Review

Role of RUNX in autoimmune diseases linking rheumatoid arthritis, psoriasis and lupus

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Abstract

Recent studies investigating the genetic susceptibility of systemic lupus erythematosus, rheumatoid arthritis and psoriasis have revealed a potential role for the RUNX proteins in the development of autoimmune disease. A new pathway of disease pathogenesis opens new avenues of research with thousands of questions that remain to be answered. In this review I attempt to propose how the RUNX proteins might be involved in these diseases and review current knowledge on this very interesting trio of transcription factors that was previously only suspected to be involved in cancer.

Keywords: autoimmunity, repression, runt-domain, susceptibility, transcription

Introduction

The study of the genetics of complex diseases is now advancing rapidly as new genes are being discovered that are involved in susceptibility for a variety of diseases. However, more impressive is the fact that the identification of the genes and the polymorphisms involved in susceptibility is opening new avenues of study. The best example at hand is the recent identification of a polymorphism in the *PDCD1* (programmed cell death 1) gene as a susceptibility factor for systemic lupus erythematosus, coding for the immunoreceptor PD-1 [1]. The polymorphism identified, named PD1.3 and whose allele A is strongly associated with the disease, is so far the only polymorphism within the *PDCD1* gene that can provide a functional explanation for the susceptibility related to this gene. Furthermore, the same allele A was associated to diabetes type 1 [2]. Association was also identified with rheumatoid arthritis [3].

The PD1.3 polymorphism is located in the fourth intron of the *PDCD1* gene [1]. Within the fourth intron there is a sequence of 160 base pairs enriched in binding sites for various transcription factors important in hematopoiesis, suggesting that this element might act as a regulatory enhancer. Importantly, the regulator element is not conserved in the mouse (ME Alarcón-Riquelme and L Prokunina, unpublished data), suggesting that the regulation of PD-1 is different in both species. The polymorphism associated with human lupus changed a common G nucleotide to an A nucleotide, thereby disrupting a binding site for what seemed to be the *RUNX1* transcription factor. The binding was tested on a simple band-shift assay (electrophoretic mobility-shift assay) with specific antibodies, experiments that supported the notion that the associated allelic variant did not allow binding of a protein complex and that the complex included, among other proteins, RUNX1 [1], thereby providing a functional explanation for the genetic association.

The potential role of *RUNX1* was underscored by the recent finding by two groups describing polymorphisms strongly associated with psoriasis and rheumatoid arthritis [4,5], both of which, even if present in completely different genes, also disrupted binding sites for what seemed to be *RUNX1*. For rheumatoid arthritis [5], the authors investigated a complete 3-centimorgan genomic segment from human chromosome 5q31 that included the cytokine

TGF = transforming growth factor; Th = T helper; VEGF = vascular endothelial growth factor.

gene cluster, a cluster previously also linked to rheumatoid arthritis [6] and Crohn's disease [7] with a high-resolution single-nucleotide polymorphism genotyping. The search led to the pinning down of a single polymorphism disrupting the *RUNX1*-binding site within the organic cation transporter gene *SLC22A4* [5]. Furthermore, and providing a stronger case, the authors identified a preliminary association of rheumatoid arthritis with the *RUNX1* gene itself, with a SNP located in intron 6 of RUNX1 in chromosome 21q22. This is an interesting test and a first attempt to define disease pathways and identify susceptibility genes or susceptibility effects that might be epistatic, additive or independent.

Similarly, the psoriasis study analyzed a region previously identified by linkage in sibling pairs, and by thorough haplotype analysis narrowed it down to a single polymorphism (having excluded the remaining nine that showed association out of hundreds studied) that also disrupted a binding site for *RUNX1* [4]. This time the polymorphism was found in a non-coding intergenic region between *SLC9A3R1*, a solute carrier gene, and the *N*-acetyltransferase gene *NAT9*. It was impossible for the authors to determine which of the two genes was the target for the effects of the polymorphism, but *SLC9A3R1* was found expressed in skin and in T cells [4].

Thus genetics, in three studies, has led to the identification of at least four new genes potentially involved in autoimmunity. In the center, the runt-domain family of transcription factors seem to be potential major regulators.

In the studies described, the authors performed mobility assays and transfection experiments with which they could show the allelic effect of the polymorphisms on gene expression in reporter assays and their effect by co-transfection of *RUNX1*. In spite of these experiments, the possibility still remains that it is not *RUNX1* the transcription factor that is binding to the altered sites, but that it might also be any of its sisters, *RUNX2* or *RUNX3*. The reason for this is that the consensus sequence that is the binding site for the runt family of transcription factors is the same for all three members, so the artificial use of oligonucleotides or even co-transfection does not fully resolve the issue. At this point, only chromatin immuno-precipitation can directly provide an answer; with this technique we can analyze specifically which of the three transcription factors is binding *in vivo* to the target sequence in the gene of interest.

However, it is clear that the RUNX proteins have a role not yet understood in autoimmune diseases. What could this role be? The runt-domain family of transcription factors is involved in several diseases and acts on target genes in a variety of tissues [8]. The three members, RUNX1, RUNX2 and RUNX3, can be expressed in the same cell, but their binding to the consensus sequence is dependent on their relative levels and their affinity for the adaptor CBFβ (core binding factor β), with which all of the three can heterodimerize [9,10]. It is clear that each of the three RUNX proteins has different roles and that their tissue expression is different, but they might overlap in some of their functions. The runt domain is highly conserved down to *Drosophila* [11]. Indeed, the first member of the family of runt-domain transcription factors was the *Drosophila* regulatory gene runt, shown to determine segmentation patterns during embryogenesis and later found to have functions in sex determination and neurogenesis [12]. A second member, named lozenge, is required for cell patterning in the eye and for hematopoiesis. In humans the three genes are located in completely different chromosomes. RUNX1 is located in human chromosome 21, RUNX2 is located in chromosome 6, and RUNX3 is located in chromosome 1.

The runt-domain family

Generally, the runt-domain transcription factors are considered to be repressors. Most of the studies performed so far in humans include the RUNX1 protein previously known as AML1a. AML1a was originally identified because it is frequently involved in mutations and translocations associated with acute myeloid leukemia [13]. The Aml1a-related translocations have provided an important source of study for the function of RUNX1 as a repressor as well as the proteins that have been found to be forming a fusion protein in various of the translocations. The t(8;21) translocation results in a fusion protein between RUNX1 and ETO, a zinc-finger protein that is most probably a transcription factor acting as a nuclear repressor [14–16]. Further translocations have been identified, including the t(12;21) translocation resulting in the fusion of RUNX1 with TEL [17–19], also a transcription factor, and a t(16;21) translocation in which RUNX1 fuses with MTG16 (myeloid transforming gene-related protein 1) or the t(3;21) translocation involving the *Evi-1* gene [20,21].

Thus, studies on the translocations and the resulting fusion proteins that disrupt RUNX1 or the fusion partner suggest a dominant-negative effect for RUNX1. Indeed, mice made deficient for RUNX1 lack development of their hematopoietic system in a dominant fashion [22]. In humans, haploinsufficiency due to structural mutations in RUNX1 leads to familial thrombocytopenia and a greatly increased risk for the development of acute myeloid leukemia [13,23,24]. As an observation, within a family described for RUNX1 haploinsufficiency, an individual with the mutation had rheumatoid arthritis [23].

Deficiency in RUNX2 (also called AML3) leads to bone malformation and boneless mice; RUNX2 is therefore of

major importance in skeletal development and in osteoblast and chondrocyte development [25,26], although recent evidence shows that RUNX1 might also be involved in skeletal development [27] and has been found expressed in the skin and other epithelial tissues [27]. Mice made deficient for RUNX3 develop gastric cancer, and these studies have also shown that RUNX3 is involved in the development of basal root ganglia [28,29].

However, there has never been any previous evidence that the RUNX proteins are involved in autoimmunity, either in mouse models or in human studies. The main reasons for this lack of evidence are that the recently produced deficiency models have strong dominant loss-of-function effects, and that RUNX1, the only one of the three to have been studied extensively in humans, has been related to leukemias.

This suggests that the effects of the RUNX proteins in autoimmunity are much more subtle and are possibly readable only at the level of specific cellular compartments; this is in line with what is expected for complex diseases.

The RUNX proteins in immune development

Interestingly, conditional cellular models and the use of retroviral vectors have permitted the study of the RUNX proteins in more detail, although still in the mouse, and have provided evidence for the importance of the RUNX proteins in the immune system.

Both RUNX1 and RUNX3 are required in T cell development. It has recently been reported that RUNX1 is required for active repression in $CD4^{-}CD8^{-}$ thymocytes, whereas RUNX3 is required for establishing epigenetic silencing in cytotoxic lineage thymocytes [30]. RUNX3-deficient cytotoxic T cells, but not T helper (Th) cells, were reported to have defective responses to antigen, suggesting that RUNX proteins could have critical functions in lineage specification and in homeostasis of CD8-lineage T lymphocytes. In addition, RUNX1 and RUNX3 have been found to regulate the expression of CD4 during CD8 lineage commitment [31].

It has also been observed that RUNX1 inhibits the differentiation of naive $CD4^{+}$ T cells into the Th2 lineage [32]. This is done through direct influence on the main transcription factor regulating Th2 development, GATA-3.

Another interesting and recent finding is that the lack of RUNX3 in a mouse model results in eosinophilic airway inflammation. Interestingly, RUNX3 was found to be expressed in mouse mature dendritic cells and to mediate dendritic cell responses to transforming growth factor (TGF)-β [33]. The authors observed that in the RUNX3 knockout mice, maturation of dendritic cells was accelerated when induced with lipopolysaccharide or without induction, and showed an increased efficiency in stimulating T cells. It is also interesting that the skin epidermis of the RUNX3 knockout mice lacked epidermal Langerhans cells but not dendritic epidermal T cells.

RUNX3 is known to mediate lymphoid and myeloid activity of CD11a through direct interaction with its promoter, and the RUNX3 knockout mice showed aberrant expression of CD11a, CD11b and CD11c, the β_2-integrins.

The findings revealed by the RUNX3 knockout mouse might provide us with some ideas about how the involvement of the RUNX proteins could be explained in systemic lupus erythematosus, rheumatoid arthritis and psoriasis. It would be interesting to investigate the effect of the RUNX3 deficiency in another genetic backgound, to test whether a 'permissible' background would allow the development of an autoimmune phenotype.

Regulation of targets of the RUNX proteins

As mentioned previously, the RUNX proteins are transcription factors or repressors for various target genes, and their action might be modulated through many different signaling pathways exerting their affect at various cellular levels as well as at various developmental levels.

For example, RUNX2 is essential for skeletal development. It has been shown that RUNX2 is essential in osteoblast differentiation. RUNX2 regulates osteocalcin, osteoprotegerin, TGF-β receptor 1, osteopontin and collagenase 3, among others, in osteoblasts [8,34,35]. Furthermore, RUNX2 is known to regulate the expression of osteopontin, collagenase 3 and vascular endothelial growth factor (VEGF) in chondrocytes [7,36–38].

A possibility exists that susceptibility to rheumatoid arthritis and part of the development of the disease might be related to the activity of RUNX2 in these tissues and its effect on some of the target genes, many of which, such as osteopontin [34,35], collagenase 3 [39] and VEGF [37], have been shown to have altered expression or have been otherwise implicated in rheumatoid arthritis. VEGF, a mediator of angiogenesis, has been correlated with disease severity and has also been found to be involved with psoriasis [40].

Both RUNX1 and RUNX3 have mainly been found to regulate genes expressed in lymphoid and myeloid cells. Among the targets of RUNX1 are the B cell-specific tyrosine kinase BLK, the T-cell antigen receptor α, β, γ and δ chains, CD3 and granulocyte/macrophage colony-stimulating factor in lymphoid cells. The genes encoding myeloperoxidase, complement receptor 1 and $p21^{Waf1/Cip1}$ have been shown to be among the target genes for RUNX1 in myeloid cells. Of these, p21 has been found to have a role in systemic lupus erythematosus [41] in animal

models, and there is extensive literature on the role of complement receptor 1 (previously known as the C3b receptor or CD35) in lupus and even in drug-induced systemic lupus erythematosus [42,43]. No targets have been thoroughly investigated for RUNX3. A more extensive list of target genes can be found in [8].

Regulation of the RUNX proteins

Little is known about the regulation of the RUNX proteins and the pathways in which they are controlled. Most of our knowledge comes from studies of RUNX2.

Structurally, the RUNX genes are very similar. In mammals, it seems that the gene encoding RUNX3 might have been the one from which the other two evolved [11]. Each of the RUNX genes is transcribed from two promoters [8]. For instance, RUNX2 is regulated distinctively in different tissues. Activator protein 1 regulates RUNX2 through binding to FosB in osteoblasts, whereas non-fimbrial adhesin (NFA)-1 regulates RUNX2 in non-osseous cells [44–46].

RUNX2 is also regulated by TGF-β, and regulation by TGF-β is dependent on the cellular compartment [47]. TGF-β represses RUNX2 in an osteosarcoma cell line, whereas it induces RUNX2 in a myoblast precursor cell line. The effects of TGF-β on RUNX2 seem to be mediated by the Smad factors [48]. Other proteins that regulate RUNX2 are the bone morphogenetic proteins, members of the TGF-β superfamily [47]. These are also known to exert their effects through recruitment of the Smad proteins, in which case other Smads are involved. Tumor necrosis factor-α and FGF have also been shown to regulate RUNX2 [49]. In particular, tumor necrosis factor-α inhibits RUNX2.

It is interesting that retinoids bring about increased expression of the three RUNX proteins. Similarly, vitamin D3 also augmented the expression of the RUNX proteins in myeloid leukemia cells. It has recently been shown that estrogen (estradiol) enhances RUNX2 activity without changing RUNX2 expression or DNA binding affinity but through direct interaction with estrogen receptor α. Glucocorticoids have been found to inhibit RUNX2 activity. All previous work suggests that RUNX2 might be very important in bone regeneration, bone formation and repair, and it is of particular interest when considering the susceptibility to response to treatment of patients with rheumatoid arthritis or to disease severity and damage.

Very little is known about the regulation of the other RUNX proteins, and it is evident that these have profound effects at numerous levels of cellular activities.

At present it is unclear how the RUNX proteins exert their effects and how their aberrant function leads to autoimmunity and inflammation. However, a new chapter of investigation has now been opened that might lead to many surprises [50].

Competing interests

MEA-R is a shareholder or Everygene AB.

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