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RESEARCH HIGHLIGHT

AKNA: Another AT-hook transcription factor "hooking-up" with inflammation

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Previous studies highlight a key role for AT-hook transcription factors as master regulators of fundamental cellular processes involved in development, immune function, cancer, diabetes and other human diseases [1, 2]. The high mobility group A (HMGA) proteins are an important family of AT-hook chromatin remodeling proteins that orchestrate transcriptional complexes to regulate gene expression [1]. Recent studies have uncovered links between HMG AT-hook transcription factors and inflammation [1-8]. Moreover, emerging evidence also indicates that inflammatory pathways and downstream effects on tissues are important precursor lesions in diverse cancers [1]. Indeed, several previous studies suggest that HMG-AT-hook transcription factors drive inflammatory pathways to promote a poorly differentiated stem cell phenotype, tumor progression and refractory disease [1-9]. Thus, a better understanding of transcriptional networks downstream of AT-hook proteins should provide insights, not only into normal development, but also relevant to cancer and other diseases associated with inflammation and a stem-like state.

In a paper recently published by *Cell Research*, Ma and colleagues report the effects of targeted deletion of the murine *AKNA* gene, which encodes a hypothetical AT-hook transcription factor [10]. They discovered that loss of *AKNA* results in small, frail mice that die suddenly at 10 days of life with diffuse inflammatory lesions. This phenotype fits well with the protein's name, AKNA, which means "mother" and originates from Inuit and Mayan mythology where AKNA is the goddess of fertility and childbirth. The mice lacking AKNA are weak and fail to thrive, as expected for "motherless" mice (Figure 1). At necropsy, they have systemic inflammation with marked, neutrophilic infiltrates within the lungs and diffuse alveolar damage. Interestingly, a small size was observed in mice null for *HMGA2*, another AT-hook transcription factor important in development and neoplasia [11]. The *HMGA2* knockout mice had decreased fat, while transgenic mice expressing a truncated *HMGA2* have increased fat tissue and lipomas [12, 13]. It is not known if fat content was decreased in the *AKNA* knockout mice, although their size was clearly decreased in the homozygous knockout state.

Prior to this study, it was suspected that AKNA plays a role in mediating immune responses because it was discovered in lymphoid tissues, including B and T lymphocytes, natural killer cells and dendritic cells [14]. During B-cell differentiation, *AKNA* is expressed primarily in lymphocytes located in the germinal centers at a stage in lymphoid development, in which receptor and ligand interactions are crucial for B-cell maturation [14]. Although structural data are not yet available, the human AKNA protein is predicted to include an amino-terminal and carboxyl-terminal AT-hook DNA binding domain, while its murine ortholog has an amino-terminal AT-hook domain and a carboxyl-terminal AT-hook-like motif (ALM; Figure 1). Previously published *in vitro* experiments show that AKNA binds to AT-rich regions in both the *CD40* and *CD40 Ligand* promoters to activate their expression and promote B-cell differentiation. Interestingly, the human *AKNA* gene is located within the FRA9E region of chromosome 9q32, a common fragile site linked to loss-of-function mutations associated with inflammatory and neoplastic diseases. In addition, single nucleotide polymorphisms within the human AKNA AT-hook motif are associated with an increased risk of cervical cancer [15]. This association of AKNA with cervical cancer (and thus HPV infection) supports the hypothesis that AKNA functions in inflammation and cancer.

The thoughtful and well-executed studies performed by Ma and colleagues represent an important advance to our understanding of AKNA in development, myeloid hematopoieisis and inflammatory signals [10]. In wild-type

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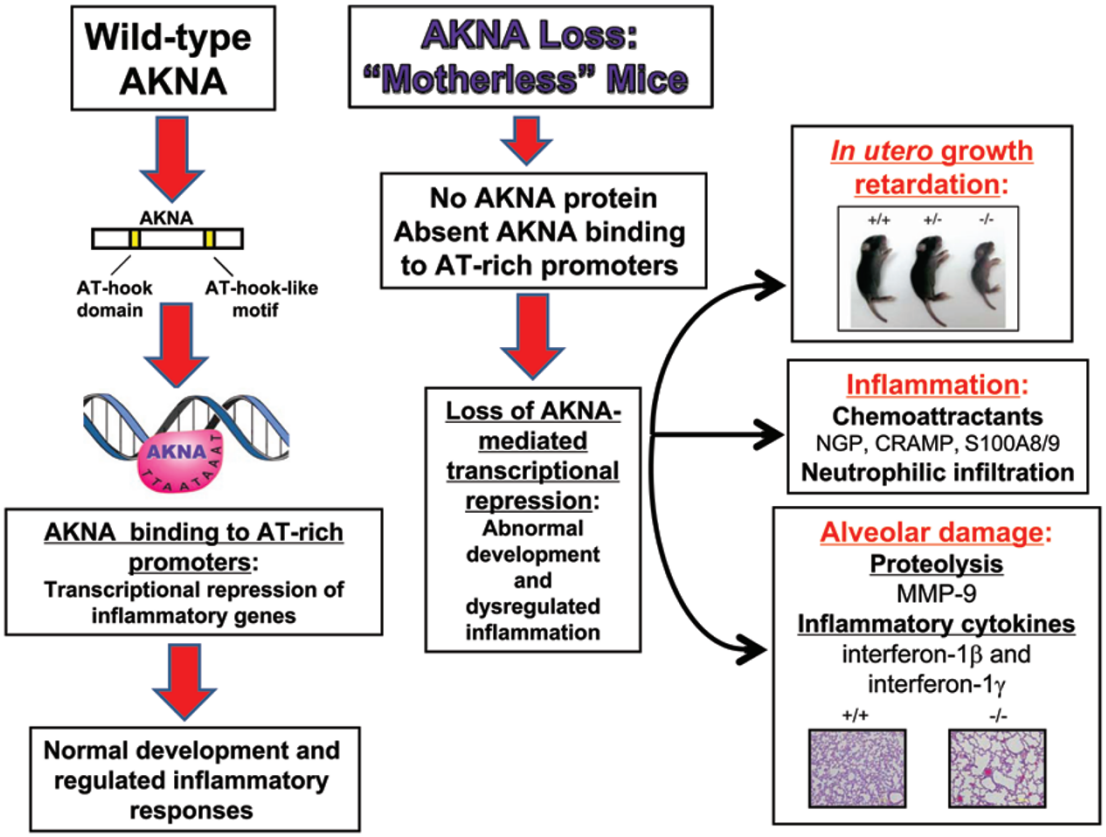

Figure 1 AKNA function in development and inflammation. *AKNA* knockout mice fail to thrive and die with systemic inflammation, neutrophilic infiltration into the lung tissue, and destruction of the alveolar tissue. NGP: neutrophilic granule protein; CRAMP: cathelin-related antimicrobial peptide.

mice, *AKNA* expression is enriched in the neutrophil fraction of the bone marrow. In contrast, neonatal *AKNA* knockout mice had higher neutrophil counts in the bone marrow and peripheral blood by over 2-fold compared to their wild-type counterparts. Moreover, CD45 blood cells isolated from the lungs were also enriched for neutrophils in the knockout mice. Although AKNA was first discovered in developing lymphoid cells, there were no alterations noted in other leukocytes. Because AKNA functions as an AT-hook transcription factor, Ma and colleagues investigated expression of a broad range of genes related to neutrophil function using cDNA arrays. They found a significant enrichment in genes encoding cytokines, proteases and chemotactic factors in the knockout mice, consistent with repression of these genes by AKNA. The authors went on to confirm that expression of the neutrophil collagenase, *matrix metalloproteinsase-9* (*MMP-9*), is increased in the knockout mice, and MMP-9 has been implicated in alveolar damage and inflammation. MMP genes (*MMP-2, MMP-9, MMP-13*) are also downstream of the HMGA1 AT-hook transcription factor [6-8, 16], although they are induced rather than repressed. This study also showed that inflammatory cytokines (interferon-1β, interferon-1γ) and inflammatory proteins (neutrophilic granule protein, cathelin-related antimicrobial peptide, S100A8/9) are induced in the *AKNA* knockout mice and likely contribute to the alveolar damage.

These interesting studies raise important questions and further avenues for investigation. For example, the enrichment of AKNA in wild-type neutrophils and excess neutrophil counts in knockout mice suggest that AKNA is important in the negative regulation of myeloid differentiation or neutrophil survival. It will be interesting to determine if loss-of-function mutations, polymorphisms or epigenetic alterations in *AKNA* contribute to myeloid diseases, such as myeloproliferative neoplasms. In addition, the prominent inflammatory response in *AKNA* knockout mice suggest that restoring AKNA function could protect against some of the deleterious effects of inflammation. Interestingly, a prior agent (FR900482) was developed to block HMGA1 function by covalently linking HMGA to AT-rich DNA binding sites. It was found to link other AT-hook proteins to DNA and resulted

in inflammation and a severe vascular leak syndrome, which mimics some of the findings in the *AKNA* knockout mice. This suggests that FR900482 could also interfere with AKNA function [17]. The association of *AKNA* polymorphisms and cervical cancer [15] also suggests that loss of AKNA function could potentially enhance HPV-mediated inflammation to promote cervical carcinogenesis. Fortunately, the present study provides a useful model to further investigate the role of AKNA in myeloid function, inflammation and neoplastic transformation.

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