Viral Myocarditis
Receptors That Bridge the Cardiovascular
With the Immune System?

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Viral myocarditis exhibits different clinical phenotypes depending on the age of the patient. In pediatric patients, viral myocarditis can present as acute heart failure and cardiogenic shock, and in older patients, it often presents as chronic, slowly progressive heart failure and dilated cardiomyopathy. The severity of viral myocarditis is determined by a delicate balance between the viral infection and the inflammatory response that is engendered in the host. The commonest viral causes of human myocarditis include coxsackievirus B group and adenovirus. It is no accident that these two viruses emerged as the commonest etiological agents of myocarditis. Recent elegant work by Bergelson et al demonstrated that both of these viruses share a common cell surface receptor—coxsackie-adenoviral receptor (CAR).

CAR is a 46-kDa member of the immunoglobulin (Ig) superfamily, featuring the Ig loops maintained by disulphide bonds between appropriately positioned cysteines. The extracellular domain is the key functional component for coxsackievirus internalization.\(^2\) CAR also serves as an attachment receptor for adenovirus. However, the natural function and regulation of CAR are still relatively unknown.

The efficiency in targeting the host cell by coxsackievirus and adenovirus depends on their distinct coreceptors. Coxsackievirus B (CVB) uses the complement deflecting protein decay accelerating factor (DAF, CD55) as its coreceptor,\(^3\) whereas adenovirus uses integrin \(\alpha_v\beta_3\) and \(\alpha_v\beta_5\) as its coreceptors.\(^4\) DAF as a coreceptor serves an important function by significantly increasing the binding efficiency of coxsackievirus onto the DAF-CAR receptor complex to facilitate internalization by CAR.\(^5\)

Role of the Receptors in Viral Myocarditis
Myocarditis is a viral and inflammatory disease. The virus uses the T and B lymphocytes as part of its trafficking in the host, increasing viral load in the heart (a classic Trojan Horse scenario). The localization of the virus in the heart determines the subsequent development of the inflammatory foci in the heart, as the immune system is activated trying to clear the virus.\(^6\) Therefore, the ability of the virus to enter the target cells such as the myocyte will very much influence the subsequent course of the disease. Hence, information on the receptor repertoire in the myocytes, as studied by Ito et al\(^7\) and reported in this issue of *Circulation Research*, contributes significantly to our understanding of the pathogenesis of the disease and the corresponding clinical phenotype.

In the case of coxsackieviral myocarditis, the internalization receptor (CAR) collaborates with the attachment coreceptor (DAF), probably through a stereochemical interaction (Figure). DAF facilitates the binding of the virus onto the receptor-coreceptor complex, and CAR is responsible for the internalization of the virus to permit subsequent viral replication. As noted by Ito et al,\(^7\) DAF and CAR are part of an immune family of receptors, suggesting an interaction between cardiovascular development and immune signaling pathways. Paradoxically, these immune molecules such as CAR when expressed in the cardiovascular system are used by an external infectious agent as portal of entry into the myocyte.

How Are the Receptors Regulated?
How receptors such as CAR are regulated will be important in understanding the kinetics of the disease. It is of interest that CAR is expressed in higher quantities in younger hearts than older hearts, suggesting a developmental role. In addition, it may also explain the higher propensity of coxsackieviral infections in newborns and young children with a more clinically acute disease. The most interesting aspect of the present study suggested that the CAR receptor can be induced under immunological activation. In the present study, this was generated through an autoimmune mechanism by immunizing with myosin. The myosin autoimmune murine model is a good general noninfectious model to study the inflammatory component of myocarditis.

Thus, immune stimulation increases expression of the CAR receptor, making the target organ even more susceptible to further uptake of the virus. As suggested by Ito et al,\(^7\) CAR may in addition play a role in cell-cell communication and may further enhance the inflammatory interaction between immune cells and the myocyte and the subsequent repair process.

Because the immune system is often activated by cytokine signaling pathways, CAR may also be regulated through this mechanism. It is therefore of interest that when the immune system is specifically inhibited through targeted knockout strategy, such as with CD4\(^+/+\)/CD8\(^+/+\) null transgenics\(^8\) or through knockout of the tyrosine kinases such as p56\(^lck\) associated signal amplification pathways,\(^9\) coxsackieviral
Both CAR (coxsackievirus and adenovirus receptor) and DAF (decay accelerating factor) are molecules that function as coreceptors for coxsackievirus B entry into myocytes. As the infected host myocyte is targeted by immune cells, the inflammatory process further increases expression of the CAR receptor, thus enhancing the viral internalization capacity.

myocarditis is dramatically reduced in severity, without an increase in viral titers. This may be facilitated by a decreased upregulation of CAR, significantly impairing the kinetics of replication of the etiological viral agent.

**Could the Immune-Cardiovascular Linkage Have a Happy Ending?**

Insights into the virus-receptor interaction and its regulation by the immune system, as elucidated by the present study, further enhance our understanding of myocarditis. Inflammation can lead to increased expression of CAR, which in turn may lead to an increase in viral infection and amplify the inflammatory process. This positive feedback loop may point toward novel therapeutic strategies. Specific peptide or non-peptide blockers that interfere with the interaction of the virus with its receptor is one approach. Reduction of specific elements of the inflammatory response may secondarily decrease CAR receptor expression and, in turn, protect the host from viral myocarditis. CAR provides the first example of a unique linkage between the cardiovascular and immune system. It also opens the door to fully explore its scientific implications and develop novel therapeutic opportunities.

**References**


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