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Mathematical model for alopecia areata

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HIGHLIGHTS

- We develop a model to explore the dynamics of alopecia areata (AA).
- The model reflects interactions between hair follicles and the immune system.
- Interferon-γ and immune privilege guardians govern disease development and recovery.
- Our results agree with the immune privilege collapse hypothesis for AA pathogenesis.

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ABSTRACT

Alopecia areata (AA) is an autoimmune disease, and its clinical phenotype is characterized by the formation of distinct hairless patterns on the scalp or other parts of the body. In most cases hair falls out in round patches. A well-established hypothesis for the pathogenesis of AA states that collapse of hair follicle immune privilege is one of the essential elements in disease development. To investigate the dynamics of alopecia areata, we develop a mathematical model that incorporates immune system components and hair follicle immune privilege agents whose involvement in AA has been confirmed in studies and experiments. We perform parameter sensitivity analysis in order to determine which inputs have the greatest effect on outcome variables. Our findings suggest that, among all processes reflected in the model, immune privilege guardians and the pro-inflammatory cytokine interferon-γ govern disease dynamics. These results agree with the immune privilege collapse hypothesis for the development of AA.

1. Introduction

Alopecia areata (AA) is a noncontagious disease which causes loss of hair on the scalp or other parts of the body. Males and females of different ages and ethnicities can be affected, and about 2% of the U.S. population suffers from the disease (Gilhar et al., 2012). Alopecia areata causes frustration for patients and negatively impacts their social lives (Kalabokes, 2011). The most common clinical presentation is patchy alopecia characterized by the formation of round or oval hairless lesions (Gilhar et al., 2012; Alkhalifah et al., 2010a). In the majority of cases hair loss is not permanent, and there is a potential for regrowth. However, at present there is no cure or preventative measure for AA. Existing remedies have only temporary effect, so when treatment is discontinued relapse is very frequently observed. Also, there is no universally accepted remedy that would work for every patient which often makes disease management problematic. Immunosuppressants are most frequently used to treat the disease, and these can be given in the form of pills, injections, or ointments (Gilhar et al., 2012; Alkhalifah et al., 2010b; Kutner and Friedman, 2013). When such remedies fail to be effective, there are patients who even try treatments from alternative medicine such as acupuncture, rubbing lesions with garlic and herbs, or taking vitamin supplements (Hajheydari et al., 2007). In some cases, spontaneous recovery could also occur (Gilhar et al., 2012).

There has been controversy as to what causes AA. Prevalent hypothesis is that AA is an autoimmune disease, so hair loss occurs due to an immune system response directed against autoantigens synthesized in hair follicles (Giordano and Sinha, 2013; McElwee et al., 2013). In producing hair, follicles go through a natural constantly repeating cycle comprising three phases: anagen (growth phase), catagen (regression phase), and telogen (resting phase), and AA interrupts the growth phase (Gilhar et al., 2007; Ito et al., 2004). In addition, hair follicles are among the body sites that enjoy immune privilege, so normally hair follicles are protected from immune system attacks (Gilhar, 2010; Ito, 2010). Because of this reason, it is believed that the pathogenesis of AA involves collapse of hair follicle immune privilege (McElwee et al.,

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2013; Ito et al., 2004; Paus et al., 1994). However, the interactions and events occurring during disease onset as well as during relapse and remission are still not completely elucidated (McElwee et al., 2013).

Genetic factors associated with AA have been explored through a computational model (Catanzaro et al., 2010), and the hair cycle has been simulated with a cellular automata model (Halloy et al., 2000, 2002) as well as ordinary differential equations (Al-Nuaimi et al., 2012) and stochastic differential equations (Murray et al., 2012). While these models capture important characteristics of the disease, namely, genetic predisposition, circular lesion pattern, and hair cycle disruption, they do not provide an insight into the interactions between hair follicles and the immune system. Also, some mathematical models exist for animal autoimmune conditions that damage immune-privileged sites, such as experimental autoimmune uveoretinitis, which affects the eye (Nicholson et al., 2012), and experimental autoimmune encephalomyelitis, which affects the brain (Borghans et al., 1998). However, to our knowledge, there have not been previous attempts to mathematically model an autoimmune reaction in the hair follicle environment. This is why, to aid in the effort of better understanding AA development and recovery, we construct a mathematical model that includes immune system constituents and hair follicle immune privilege agents.

The structure of our study is as follows. Section 2 discusses immune privilege of hair follicles and presents the immune privilege collapse hypothesis for disease pathogenesis. We also elaborate on the hair growth cycle, and how it is affected by AA. Section 3 first presents the conceptual formulation of our mathematical model. Then, in Section 3.1, we introduce the full system of equations, and in Section 3.2, we reduce the model in order to make it simpler to analyze. In Section 3, we explore the qualitative behavior of the reduced model through simulations, parameter sensitivity analysis, and linear stability and bifurcation analysis. Finally, Section 4 concludes the paper with a discussion of our findings, and how they pertain to treatment strategies for AA.

2. Alopecia areata and immune privilege

Immune privilege (IP) is a temporary state established only when follicles make pigmented hair because this is when autoantigens are produced (Gilhar et al., 2012; Ito, 2010). Furthermore, IP is restricted to the follicle's lower part which is called hair bulb and constitutes the hair production and pigmentation machinery (Paus et al., 2005). Immune privilege is established and maintained through the secretion of immune privilege guardians such as transforming growth factor-β (TGF-β) and α-melanocyte-stimulating hormone (α-MSH) (Ito et al., 2004; Ito, 2010; Paus et al., 2003). These immunosuppressive substances, synthesized in hair follicles, downregulate the expression of MHC class I molecules in the hair bulb and inhibit lymphocyte accumulation and activation (McElwee et al., 2013; Ito et al., 2004; Paus et al., 2005, 2008). So, IP serves to prevent the immune system from recognizing autoantigens made in the hair bulb during hair production and pigmentation (Gilhar et al., 2007). An AA-affected follicle loses its immune privilege, and as a result its hair bulb becomes MHC class I-positive. Also, a significant amount of leukocytes migrate to the diseased hair follicle (Gilhar et al., 2007; McElwee et al., 2003, 2002).

Hair follicles are organs that constantly cycle throughout a person's life (Al-Nuaimi et al., 2012, 2010; Paus and Cotsarelis, 1999; Millar, 2002). Alopecia areata disrupts this natural cycle, but it does not cause damage to hair follicles' structure, so affected follicles do not lose their capability to produce hair (Gilhar et al., 2012, 2007). The hair follicle cycle has three stages: anagen, catagen, and telogen (Al-Nuaimi et al., 2012, 2010; Paus and Cotsarelis, 1999). Anagen is the active growth phase during which pigmented hair is produced. During catagen, hair growth stops, and the follicle shrinks due to apoptosis of its bulb keratinocytes. Throughout telogen, the hair follicle is dormant. Production of a new hair shaft commences at the end of telogen, and as this new fiber grows, the old one is pushed out of the hair canal and discarded (Al-Nuaimi et al., 2012, 2010; Paus and Cotsarelis, 1999). The three cycle phases have different lengths on average: anagen lasts 2–5 years, catagen 3–6 weeks, and telogen 3–5 months (Al-Nuaimi et al., 2012; Bergfeld and Mulinari-Brenner, 2001). Almost always, hair follicles get affected by AA when they are in anagen. The infiltrates of leukocytes observed in diseased hair follicles cause these follicles to exit anagen much earlier than normal and enter catagen. On the other hand, AA does not interfere with the lengths of catagen and telogen. After affected hair follicles exit anagen prematurely and go through catagen and telogen, they could re-enter the growth stage. However, if by that time immune privilege has not been restored, anagen would again have significantly shortened duration (Gilhar et al., 2007).

The pro-inflammatory cytokine interferon-γ (IFN-γ) plays a crucial role in the premature termination of anagen and consequent induction of catagen (Freyschmidt-Paul et al., 2006; Ito et al., 2005). Evidence from experiments also shows that autoreactive $CD4^+$ and $CD8^+$ T-cells/$NKG2D^+$ cells are involved in the pathogenesis of AA, and that hair loss results from cooperative activities of these lymphocytes (Gilhar et al., 1998, 2002, 2007; Freyschmidt-Paul et al., 2006). According to the hair follicle immune privilege collapse hypothesis of Paus et al. (2003), disease development is characterized by overlap of the following key events:

1. Hair follicles enter the anagen phase of the hair cycle during which pigmented hair is produced.
2. Due to some external factors, such as stress, local injury, or inflection, IFN-γ secretion is increased, and this induces collapse of immune privilege of anagen hair follicles.
3. The loss of immune privilege results in MHC class I expression in the hair bulb. In a healthy hair follicle, MHC class I molecules are either absent, or their expression is very low.
4. MHC class I expression in the hair bulb promotes autoantigen presentation to autoreactive $CD8^+$ T-cells/$NKG2D^+$ cells.
5. Autoreactive $CD8^+$ T-cells/$NKG2D^+$ cells, assisted by $CD4^+$ T-cells, attack the epithelium of anagen hair follicles, and this results in premature termination of the growth phase and subsequent shedding of hair fibers (Gilhar et al., 2012, 2007; Paus et al., 1994, 2003).

In addition, the hypothesis states that sufficient amount of potent immune privilege guardians can inhibit IFN-γ secretion, suppress MHC class I expression, and restore hair follicle immune privilege (Gilhar et al., 2012, 2007; Paus et al., 2003).

3. Mathematical model

In order to study how alopecia areata (AA) develops over time, we construct a mathematical model which includes the dynamics of immune system constituents and hair follicle immune privilege agents. We consider a small cluster of hair follicles and assume that they are in the anagen phase of the hair growth cycle. This assumption allows us to focus on the interactions between hair follicles and immune system components, which is a very important initial step in understanding the temporal disease dynamics. In addition, we assume that hair follicles are homogeneous. Fig. 1 shows the conceptual formulation of the model, which is as follows:

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