

Lessons Learned from the Differential Upregulation of 2'5'-Oligoadenylate Synthetase Genes in Systemic Sclerosis

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Received date: May 05, 2015; Accepted date: June 06, 2015; Published date: June 11, 2015

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Abstract

Precise regulation of the immune system is crucial for homeostasis maintenance. Autoimmunities are complex disorders that have in common alterations in immune homeostasis, and in order to be fully understood approaches that take into consideration their complexity are needed. In systemic sclerosis patients, levels of type I Interferons and 2'5'-oligoadenylate synthetase genes are found upregulated. In 2013, an approach that quantified each individual 2'5'-OAS gene in patients revealed that there is a differential upregulation of this gene family. The hypothesis is that during the disease patient cells are refractory to circulating type I Interferons and that an unknown stimuli is differentially inducing OAS2 and OASL genes. It can be taken as an example that the complexity of the immune system and its components must be taken into consideration to satisfactory understand autoimmunities.

Keywords: Autoimmunities; Systemic sclerosis; 2'5'-OAS; Interferon

Abbreviations:

2'5'-OAS: 2'5'-Oligoadenylate synthetases; ISGs: Interferon stimulated genes

Introduction

The immune system is composed of biological agents and processes with the protection against infectious diseases being its most well-known function. Due to the complexity of the system the regulation of its components and effector activities must be precise and well-coordinated. Besides, its complexity also hints to activities that fall outside strict defense purposes. After millennia of internal and external evolutionary pressures and gain of complexity, the immune system is not only important for defense but is also crucial for homeostatic regulation [1].

Autoimmunities are a group of complex disorders that have in common alterations of the immune homeostasis. Although peculiarities can be associated to each known autoimmunity, all shares characteristics such as presence of autoantibodies and altered levels of immune molecules. Even though it is hard to determine if these alterations are causes or consequences of the disorders, investigating the immune homeostasis disruption is crucial for better understanding these diseases [2].

Systemic sclerosis is an autoimmune disease characterized by excessive fibrosis, vascular damage and presence of autoantibodies. Its causes are unknown, and similarly to other autoimmune diseases distinct profiles of immune cell populations and differential expression of immune molecules can be found when patients are compared to controls [3,4]. Of the immune molecules found deregulated in Systemic Sclerosis, two important classes are type I Interferons and 2'5'-OAS genes [5,6]. Interferons are molecules produced by infected

cells that are capable of inducing an antiviral state, acting by autocrine and paracrine ways. The effectors of Interferon actions are the products of the ISGs, a particular subset of genes regulated by signaling pathways activated following the binding of Interferons to their cellular receptors. One important class of ISGs are the 2'5'-OAS genes, that after being induced by interferons exerts their antiviral activity by inhibiting protein synthesis in the presence of double stranded RNA [7].

Interferons and 2'5'-OAS genes were first described as important immune molecules for viral infection clearing. It was only a long time after their discovery that other activities, not directly linked to antiviral responses, were described. The complexity of both systems also hints to more functions besides strictly immunological ones. Interferons are represented by several types and subtypes found in most chordates (there are three main Interferon types in humans, comprising more than 20 subtypes). 2'5'-OAS are ancient enzymes found in the genome of metazoans, composed of at least ten different splice variants of four distinct genes in humans [8,9]. All this diversity points to a multiplicity of functions and complex multilayered regulatory pathways that when disrupted can lead to, and maintain, an autoimmune disorder.

It is a big challenge to consider all the complexity of the immune system when studying an autoimmunity. Typically studies focuses on specific molecules or pathways, while assuming that all the rest are constant or unaltered. By using this approach it was possible to amass a vast quantity of information and relevant conclusions throughout the years, but at the same time a lot has been neglected. There is no simple answer on how to properly evaluate the complexity of the immune system in a study. One approach is to methodically analyze certain components of the system using simpler techniques, and then hypothesize scenarios that can be tested by subsequent refined experiments.

One example is the study of 2'5'-OAS genes in systemic sclerosis. It was already been shown that certain isoforms of OAS2 gene are found

upregulated on patients, but the broader picture concerning 2'5'-OAS genes was not known at the time [5,10]. For better understanding that, specific qPCR reactions were designed to quantify each individual human OAS gene family. When patients and controls were compared, it was seen that OASL and OAS2 genes were upregulated in patients while OAS1 and OAS3 genes were not [6]. This finding was surprising, since Systemic Sclerosis patients have abnormal circulating levels of type I, but not type III Interferons, that could be inducing all OAS genes [5]. The differential upregulation of OAS2 and OASL was not due to impairment of patients cells in expressing OAS1 and OAS3, since interferon beta treatment induced these genes as expected. The hypothesis formulated was that circulating interferons could be making immune cells refractory to interferon activity, by a desensitization mechanism, and that OAS2 and OASL genes were being induced by Interferon independent stimuli [6,11]. If that is indeed the case, other immune stimuli can be differentially inducing 2'5'-OAS genes and thus playing an important overlooked role in the disease. There is still a lot to be learned concerning each 2'5'-OAS genes isoforms functions. OAS2 has already been shown as a NOD2 binding partner, while at least one isoform of OASL negatively regulates type I IFNs [12,13]. Both these functions are important for immune homeostasis. More refined techniques, such as transcriptomic and metabolomics analysis of patients cells, will be crucial for determining the specific mechanism and its impact on the disease.

Conclusion

In conclusion, the complexity of the immune system regulation and crosstalk between its pathways makes studying autoimmune disorders difficult and challenging. Focusing on specific molecules or pathways is important, but a broader view is necessary for discovering novel regulatory aspects or new interactions between pathways and molecules. In the example given above, a simple strategy focused on quantifying each human 2'5'-OAS gene on Systemic Sclerosis revealed a differential upregulation that could not be explained by the conventional line of thought concerning Interferons and its ISGs. The hypothesis formulated was that other unconventional stimuli can be involved, opening a new line of investigation in order to better understand Systemic Sclerosis pathogenesis and hopefully reach some kind of treatment or relief medication for the patients.

Acknowledgements

I would like to thank Oliveira DB, Botelho LM, Silva LKS, Guedes ACM, Santos FPST, Bonjardim CA, Peregrino PC and Kroon EG from

Laboratorio de Virus (ICB, UFMG, Brazil), co-authors of the "Differential upregulation of human 2'5'-OAS genes on systemic sclerosis: Detection of increased basal levels of OASL and OAS2 genes through a qPCR based assay" publication [6] that was the target of this commentary article.

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