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TRAUMA-INDUCED X-LINKED WHITE BLOOD CELL SELECTION CONTRIBUTES TO A SEX-BIASED INNATE IMMUNE RESPONSE IN HUMANS

Zoltan Spolarics, Yong Qin, Pena Geber

Department of Surgery, Rutgers-New Jersey Medical School, Newark, NJ, USA

Sex-related disparities in the immune response manifesting female disadvantage in autoimmune diseases whereas improved outcomes over males following injuries and infections are well known. Whereas the role of sex hormones in modulating the immune response is well accepted, the potential contribution of X chromosome (ChrX)-related sex differences in the context of common genetic polymorphisms has not been well investigated. The fact that females carry two parental ChrXs whereas males carry only one suggests sex differences in the load of common polymorphic alleles. Furthermore, random ChrX inactivation, which is unique to females, results in cellular mosaicism for the expression of X-linked polymorphic alleles, possibly causing additional sex-related differences in cellular variability. Thus, we tested whether ChrX mosaicism manifests skewed white blood cell responses following injuries in humans. Serial blood samples were analysed for ChrX inactivation-ratios (XCI-R) testing methylation at the polymorphic HUMARA locus in neutrophils and lymphocytes from female trauma patients (n=99). About a third of the patients presented trauma-induced change in XCI-R of 30% or greater over initial during the hospital course. XCI-R changes correlated with the severity of trauma, ventilator support and pneumonia. XCI-R kinetics of neutrophils and lymphocytes indicated that more marked changes occurred during the earlier phases of injury or at the onset of post-injury complications like sepsis or pneumonia. During the recovery phase, XCI-R tended to return to initial values similar to that found at admission. The findings indicate that during the innate immune response, female patients may manifest acute and reversible immune cell selection through subtle phenotypic differences driven by respective polymorphic parental ChrXs. X-linked cellular mosaicism in females with variable responsiveness to dynamically changing pathophysiological conditions, together with an apparent lack of this mechanism in males, implies differences in immuno-modulatory mechanisms, which may contribute to sex-based outcome differences in the critically ill.

Biography

Zoltan Spolarics has received his MD from the Semmelweis Medical University in 1980 and PhD degree from the Hungarian Academy of Sciences in 1989. He had postdoctoral trainings at Semmelweis Biochemistry Institute and later in the USA at the Medical College of Virginia, Richmond VA then Louisiana State University Medical Center, New Orleans LA. Since 1993, he is a principal investigator at Rutgers-New Jersey Medical School, Newark NJ, USA where he leads NIH-sponsored studies investigating various aspects of the innate immune response. He published over 80 peer-reviewed papers in reputed journals, has been serving on NIH scientific review panels and journal editorial boards, Shock and Critical Care Medicine.

spolaric@njms.rutgers.edu