [15]. An example of one such viral infection is dengue. Although dengue virus infects people from a wide range of ages, the peak in incidence of severe dengue coincidentally occurs in the young adults, with individuals that have not completed their bone marrow conversion [16]. Thus, it is likely that the contents of the bone marrow could play a significant role in dengue pathogenesis.

Dengue has been recognized as one of the most important vector-borne human diseases in recent years [17]. It is predominant in tropical and subtropical zones but its geographical distribution is progressively expanding, making it an escalating global health problem of today. Dengue disease presents with a wide spectrum of clinical manifestations, ranging from asymptomatic, undifferentiated mild fever, dengue fever, to dengue hemorrhagic fever with or without shock, which is a life-threatening illness characterized by plasma leakage due to increased vascular permeability. The mechanisms leading to dynamic clinical presentations in dengue patients remain a mystery in spite of many decades of intensive investigations.

A couple of key clinical characteristics of dengue virus infection in patients are cytopenia, particularly platelets, and the excruciating bone pain [18]; hence, an alternative name for dengue in old communities has been "breakbone fever". These phenomena are likely to indicate that the bone marrow is either directly and/or indirectly involved in dengue manifestations. Interestingly, early bone marrow suppression has long been recognized as a common clinical feature in dengue infected patients [19]. An early investigation of dengue cases in Southeast Asia suggested that the bone marrow mass is at its nadir prior to the onset of fever and at its peak 2-3 days later (the time when symptoms become severe and patients seek professional help in the hospital) [19-21]. Cumulative data supporting the involvement of bone marrow in dengue virus infection include i) isolation of virus from autopsy bone marrow of patients dying of severe dengue [20,22,23], ii) isolation of virus from bone marrow suspensions of dengue survival patients [22], iii) the occurrence of bone marrow associated aplasia in dengue patients [1,24,25], iv) efficient dengue virus infection in hematopoietic cells in ex vivo experimental studies [26,27], and v) dengue virus replication in leukocytes derived from the bone marrow and not from other lymphatic tissues (spleen, thymus and lymph node) [28]. Furthermore, dengue virus infection has been documented following accidental transfusion of contaminated bone marrow. In this case study, the donor was at an early stage of infection and did not have any signs of illness. Fever was later noticed 2 days after the donation, indicating the early involvement of the bone marrow cells in dengue virus infection, likely prior to the development of clinical symptoms [29]. These earlier findings in humans are supported and substantiated by data derived in monkeys,

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in which the bone marrow was identified as a potential early site of dengue virus replication [30-32].

Timing is a key factor that needs to be considered when attempting to obtain accurate information about the involvement of the bone marrow in the context of dengue virus infection, and perhaps other infections as well. Since in the case of dengue virus infection, the majority of dengue affected patients do not seek help until several days after onset of clinical symptoms, studying the kinetics of bone marrow changes in human disease will be very challenging [16,19,33]. This difficulty is further complicated by the concern of increased risk of bleeding in these patients, making it clinically impractical to acquire BM samples. Even though recent evidence clearly reveals that bone marrow is highly permissive to dengue virus infection and that the hematopoietic progenitor cells appear to be the main target of the virus [32], the actual relationship between dengue virus infection and the role of the bone marrow during acute infection remains to be ascertained and information about its early involvement in virus production and pathogenesis in acute dengue disease is largely unexplored.

There are many aspects that remain unknown about the functioning of the bone marrow under pathogen attacks. For example, in vector-borne human diseases, does bone marrow sense the bite of the mosquito? How does the virus travel to the bone marrow after initial deposition at the site of the mosquito bite? There are a couple of possible explanations to the question. Platelets and/or neutrophils are often the first cells to arrive at the site of the injection or infection. Recently, data revealed that neutrophils at the site of infection/injection can capture virus in the dermis and subsequently transfer the virus to the peripheral blood and migrate to the bone marrow [34], where an interaction of virus with permissive cells occurs, resulting in an infection. Alternatively, biomolecules generated at the local site may send a warning signal to the distal organ to ask for help to defend against the local intruder. For instance, during respiratory virus infection, the lung tissue/local immune cells communicate with the primary site of hematopoiesis-the bone marrow-through cytokines, likely type I interferons. The cytokines produced then instruct cells produced by the bone marrow to migrate to the lungs to help fight off the infection [35]. However, the details of the signaling pathway and the surface markers of the population involved in stimulating the migration of cells from the bone marrow remain largely unknown, and thus warrant more investigation on the subject. If a well-developed animal model for a disease is available, our knowledge on the pathways by which the local cells and molecules communicate with the distal sterile bone marrow could significantly advance our understanding of virus clearance and pathogenesis.

With the heterogeneity of the cell composition in the bone marrow, we can envisage that many functions may be present in the bone marrow. These include but are not limited to priming of the T cells to blood-borne antigen [34,36] and phagocytosis and clearance of damaged and aged cells or cell debris [37]. The mechanisms by which these activities are initiated remain an open field to the field of bone marrow research.

It is well known that the bone marrow is composed of a highly plastic mixture of cell lineages that can vary greatly in composition from individual to individual. The unique and isolated compartment does have open access to the peripheral system, and is highly sensitive to any subtle stimulation, which may alter or modify the cellular constituents and its functional capacity significantly. It is essential that the complex cells of the bone marrow system cooperate in a well-organized manner with the various other cell lineages in orchestrating and restoring homeostasis after the stimulation by infectious agents. The plasticity of hematopoietic progenitor cells in the bone marrow gives it the ultimate authority to respond and amplify the appropriate sets of cells during an infection and restore order back to the system. And yet how this sophisticated program operates remains largely unexplored. New technology, such as CyTOF mass cytometer, that can simultaneously identify numerous molecules in one assay [38-40] may open a new avenue for future bone marrow research. Although this is an ultimate goal to get insight into how a system operates under a condition, there are many empirical avenues that can be investigated. Many scenarios are in urgent need of clarification.

OMICS publishing group has recently launched a new peer-reviewed Open Access Journal, Journal of Bone Marrow Research (JBMR), which provides a platform for researchers working on this subject to communicate their discoveries with peers as well as to other interested parties. The JBMR aims to publish translational work including scoping reviews and original articles on multi- or trans-disciplinary research to uncover the role of bone marrow in infectious diseases. Our objectives are to:

1. Identify and highlight the diversity of information and research gaps in our understanding of bone marrow and how this blocks progress towards new interventions for particular viral infections.
2. Provide a platform for the translation of new knowledge into practice, propose research priority settings and promote large scale programs to dissect the bone marrow involvement during viral infections.
3. Evaluate research results and direct the underlying important theme for the future options, choices, and decisions in bone marrow research.
4. Review a wide spectrum of subjects, methods and strategies targeted on viral infections in regards to bone marrow research.
5. Facilitate communication between clinicians, public control staff, policy makers and academic researchers, as well as bone marrow donors.

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