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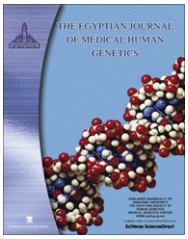

REVIEW

Models to explore the molecular function and regulation of AIRE

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Abstract Mutations in the *Autoimmune Regulator* (*AIRE*) gene are responsible for Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED). Within the thymic medulla, AIRE regulates the expression of a large number of tissue-specific self-antigens (TSAs) and the recognisation of these TSAs by auto-reactive T-cells is a prerequisite step for thymic negative selection. APECED patients will therefore develop multi-organ autoimmune disease because of the defective role of AIRE in thymic negative selection. Aire-deficient mice also develop multi-organ autoimmune disease and in this review we will focus on how both animal and cellular models have been used to dissect biochemical function of AIRE/Aire which is an essential step toward the understanding disease pathogenesis.

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1. Introduction

Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED) (also known as Autoimmune Polyglandular syndrome 1 – APS1) is an autosomal syndrome, diagnosed by the occurrence of two components of the clinical triad of chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency (Addison's disease) [1–3], and was first reported in 1946 [4]. A wide variety of secondary disorders have been identified in APECED patients, but as these manifest with lower incidences, they are not required for diagnosis of APECED. These other clinical diseases include a variety of autoimmune endocrinopathies, ectodermal dystrophies and gastrointestinal diseases (Table 1), as well as Sjögren's syndrome and keratoconjunctivitis. APECED patients also have a high incidence of squamous-cell carcinoma of the oral mucosa [1,2,5–10].

Studies reporting in 1997 had identified mutations in the *Autoimmune Regulator* (*AIRE*) gene as the causative factors of APECED [11,12]. Since then, a wide variety of different models systems have been used to investigate both human AIRE and murine Aire, varying from *Aire* knockout mice, developed as a systemic model to mimic APECED, to cell lines expressing recombinant AIRE or Aire and derivative variants, to in vitro methods using purified proteins. Over the course of these studies, AIRE/Aire has been identified to play an important role in negative selection in the thymus and the development of central tolerance. Model systems to study AIRE/Aire are therefore important, not only in the context of APECED, but also as a single causative gene disease model that can be used to discern key regulatory aspects of the central tolerance mechanism. Here, we review the models systems used to study the regulation and biochemical function of AIRE and Aire, what we have learned from these, and discuss the relevant merits and limitations of each system.

1.1. Tissue and cellular distribution of AIRE/Aire

The knowledge of the tissues and cells displaying AIRE/Aire expression (summarised in Table 2) can be particularly useful when making decisions upon which model system to use for further functional studies into AIRE/Aire. If using mice, these decisions can include which tissues to investigate in the study, or if using cell lines, whether to choose a cell line derived from a tissue that expressed AIRE/Aire natively, or to use a cell line identified to have some degree of AIRE/Aire expression.

Thymic expression of AIRE/Aire at both the RNA and protein level has been confirmed in both human and mice and identified in several other tissues across many studies investigating AIRE/Aire expression. However, it must be noted that the majority of studies investigating AIRE/Aire expression used mice, predominately the C57BL/6 strain, although Aire expression in the BALB/c, CD1, NIMR (Naval Medical Research Institute), NOD (Non-Obese Diabetic) and TRAMP (TRansgenic Adenocarcinoma of the Mouse Prostate) mice has been explored. Additionally, approximately half of the studies investigating extra-thymic AIRE expression in humans only examined PBMCs (Peripheral Blood Mononuclear Cells).

The reported extra-thymic expression of AIRE/Aire has proven to be much more contentious than that of thymic expression, as there has been an element of disparity between the different studies, with a recent review discussing these extra-thymic AIRE/Aire expression studies in more depth [13]. A major contributory factor to these differences between reports is the sensitivity of the assay used to detect AIRE/Aire expression. This is most clearly seen when certain studies using whole tissue homogenates could not detect AIRE/Aire in certain tissues, yet techniques that were able to detect AIRE/Aire at the cellular level, identified AIRE/Aire expression in specific cell sub-types of these tissues, typically either epithelial cells or cells of the myeloid lineage. Additionally, AIRE/Aire expres-

Table 1 Diseases associated with APECED that are not part of the diagnostic triad [1,2,5–10].

Type of disease	Disease
Autoimmune endocrinopathies	IDDM, thyroid diseases, pituitary defects and hypergonadotrophic hypogonadism
Ectodermal dystrophies	Alopecia areata, vitiligo, keratopathy, nail and dental enamel dystrophy
Gastro-intestinal diseases	Pernicious anaemia, malabsorption, cholelithiasis, hepatitis and chronic atrophic gastritis