7 Innovative Therapies in Nail Disorders

Smail Hadj-Rabia

Introduction

Recent advances in biology and bioinformatics have led to a much deeper understanding of the genetic underpinnings of disease and drug targets. In the field of genodermatoses, the detection of mutant alleles, in new genes and/or previously known genes, is now allowed in low as 1% of cells in a skin sample through parallel sequencing (or next-generation sequencing). Therefore, the extensive acquisition of significant data permits (1) a better classification of these rare disorders, (2) the identification of signaling pathways to which belong the proteins encoded by those genes, and (3) finally the identification of promising therapeutic targets. During the last decade, this was particularly true for mosaic disorders and ectodermal dysplasias (EDs).

Mosaic Disorders

Mosaicism has traditionally been defined as the coexistence of at least two genotypes in an individual derived from a single zygote, and this was considered to be an abnormal state. Neonates may present with "normal range" birthmarks that are the manifestation of cutaneous mosaicism [1]. Acquired mutations in the *FGFR3* gene may explain late seborrheic keratoses. Finally, we are all mosaic by this definition, owing to a strikingly high but normal postzygotic mutation rate in utero. Therefore, Kinsler et al. propose to define a mosaic abnormality of the skin as the coexistence of cells with at least two genotypes, by the time of birth, in an individual derived from a single zygote, and which leads to a disease phenotype. For example, distinct clinical entities such as congenital lipomatous overgrowth vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES) syndrome, fibroadipose overgrowth (FAO), megalencephaly-capillary malformation (MCAP), and some cases of isolated macrodactyly or Klippel-Trenaunay syndrome (KTS) are now related to postzygotic activating mutations of *PIK3CA* gene. To avoid any further confusion in the field, the umbrella term of *PIK3CA*-related overgrowth spectrum (PROS) designates known and emerging phenotypes caused by postzygotic *PIK3CA* mutations [2]. The main feature of PROS is congenital, sporadic, and segmental overgrowth of adipose, muscle, skeletal, and/or cerebral tissue. Patients presenting with PROS were treated with supportive care including surgery, sclerotherapy, and psychology.

S. Hadj-Rabia (✉)
Department of Dermatology, Reference Center for Genodermatoses and Rare Skin Diseases (MAGEC) Hôpital Universitaire Necker– Enfants Malades, Assistance Publique – Hôpitaux de Paris-Centre (AP-HP), Paris, France
e-mail: smail.hadj@inserm.fr

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PIK3CA gene encodes the p110a catalytic subunit of the phosphatidylinositol 3-kinase and is involved in cell proliferation, motility, survival, and metabolism. PIK3CA belongs to the PIK3-AKT-mTORC pathway. Allosteric mTORC inhibitors, such as sirolimus, are used for posttransplant immunosuppression. An open-label study in 39 PROS patients receiving a low dose of sirolimus suggests a modest reduction of overgrowth. In parallel, several PIKC3A inhibitors are under development as treatments for oncological conditions, where gain-of-function mutations in *PIK3CA* are identified [3]. Among them, BYL719 shows the dose- and time-dependent inhibition of the PI3K/AKT pathway in *PIK3CA*-dependent xenograft tumor. BYL719 has good tolerability in clinical trials in patients with *PIK3CA*-dependent tumors. BYL719 was therefore administrated orally once a day to 19 patients with PROS who had life-threatening complications. All the patients carry a PIK3CA mutation. In addition to the clinical improvement (reduction in the size of the hypertrophy), a radiological response in all patients was noted. After 90 and 180 days of therapy, the mean volume of the target lesions had decreased by 27.2 ± 14.6 and 37.8 ± 16.3%, respectively. Repositioning an innovative molecule (BYL719) under investigation in oncology for patients with a genetic disorder remains fascinating [4].

Ectodermal Dysplasias

Ectodermal dysplasias comprise a large clinically and etiologically heterogeneous group of genetic disorders that are characterized by abnormalities in tissues derived from the embryonic ectoderm. Initial classification systems for the EDs predate molecular genetics and were categorized and grouped according to phenotypic features and mode of inheritance. The most widely known such nosology was developed by Dr. Newton Freire-Maia in the 1970s and included conditions with "classical signs" involving hair, teeth, nails, and/or sweat glands [5]. The disorders were subdivided into Group A, those having at least two of these tissues affected, and Group B, conditions affecting one of the aforementioned tissues and at least one other tissue of ectodermal origin (e.g., mammary gland) [5]. This classification remained difficult to use for daily practice.

In 2017, an international working group of individuals met on the National Institutes of Health campus in Bethesda, Maryland. The definition of ED was refined, and a classification was proposed. This classification incorporates phenotype, inheritance, and molecular etiology including developmental pathways or structural assembly to organize and cluster the ED conditions [6].

To include the broad variety of tissues that derivate from the ectoderm and to mention dysfunction of ectodermal derivatives that may a normal "morphological" aspect, the following consensual definition of ED was proposed: EDs are genetic conditions affecting the development and/or *homeostasis* of two or more ectodermal derivatives, including hair, teeth, nails, and *certain* glands. Sweat glands was replaced by certain glands, and homeostasis was added. Genetic alterations of ED-associated genes that only affect one derivative of ectoderm (e.g., hair, teeth, nails, sweat glands) should be grouped as nonsyndromic traits of the causative gene (e.g., nonsyndromic hypodontia or missing teeth associated with pathogenic *EDA* variants).

To further develop a useful classification including recent genetic knowledge and involved pathways, the following points were discussed:

- Conditions already included as part of other classifications or groups of diseases and/or presented in different chapters in textbooks (e.g., vesiculobullous disorders) were not included, although they may be associated with alterations in ectodermal structures.
- Complex syndromes that have ED signs but also major non-ED signs (e.g., affecting the bone, brain) were also excluded (e.g., trisomy 21).
- Conditions listed in OMIM with only one case report and no known molecular etiology were excluded.

Therefore, from the 186 ED reported in 2013, 97 were finally retained. They were grouped based on genotype, molecular pathway, and phenotype. Three major molecular pathways gather most of the ED phenotypes and involved genes: the EDA, WNT, and TP63 pathways, respectively. Further clinical investigations will probably identify specific features for each pathway. For example, nails seem to be normal in the syndromes belonging to the EDA pathway, while hyponychia are more frequent for those associated with the WNT pathway.

The most frequent ED phenotype is known as ectodermal dysplasia 1, or hypohidrotic X-linked ED or Christ-Siemens-Touraine syndrome (MIM305100). It is characterized by hypohidrosis or anhidrosis, spoon-shaped nails, hair anomalies (hypotrichosis, absent or scanty eyelashes and eyebrows, and fine scalp hair), and teeth anomalies (hypodontia with conical teeth). It is caused by mutations in the *EDA* gene that encodes ectodysplasin. *EDA* gene is localized on chromosome X explaining the higher frequency of male patients. The EDA1 protein, acting through its receptor EDAR, is essential for the proper formation of skin appendages through the EDA pathway. The Tabby mice presented spontaneously with hypohidrotic ED related to *eda* mutations.

In 2003, Gaide and Schneider showed that the treatment of pregnant Tabby mice with a recombinant form of EDA, engineered to cross the placental barrier, permanently rescued the Tabby phenotype in the offspring. Notably, sweat glands can also be induced by EDA after birth. The developmental genetic defect was permanently corrected by short-term treatment with the recombinant protein [7].

In 2018, Schneider et al. [8] showed that the recombinant fusion protein, Fc-EDA, consisting of the receptor-binding domain of EDA and the Fc domain of human IgG1 administered intraamniotically to two affected human twins at gestational weeks 26 and 31 and to a single affected human fetus at gestational week 26 were able to permanently produce sweat normally and regulate their body temperature by the age of 3. The Fc-EDA provided in amniotic fluid must first enter the organism in a manner that is dependent on the neonatal Fc receptor, presumably through the gut, before it can act on developing EDA-dependent structures.

In the examples mentioned above, i.e., PROS syndrome and X-linked hypohidrotic ectodermal dysplasia, the therapeutic approaches were based on a deep understanding of the involved pathways. The respective genes were not corrected. In PROS syndrome, the PIK3-AKT-mTORC pathway was inhibited through the daily use of a small specific molecule. In X-linked hypohidrotic ED, the sweat development and function was permanently corrected through the direct trigger of the EDA pathway by a recombinant protein.

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