Coronary Heart Disease Risk Factors Take a Disproportional Toll on Women

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In this issue, Koupenova et al demonstrate that the transcripts of all 10 Toll-like receptors (TLRs) are expressed in platelets. Using the Framingham Heart Offspring cohort, the authors were able to identify a novel positive correlation between TLR transcript expression in platelets and coronary heart disease (CHD) risk factors, including obesity, sex, and inflammation (Figure).

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TLRs are invariant, innate immune receptors that recognize evolutionarily conserved molecular patterns expressed by pathogens or endogenous molecules associated with cellular damage. TLRs can be characterized into 2 groups based on their subcellular location and substrate specificity. Surface-expressed TLRs (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) recognize structural components (lipids and proteins), whereas intracellular TLRs (TLR3, TLR7, TLR8, and TLR9) recognize nucleic acids from pathogens..

Recent studies have begun to characterize the function of TLRs in the platelet and how they contribute to inflammatory and thrombotic processes associated with CHD risk. Interestingly, although the canonical TLR signaling pathway components are expressed in platelets, TLRs have also been shown to signal through noncanonical pathways, including integrin and immunoreceptor tyrosine-based activation motif pathways to name a few. Thus, it is not surprising that certain TLRs in platelets have been shown to have a proinflammatory and a prothrombotic effect. Ligation of TLRs, for example, may have the potential to signal in a prothrombotic manner by either directly causing (TLR9 and TLR2/1 heterodimer) or potentiating aggregation (TLR4). In addition, TLRs can modulate platelet reactivity through enhancement of thrombin generation, which has been shown to be mediated through TLR2 and TLR4. Finally, TLR7 has been shown to mediate thrombocytopenia after exposure to the encephalomyocarditis virus, a TLR7-specific ligand.

In this issue, Koupenova et al have expanded our understanding of TLRs by demonstrating that platelets have variable expression of all 10 TLR transcripts. The transcripts for TLR5, TLR9, and TLR10 are present in platelets from >80% of individuals, whereas transcripts for TLRs 1 to 4 were present in the platelets of 50% to 70% of individuals. Interestingly, <30% of individuals expressed TLR6, TLR7, and TLR8 transcripts. Unexpectedly, there was an increase in the transcript levels for all 10 TLRs in isolated platelets from women compared with men. The observed difference in TLR expression by sex may be highly informative because this may give some insight into functional differences in platelet reactivity by sex not previously considered. Furthermore, the authors were able to show that this expression difference was not attributable solely to X-linked genes because the majority of TLRs are autosomal, except for TLR7 and TLR8.

Although sex differences in the expression pattern and level of TLRs in human platelets are themselves novel, the authors were additionally able to correlate inflammatory biomarkers with an increase in the number and level of platelet TLR transcripts in a sex-dependent manner. In addition, the authors were able to demonstrate that TLR transcript expression in women, but not in men, correlates with platelet activation.

By virtue of its population and genetic underpinnings, this study has the potential to greatly expand exploration of the connections between TLRs and CHD risk factors. Future studies are required to determine how CHD risk factors affect TLR transcript expression and whether expression is affected by age or ethnicity. This study opens up the exciting possibility that the TLR transcript profile of the readily accessible platelet could be used as a diagnostic tool to monitor CHD progression. However, further work is required to determine whether TLR transcripts in platelets are predictive of CHD outcomes. Finally, although the functions of some members of the TLR family have been elucidated in platelets, this study supports a potential role for a diverse compliment of TLRs in inflammation and thrombosis.

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Disclosures

None.

References


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