Mouse models of alopecia areata: C3H/HeJ mice versus the humanized AA mouse model

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Abstract

The C3H/HeJ model has long dominated basic AA in vivo research and has been used as proof-of-principle that Janus kinase (JAK) inhibitors are suitable agents for AA management in vivo. However, its histological features are not typical of human AA, and it is questionable whether it is sufficiently clinically predictive for evaluating therapeutic effects of candidate AA agents. Instead, the humanized mouse model of AA has been used to functionally demonstrate the role of key immune cells in AA pathogenesis, and to discover human-specific pharmacologic targets in AA management. Therefore, we advocate use of both models in future preclinical AA research.

INTRODUCTION

The mainstream autoimmunity research community has been slow to recognize and acknowledge that the hair loss disorder, alopecia areata (AA), is one of the most common human autoimmune diseases (Inui et al., 2013; Gilhar et al., 2012) prevailed in incidence and prevalence only by type 1 diabetes mellitus and rheumatoid arthritis, the clinical and psychosocial importance of this disease is notoriously underestimated, since AA is neither life-threatening nor recognized to be life-shortening or physically crippling. However, patients affected by AA, namely by its maximal variants, alopecia areata totalis or universalis, often experience AA as a psychologically devastating illness, whose burden of disease is very substantial (Gilhar et al., 2012; Matzer et al., 2011; Monselise et al., 2013). This is aggravated by the fact that there is no fully satisfactory, universally effective therapy

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available for the established disease, nor convincing management strategies for the reliable prevention of AA progression (Harries et al., 2010; Paus et al., 2018).

These facts alone call for clinically relevant AA research models, in which the as yet insufficiently understood pathobiology of AA can be systematically and mechanistically dissected, and in which new AA treatment and prevention strategies can be explored in vivo at the preclinical level, ideally with good predictive value for the outcomes that can realistically be expected in AA patients. Mouse models have provided invaluable research tools for dissecting the roles of extrinsic and intrinsic factors and various underlying immune pathologies in various autoimmune skin diseases (Yu et al., 2015,2018). Lessons that have been learned from mouse models for psoriasis (Nakajima et al., 2018; Jin et al., 2018; Mykicki et al., 2017), atopic dermatitis (Nakajima et al., 2019; Lin et al., 2018; Yamada et al., 2018) and vitiligo (Riding et al., 2019) have greatly advanced our understanding of disease pathogenesis, and for exploring novel therapeutic strategies at the preclinical level.

According to the literature, there are at least 20 models for psoriasis, 19 for atopic dermatitis, and 11 for vitiligo, but only three for AA. Since one of the latter, i.e. the "Dundee experimental balding rat (DEBR)" model (McElwee et al., 1995,1999), is no longer available, this has left us with just two in vivo models of AA: the most widely used murine AA model that has long dominated preclinical AA in vivo research, i.e. aging C3H/HeJ mice (Sundberg et al., 1994,1995; de Jong, et al., 2018; Dai et al., 2016; Shin et al., 2018), in which spontaneously developing AA-like lesions can be studied, and the humanized AA mouse model (Gilhar et al., 2013, 2016).

The C3H/HeJ mouse model has produced many novel results with important implications for human AA by accessing the powerful tools of mouse genetics (de Jong et al., 2018), and has helped to identify candidate autoantigens (Wang et al., 2016) and novel treatment strategies (Dai et al., 2016; Jalili et al., 2018; Xing et al., 2014). It also provided insight into the role that could be played by psychoemotional stressors and associated neuropeptides in AA pathogenesis (Paus and Arck,2009; Zhang et al., 2009; Siebenhaar et al., 2007; Peters et al., 2007), and has confirmed the key role of IFN-γ in AA pathogenesis (Ito et al., 2004; Paul et al., 2006). Advanced variations of this model that accelerate the development of AA by transplanting lesional skin from older mice to young ones (McElwee et al., 1998) or that transfer draining lymph node-derived cells from affected older to as yet unaffected young C3H/HeJ cells (Wang et al., 2015) have further facilitated the use of is murine AA model.

The C3H/HeJ mouse model was also used to identify key immune cell and molecular principles in murine AA and proof-of-principle that Janus kinase (JAK) inhibitors are suitable agents for AA management in vivo, since both IFN-γ and IL-15 signal via the JAK pathway, thus rendering JAK inhibitor therapy a highly promising intervention strategy in AA management (Xing et al., 2014; Phan and Sebaratnam, 2019; Wang et al., 2018). However, their potential adverse effects deserve to be more rigorously contemplated and evaluated, especially when JAK inhibitors are systemically administered long-term to children (Gilhar et al., 2019).

Despite it undisputed usefulness for and major contributions to preclinical AA research, the C3H/HeJ mouse model carries a number of important disadvantages that are often ignored, yet must be kept in mind (See Table 1). These include a major constitutive TLR signaling defect (Sundberg et al., 1994; Kamath et al.,2005) that is absent in AA patients, and alopecic lesions induced itch-related grooming behavior-induced (Sundberg et al., 1994; King et al., 2014). A key disease-promoting "danger" signal in AA pathobiology, the NKG2D agonistic ligand, MICA (Ito et al., 2008; Petukhova et al., 2010; Li et al., 2016), is strikingly absent in mice (the murine homolog protein has only 27% amino-acid identity with human MICA) (Sundberg et al., 1994). Moreover, the histological features are not typical for human AA (Sundberg et al., 1994; McElwee et al., 1998), since in the murine AA-like phenotype the inflammatory cell infiltrate extends to the distal follicle between the hair bulb and sebaceous gland, sometimes reaching the bulge, whereas human AA is characterized by a largely peribulbar lymphocytic infiltrate (Sundberg et al., 1994; King et al., 2014). Additionally, these mice cannot serve as a valid model for evaluating therapeutic effects of selected immunoinhibitory agents of interest in AA, such as Kv1.3 blockers because the K+ channel expression pattern of mouse T cells is different from that of human T cells (Beeton et al., 2006). It has been argued that, given the major differences between the immune systems of mice and humans (Zschaler et al., 2014), spontaneous models of autoimmunity that arise in mice do not satisfactorily recapitulate the human condition, and thus make the development of new therapeutic strategies that will also work in the human system particularly challenging (Walsh et al., 2017). Unsurprisingly, there is growing concern that laboratory mice do not reflect relevant aspects of the human immune system, which may account for failures to translate disease treatments (Beura et al., 2016).

Furthermore, the major differences between non-conventional T cells populations in humans and mice must be taken into account, when using mice as preclinical models of human disease (Zschaler et al., 2014). For example, there are several distinct subsets of γδ T cells in mice and humans, but mouse and human subsets have notably different TCR use, antigen reactivity and patterns of tissue homing (Godfrey et al., 2015). Buscher et al demonstrated that mouse models failed to account for the natural diversity in human immune responses and as a result, insights gained in the lab may be lost in translation (Buscher et al., 2017).

Therefore, it constituted an important advance in the field when lesional human skin from AA patients was successfully transplanted onto SCID mice (Gilhar et al., 1998, 2001,2002). This permitted one, for the first time, to study and experimentally manipulate the AA-affected human target organ directly in a preclinical in vivo-setting. Moreover, this model confirmed the proposed key role of CD8+ T cells and of anagen HF-derived autoantigens in AA (Paus et al., 1993,2018) and the importance of CD4+ T cell help for developing a maximal AA phenotype (Gilhar et al., 2002,2003). However, this model has not been adopted by the field, since it is too unpractical, since it requires the availability of substantial amounts of diseased human scalp skin from AA patients as well as autologous, intracutaneous T cell populations from lesional skin (Gilhar et al., 1998).

Therefore, a more practical "humanized" mouse model of AA with a wider range of applications had been developed. Helpful leads for this came from the prior observation that the intracutaneous injection of PBMCs enriched in cell populations that express NK cell

markers into split-thickness transplants of healthy human corporeal skin onto beige SCID mice (which lack T, B, and have a low level of NK cells (Thomsen et al., 2008) suffices to induce psoriasis (Nickoloff., 1999; Guerrero-Aspizua et al., 2010; Nousbeck et al., 2011; Bracke et al., 2016).

In the new model AA-like hair loss lesions are induced in normal, full-thickness human scalp skin transplanted onto SCID beige mice by injecting autologous PBMCs enriched for NKG2D+/CD56+ cells treated stimulated with IL2 (Gilhar et al.,2013a, 2013b). Given that PBMCs from the same patient are used who has donated the scalp skin xenotransplants, a graft-versus-host scenario, which would anyway not generate an AA phenotype but a permanent, cicatricial alopecia, is avoided (Gilhar et al., 2016).

Using this model permits one to circumvent many of the disadvantages of the C3H/HeJ AA model, as they do not apply to the humanized one (Table 1). This should encourage investigators to widely use the humanized AA model, e.g. as a second step after initial screening experiments in C3H/HeJ mice, so as to optimize preclinical AA in vivo research and its predictive power for clinical outcomes. Moreover, this in vivo model should facilitate at least initial progress in the long- overdue challenge to dissect which role human hair follicles and their immune privilege actually play in the establishment, maintenance, and collapse of peripheral autoantigens (Oelert et al., 2017).

By using the humanized AA mouse model, it has been elucidated that AA pathogenesis in human skin is also affected by unconventional T cell subtypes such as NKT, iNKT10, ILC1, γ/δ-T and γ/δ-Tregs cells, whose numbers are significantly increased in AA compared to healthy human skin (Laufer et al., 2019; Ghraieb et al., 2018; Kaufman et al., 2010), whose likely role in AA pathobiology had previously escaped murine AA research. Since the experiments demonstrated that non-conventional T cells may play a role in human AA (Laufer et al., 2019, Ghraieb et al., 2018), they suggest that targeting these immunocytes offers new opportunities for innovative therapeutic intervention. The humanized mouse model has been used to discover human specific pharmacological targets such as the potassium channel Kv1.3 (Gilhar et al., 2013). In addition, the model demonstrated both preventive and therapeutic effects of α-galactosylceramide (α-GalCer), which stimulates IL-10 production by iNKT cells and their expansion (Ghraieb et al., 2018), thus introducing a promising a new candidate treatment strategy into translational AA research. Finally, in vivo-results in the humanized AA mouse model elegantly recapitulate the reported differential clinical trial results in AA patients with the JAK inhibitor, tofacinitib versus the PDE4 inhibitor, apremilast (Liu et al., 2017; Mikhaylov, et al., 2019): just as in AA patients, poor therapeutic effects were seen in the humanized AA mouse model with apremilast, contrasted by a strong therapeutic effect of tofacinitib, was also shown (Gilhar et al., data presented at the conference; manuscript has been submitted).

CONCLUSION

In summary, we advocate to make it a routine practice in future preclinical AA research to use both the C3H/HeJ (e.g. for screening purposes) and the humanized AA model as

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perfectly complementary investigation tools, and to test new candidate AA therapeutics also in the humanized AA model before entering into clinical trials.

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Abbreviations:

AA	alopecia areata
PBMCs	peripheral blood mononuclear cell
JAK	Janus kinase

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Table 1.

Differences between C3H/HeJ and humanized AA mouse model

Typical properties	C3H/HeJ mice[@]	Humanized AA mouse model
Ease of use	Basic surgical skills	Advanced surgical skills
Cost	Relatively low	Relatively high
Convenience	Good	Difficult to find donors willing to provide both scalp skin and blood
Grooming-induced hair loss	Present	Absent
Predictiveness	Unclear	Good
Disadvantages	1. The histologic feature is not characteristic to human AA 2. Absence of MICA, a recognized pathogenic key NKG2D ligand in human AA 3. Mouse-specific hair follicle immunopathology	1. Need specific conditions 2. Lack of genetic background 3. Small area of scalp skin xenotransplants
Advantages	Can easily be employed as first stage assay for in vivo candidate drug testing, even though a negative outcome may not be predictive	1. The histologic feature is characteristic to human AA 2. Mimics human AA more closely than any other animal model, good predictive power

[@]=skin graft-induced hair loss variant (McElwee et al., 1998)