Actin Remodeling Defects Leading to Autoinflammation and Immune Dysregulation

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A growing number of monogenic immune-mediated diseases have been related to genes involved in pathways of actin cytoskeleton remodeling. Increasing evidences associate cytoskeleton defects to autoinflammatory diseases and primary immunodeficiencies. We reviewed the pathways of actin cytoskeleton remodeling in order to identify inflammatory and immunological manifestations associated to pathological variants. We list more than twenty monogenic diseases, ranging from pure autoinflammatory conditions as familial Mediterranean fever, mevalonate kinase deficiency and PAPA syndrome, to classic and novel primary immunodeficiencies as Wiskott-Aldrich syndrome and DOCK8 deficiency, characterized by the presence of concomitant inflammatory and autoimmune manifestations, such as vasculitis and cytopenia, to severe and recurrent infections. We classify these disorders according to the role of the mutant gene in actin cytoskeleton remodeling, and in particular as disorders of transcription, elongation, branching and activation of actin. This expanding field of rare immune disorders offers a new perspective to all immunologists to better understand the physiological and pathological role of actin cytoskeleton in cells of innate and adaptive immunity.

Keywords: pyrin, Wiskott-Aldrich syndrome, autoinflammatory diseases, cytoskeleton, actin

“Cosa bella e mortal passa e non dura.” Francesco Petrarca

INTRODUCTION

Actin is a family of globular proteins that form microfilaments of cell cytoskeleton. In the past, the most important function of actin was related to the binding of myosin, collaborating to the muscle contraction with troponin. These properties can easily be tested adding pure myosin to water and actin, causing an increase in viscosity and birefringence of the liquid due to the formation of the actomyosin complex (1). Thus, the term of actinopathies was originally considered for a well-defined group of monogenic muscle diseases secondary to the actomyosin complex dysfunction (2). During the recent years, a growing number of disorders of the immune system have been linked to actin cytoskeleton abnormalities (numbers are related to the Table 1 and Figure 1) (3). Furthermore, evidences that actin cytoskeletal deregulation in immune cells causes inflammatory
| N | Location | Gene | Protein | Mechanism | Effect | Diseases | MIM | Inheritance | Main symptoms | Main laboratory characteristics |
|---|-----------|------|---------|-----------|--------|----------|-----|-------------|----------------|---------------------------------------------------|
| 1 | 17p13.2   |PFN1 | Profi lin 1 | LOF | Failure to differentiate pre-osteoblast | Early-onset Paget’s disease | None | AR | Polyostotic Paget’s disease, osteosarcoma | Thrombocytopenia, poor neutrophil chemotaxis and oxidative burst |
| 2 | 7p22.1    | ACTB | Beta-actin | GOF | Failure to polarize cytoskeleton in response to fMLP | ACTB-related immunodeficiency | 102630 | DN | Recurrent stomatitis and otitis media, tuberculosis pneumonia, iritis, keratoconjunctivitis, acne, polyarthritis, intellectual impairment, and short stature | | |
| 3 | 4p16.1    | WDR1 | WDR1 | LOF | Defect of coflin activation | PFIT | None | AR | Recurrent fevers and stomatitis, microstomia, Pneumocystis jiroveci pneumonia, pyoderma gangrenosum, genital ulcers, septic arthritis, and necrotizing cellulitis | | |
| 4 | 16p11.2   | CORO1A | Coronin1A | LOF | Defect of WDR1 activation | Coronin1A deficiency | 615401 | AR | Mycobacterial and viral infections, neurological disorders | Naive T-cells lymphopenia |
| 5 | 16q22.1   | RLTPR | Carmil2 | LOF | Defective regulation of capping protein and CD28-mediated costimulation in T-cell | CARML2 deficiency | 618131 | AR | Bacterial and fungal infections, atopy, disseminated EBV-positive smooth muscle tumors | T-cells functional defect |
| 6 | 21q22.3   | ITGB2 | ITGAL/M/X | LOF | Deficit of the beta-2 integrin subunit of the LFA-1 causing delayed motility of neutrophils | LAD type I | 116920 | AR | Recurrent bacterial infections, delayed separation of the umbilical cord, and delayed wound healing | Severe granulocytosis |
| 7 | 11p11.2   | SLC35C1 | GDP-L-fucose transporter | LOF | Deficit of CD15 causing delayed motility of neutrophils | LAD type II/CDG2C | 266265 | AR | LAD1-like immune deficiency, psychomotor retardation, mild dysmorphism | Severe granulocytosis, Bombay blood type |
| 8 | 11q13.1   | FERMT3 | Kindlin-3 | LOF | Deficit in inside-out signaling that enable high-avidity binding of integrin to ligands on leucocytes and platelets | LAD type III/I variant | 612840 | AR | LAD1-like immune deficiency, Glanzmann thrombasthenia-like bleeding problems, osteopetrosis | Severe granulocytosis |
| 9 | 7q31.2    | CFTR | CFTR | LOF | Defect of monocyte adhesion | LAD type IV/Cystic fibrosis | 219700 | AR | Recurrent lung infections, pancreatic insufficiency, male infertility | Hypergammaglobulinemia |
| 10| Xq11      | MSN  | Moesin | LOF | Impaired T cells proliferation, X-MAID | | 300988 | XLR | Recurrent bacterial and varicella zoster | Leukopenia with defective T-cell proliferation and |

(Continued)
| N  | Location | Gene  | Protein | Mechanism | Effect                                                                 | Diseases                                                                                     | MIM          | Inheritance | Main symptoms                                                                                     | Main laboratory characteristics                                                                 |
|----|----------|--------|---------|-----------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------|-------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
|    |          |        |         |           | migration and adhesion                                               | virus infections, eczema and other skin manifestations (recurrent molluscum, thrombotic thrombocytopenic purpura), acute stroke |             |             |                                                                              | fluctuating neutropenia, hypogammaglobulinemia, ADAMTS13+ thrombocytopenia                        |
|    |          |        |         |           | RASGRP1 deficiency                                                   |                                                                                           | 618534      | AR          |                                                                              | T-cells and B-cells functional defect                                                                 |
| Protrusion defects | 11 | 15q14  | RASGRP1 | LOF       | Defect in Ras activation in T-cells and B-cells                      | RASGRP1 deficiency                                                                      |             |             |                                                                              |                                                                                |
|    |          |        |         |           | NOCARH/TKS deficiency                                                | Fever, rash, lymphedema                                                                | 616737      | AD          |                                                                              |                                                                                |
|    |          |        |         |           | RAC2 dysfunction                                                    | Recurrent sterile abscesses (frequently perirectal)                                     | 608203      | AR/AD/DN    |                                                                              |                                                                                |
|    |          |        |         |           | DOCK2 deficiency                                                   | Early-onset invasive bacterial and viral infections, autoimmunity                      | 616433      | AR          |                                                                              |                                                                                |
|    |          |        |         |           | DOCK8 deficiency                                                   | Recurrent viral infections, early-onset malignancy, and atopic dermatitis               | 243700      | AR          |                                                                              |                                                                                |
|    |          |        |         |           | HEM1 deficiency                                                    | Increased T and memory T cells, neutrophils migration defects, decreased NK cytotoxicity |             |             |                                                                              |                                                                                |
|    |          |        |         |           | WIPF1 deficiency                                                   | WAS type 2                                                                               | 614933      | AR          |                                                                              |                                                                                |
|    |          |        |         |           | PSTPIP1 deficiency                                                | Recurrent bacterial and viral infections with warts and abscesses, autoimmunity, cardiac malformations |             |             |                                                                              |                                                                                |
|    |          |        |         |           | ARPC1B deficiency                                                 | SL-related immune deficiency                                                             | 617718      | AR          |                                                                              |                                                                                |
|    |          |        |         |           | PTPN4 deficiency                                                  | Sterile abscesses, pioderma                                                              | 604416      | AD          |                                                                              |                                                                                |
|    |          |        |         |           | WIPF1 deficiency                                                   | WAS/amp-related immune deficiency                                                        |             |             |                                                                              |                                                                                |
|    |          |        |         |           | PSTPIP1 deficiency                                                | Recurrent bacterial and viral infections with warts and abscesses, autoimmunity, cardiac malformations |             |             |                                                                              |                                                                                |
|    |          |        |         |           | ARPC1B deficiency                                                 | SL-related immune deficiency                                                             |             |             |                                                                              |                                                                                |
|    |          |        |         |           | PTPN4 deficiency                                                  | Sterile abscesses, pioderma                                                              |             |             |                                                                              |                                                                                |
| Branching defects | 17 | Xp11.23 | WAS    | LOF/GOF    | Deficit of ARP2/3 complex activation causing lack of actin branching | WAS/X-linked thrombocytopenia/ X-linked neutropenia                                      | 301000      | XLR         |                                                                              | Recurrent bacterial neutropenia, eczema, autoimmunity, neutropenia, CD4+ and naive CD8+ T-cell and B-cell lymphopenia | Thrombocytopenia, defective T-cell and NK-cell functions, increased number of NK cells/ Neutropenia |
|    |          |        |         |           | STK4 deficiency                                                   | Recurrent bacterial and viral infections with warts and abscesses, autoimmunity, cardiac malformations |             |             |                                                                              |                                                                                |
|    |          |        |         |           | WIPF1 deficiency                                                   | WAS type 2                                                                               | 614933      | AR          |                                                                              | Thrombocytopenia, defective T-cell and NK-cell functions, increased number of NK cells            |
|    |          |        |         |           | ARPC1B deficiency                                                 | SL-related immune deficiency                                                             | 617718      | AR          |                                                                              | Thrombocytopenia, hypogammaglobulinemia, reduced IgG, CD8+ T-cell count                         |
|    |          |        |         |           | PTPN4 deficiency                                                  | Sterile abscesses, pioderma                                                              | 604416      | AD          |                                                                              | High acute phase reactants                                                                       |

(Continued)
manifestations are increasing (4). In this review, we illustrate the inflammatory and immunological disorders associated with different pathways of actin-binding molecules.

### Elongation Defects

Actin is the most abundant protein in the majority of eukaryotic cells, contributing to acquire and maintain cell structure and functions. Vertebrates express three actin isoforms, including the α-isoform of skeletal, cardiac, and smooth muscles cells, and the β- and γ-isoforms (5). The conformation of actin monomer, called globular (G)-actin, is the same among different isoforms. G-actin assembles into polarized filaments, called filamentous (F)-actin, that form cortical actin network (CAcN) and cell protrusions (6). Monomer binding proteins, such as the Profilin-1, control polymerization. Individual filaments lifetime can be as short as ten seconds or lasting for days, depending on the extracellular stimulus duration and intracellular conditions (7). Inhibiting the actin polymerization through activity of the capping proteins, or stimulating actin disassembly through the Cofilin/ADF in breast tumor cells causes defects in formation of filopodia, limiting cell motility and favoring proliferation through upregulation of the transcriptional factor SMAD3 (11). On the other hand, deficiency of Profilin-1 acts against invasion of cytotoxic T lymphocytes in tumors and hapatinsufficiency of Profilin-1 seems protective against subcutaneous inflammation induced by high fat diet (12). Furthermore, activation of the Profilin-1 pathway has been related to the inflammatory vascular damage in patients with diabetic retinopathy (13, 14).

Heterozygous gain-of-function (GoF) variant of the ACTB gene, coding for the β-isoform of actin, has been reported in a female with recurrent infections and defect of neutrophil chemotaxis and oxidative burst (no. 2 in Table 1 and Figure 1) (15). The patient also presented a short stature and intellectual disabilities. No other patients have been reported to date. The

### Table 1

| N  | Location | Gene | Protein | Mechanism | Effect | Diseases | MIM | Inheritance | Main symptoms | Main laboratory characteristics |
|----|----------|------|---------|-----------|--------|----------|-----|-------------|---------------|--------------------------------|
| 22 | 16p13.3  | MEFV | Pyrin   | GOF       | Dysregulation of cytoskeleton resulting in activation of pyrin inflammasome | FMF/PAAND | 134610 | AR/AD       | Recurrent fevers with abdominal pain and arthralgia | High acute phase reactants/Neutropenia |
| 23 | 12q24.11 | MKD  | Pyrin   | LOF       | Dysregulation of cytoskeleton resulting in activation of pyrin inflammasome | MKD     | 260920 | AR          | Recurrent fevers, lymphadenopathy, arthralgia, skin rash | High concentration of mevalonate acid in urine during fever attacks |

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**Elongation Defects**

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authors showed that the mutant β-isofrom binds Profilin-1 less efficiently, despite a normal actin polymerization. Loss-of-function (LoF) variants of the ACTB gene, as well as of the ACTG1 gene, coding for the γ-isofrom of actin, have been related to the highly variable spectrum of the Baraitser-Winter syndrome, a rare condition without relevant immunological manifestations (16).

Cofilin/ADF activation is dependent by phospholipase Cγ (PLCγ) in tumors and Rac2 signaling in neutrophils (17). Reduction of Cofilin/ADF expression in leukocytes is associated with abnormal chemotaxis (18). In neurons, Cofilin/ADF controls axon elongation and regeneration (19) and serum levels are significantly higher in patient with Alzheimer’s disease (20). Cofilin/ADF is also upregulated in patients with Friedreich’s ataxia, whose mutations correlate with an altered immune-related genes transcription (21, 22).

Proteins containing a short structural motif of approximately 40 amino acids, often terminating in a tryptophan-aspartic acid (WD) dipeptide, called WD40 repeat, can accelerate the Cofilin/ADF activity. The best-known example is the WD40 repeat protein 1 (WDR1), also known as Actin interacting protein 1 (AIP1). Homozygous LoF mutations of the WDR1 gene cause a monogenic autoinflammatory disease characterized by periodic fever, immunodeficiency, and thrombocytopenia (PFIT; no. 3 in Table 1 and Figure 1) (23, 24). Patients display recurrent fever attacks lasting 3–7 days, every 6–12 weeks, with high acute phase reactants and hyperferritinaemia. Recurrent mucosal inflammation, causing a peculiar acquired microstomia, may resemble the Behcet’s disease’s attacks during childhood (25). Lymphocytes of patients with PFIT show adhesion and motility defects (26). Coronin-1A is another WD40 repeat-containing protein whose LoF mutants have been related to a severe combined immunodeficiency characterized by increased susceptibility to viral and mycobacterial infections (no. 4 in Table 1 and Figure 1) (27–30). Patients usually present with mucocutaneous manifestations, sinopulmonary diseases and neurocognitive disorders without inflammatory manifestations.

On the other hand, the capping proteins are heterodimers composed by two unrelated subunits with highly conserved amino acid sequences. The RGD, leucine-rich repeat, tropomodulin and proline-rich containing protein (RLTPR), also called CARMIL2, is a cytosolic protein that acts as scaffold between the nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and CD28 (31, 32). Autosomal recessive (AR) LoF mutations of the RLTPR gene cause a primary immunodeficiency (PID) characterized by allergy, increased incidence of bacterial and fungal infections, and virus-related tumors (no. 5 in Table 1 and Figure 1) (33). The abnormal cytoskeleton of T-cell in patients with CARMIL2
deficiency causes defects of activation and is related to an abnormal activity of the capping proteins (34).

**Activation Defects**

Over 40 years ago, studies on the ligand-induced movement of immunoglobulin on the surface of lymphocytes called attention to a special relationship between CAcN and antigen-presenting cells (35). A specialized cell–cell junction, the immune synapse (36), is required for the activation of lymphocytes and begin with the formation of thousands of transient, low affinity interactions between antigens and integrins, such as the lymphocyte function-associated antigen 1 (LFA-1) (37). These interactions require a minimum distance of 40 nm, while the major histocompatibility complexes require 15 nm. The consequent antigen-induced CAcN rearrangements leads to morphological changes that are crucial for adhesion, migration, endocytosis, division, gene expression, and calcium flux, as well as for the releasing of cytokines and cytotoxic granules in lymphocytes, neutrophils and monocytes (38).

In particular, on resting leucocytes, LFA-1 is maintained in a low activity state by an inhibitory interaction with the CAcN (39, 40). Therefore, activation of leucocytes requires the release of CAcN-integrin interactions, so that LFA-1 can diffuse in the cell membrane and start binding activities (37). The essential role of CAcN in phagocyte function can be highlighted during chronic infections (41). In fact, microbes are able to lose their integrin ligands in order to escape the immune response (42). The abnormal rolling of leucocytes seems the main affected mechanism in patients with PID caused by LFA-1 defects (nos. 6–9 in Table 1 and Figure 1) (43). The deficiency of the β2 integrin subunit of the LFA-1 causes the leukocyte adhesion deficiency (LAD) type I, and the defective activation of LFA-1 subunits has been related to the LAD type III, both nowadays effectively treated with the hematopoietic stem cells transplantation (44, 45). On the other side, LAD type II is caused by mutations of a fusoc sugar transporter gene leading to cell membrane glycans lacking fucosylation. The administration of oral fucose did not seem effective to control the LAD type II clinical manifestations (46, 47).

Finally, a monocyte-selective adhesion defect has been recently noted in patients with cystic fibrosis (CF) and called LAD type IV (48–50). CFTR heterozygous LoF variants cause hyper activation of the small G-proteins Rho family that controls integrins activation (51). Interestingly, these small G-proteins are also well-known inhibitor of the pyrin inflammasome (52). Furthermore, CFTR interacts with Ezrin protein via its C-terminal domain. Ezrin is the most prominent members of the Ezrin-Radixin-Moesin (ERM) domain-containing protein family that links CAcN to the cell membrane, regulating tension during motility and endocytosis (53, 54). In hematopoietic cells, Ezrin and Moesin are highly expressed, whereas Radixin is mostly absent. Hemizygous LoF mutations of the MSN gene coding for Moesin is associated to a PID called X-linked MSN-associated immunodeficiency (X-MAID; no. 10 in Table 1 and Figure 1) (55). Patient T cells displayed impaired proliferative responses after activation by certain mitogens, and a variable defects in cell migration and adhesion, whereas the formation of immunologic synapses is normal. Thus, CAcN dysfunctions impair epithelial tight junction formation as well as lymphocytes adhesion capability in X-MAID patients.

**Protrusions Defects**

The collapse of CAcN to the side of cells occupied by microtubule organizing centers creates an opening for new actin polymerization to form membrane protrusions at the leading edge. This process is controlled by the small G-proteins Rho family, including the Cell division control protein 42 homolog (Cdc42) and Rac2 (56).

Small G-proteins are a superfamilly of ubiquitously expressed cytosolic hydrolase enzymes that can independently bind and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP), becoming inactive (57). The best-known subfamily members are the Ras GTPases that are divided into five main families: Ras, Rho, Ran, Rab, and Arf. The Ras family is generally responsible for cell proliferation, Rho for cell morphology, Ran for nuclear transport and Rab and Arf for vesicle transport. The Ras guanyl nucleotide-releasing protein 1 (RASGRP1) is a diacylglycerol-regulated nucleotide exchange factor specifically activating Ras and regulating T and B cells development, homeostasis and differentiation. Rasgrp1 deregulation in mice results in a systemic lupus erythematosus-like disorder (58) and RASGRP1 deficiency in humans causes a PID characterized by impaired cytoskeletal dynamics (no. 11 in Table 1 and Figure 1) (59). Patients with RASGRP1 deficiency suffer from recurrent bacterial and viral infections especially affecting the lung with a severe failure to thrive and can develop EBV-related lymphomas.

The localization of small G-proteins on the cell membrane is due to their prenylation, a post-translational modification characterized by the addition of twenty-carbon lipophilic isoprene units to the cysteine residues at the C-terminus (60). Furthermore, most of the Rho family members contain a cluster of positively charged residues (i.e., polybasic domain), directly preceding their geranylgeranyl moiety that serves to fine-tune their localization among different cell membrane sites. Overall, the prenylation of small G-proteins is involved in the regulation of cytokines production (61) and can be regulated by statins in monocytes and macrophages (62).

On 2D surfaces, activated Cdc42 and Rac2 generate filopodia and lamellipodia, respectively. The formation of these membrane protrusions consents leucocytes to reach the damaged tissue passing through an intact vessel wall, a process called diapedesis. The local concentration of the complement system C3 fraction also contributes to this process (63). However, in 3D environment, the blebbing motility seems the more common migratory strategy of blood cells (64, 65). Stop-codon variants of the CDC42 gene has been recently associated with a novel autoinflammatory disease characterized by neonatal-onset of cytopenia, rash, and hemophagocytosis (NOCARH), successfully treated with interleukin-1β inhibition (no. 12 in Table 1 and Figure 1) (66). Furthermore, heterozygous CDC42 missense variants have been related to the Takencuchi-Kosaki syndrome (TKS) (67–69). TKS patients do not usually display autoinflammatory manifestations but hematologic and/or lymphatic defects, including macrothrombocytopenia, lymphedema, intestinal...
lymphangiectasia and recurrent infections. Characteristics of platelets and B cells have been recently described (70–72). A recent extensive genotype-phenotype correlation study allows to classify three groups of the CDC42 variants regarding involved protein domain (73). Based on these evidences, the NOCARH-associated variants occur at the C-terminus that usually allows PIPI2 interaction, whereas associated variants with TKS resembling Noonan syndrome occurs at the N-terminus. Thus, different roles of the Cdc42 protein may be subverted in these conditions with different clinical manifestations.

The Rho guanosine triphosphatases Rac2 is expressed only in hematopoietic cells. Patients with Rac2 dysfunction secondary to dominant negative or homozygous LoF mutations present early-onset recurrent abscesses, neutrophilia, and defective wound healing, whereas monoallelic germline GoF mutations of the same 

RAC2 gene cause a severe combined immunodeficiency (no. 13 in Table 1 and Figure 1) (74–77). Interestingly, Rac2 activation in neutrophils is primarily mediated by the dedicator of cytokinesis (DOCK) 2, an atypical guanine nucleotide exchange factor (GEF) that rapidly translocate to the plasma membrane in a phosphatidylinositol 3,4,5-trisphosphate (PIP3)-dependent manner upon stimulation, resulting in increased local Ca2N polymerization (78, 79). DOCK2 is mainly expressed in peripheral blood leukocytes and DOCK2 deficiency causes an early-onset PID characterized by a T-cell defective chemotactic responses with bacterial and viral infections (no. 14 in Table 1 and Figure 1) (80).

On the other side, DOCK8 is a Cdc42-specific GEF that regulates interstitial migration of dendritic cells and DOCK8 deficiency causes the AR Hyper-IgE syndrome (HIES), a combined immunodeficiency characterized by recurrent viral infections, early-onset malignancy and atopic dermatitis (no. 15 in Table 1 and Figure 1). Patients with DOCK8 deficiency display severe viral skin infections, such as chronic anogenital verrucae, ulcers, multiple acral warts, and desquamating molluscum contagiosum (81–84). Selective loss of group 3 innate lymphoid cell has been described in these patients (85).

### Branching Defects

Cdc42 and Rac2 transmit many signals through the GTPase-activating protein (GAP) 2/3 complex constituted by seven subunits. Two of them, the ARP2 and 3, closely resemble the structure of the G-actin, allowing the formation of a thermodynamically stable dimer that serves as a nucleation site for the new actin filaments at 70° angle from the main filament. Homozygous LoF variants of the ARPC1B gene, coding for the p41 regulatory subunits of the ARP2/3 complex, cause the platelet abnormalities with eosinophilia and immune-mediated inflammatory disease (PLTEID; no. 20 in Table 1 and Figure 1) (100–104). Patients with PLTEID usually present systemic inflammation with lymphoproliferation and immunodeficiency resembling WAS, with early onset vasculitis, severe infections, and eczema. A functional test has been recently described to detect asymptomatic carriers (105).

Additional WASP activators include the proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), PIP2, and the c-Src protein-tyrosine kinases family. Heterozygous GoF mutation of the PSTPIP1 gene causes the pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome and the PSTPIP1-associated myeloid-related proteinemia inflammatory (PAMI) syndrome (no. 21 in Table 1 and Figure 1) (106, 107). PAMI syndrome is caused by variants that substantially alter electrostatic properties of the PSTPIP1 critical region for auto-inhibiting dimerization, resulting in a GoF mutant protein that constitutively activates the underlying Pyrin inflammasome (108).

Pyrin is the pivotal protein of the related inflammasome, a member of cytosolic multiprotein oligomers family responsible for the activation of inflammatory responses in human cells. The Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) and familial Mediterranean fever (FMF) are well-known monogenic autoinflammatory...
diseases both related to GoF variants at different locus sites of the MEFV gene and associated with an excessive activation of the Pyrin inflammasome (no. 22 in Table 1 and Figure 1). Recently, the mevalonate kinase deficiency (MKD) caused by homozygous or compound heterozygous LoF mutations in the MVK gene has been related to the constitutive activation of Pyrin (no. 23 in Table 1 and Figure 1) (109).

**Production Defects**

Megakaryoblastic leukemia 1 (MKL1) is a member of the myocardin-related transcription factors and usually held in an inactive state in the cytoplasm in a reversible complex with G-actin (110). Stimulation of the small Rho GTPases promotes incorporation of G-actin into F-actin, allowing MLK1 to enter into the nucleus, stimulating transcription of actin and other cytoskeletal proteins genes. Homozygous LoF mutation in the MKL1 gene result in a PID characterized by susceptibility to severe bacterial infection and recurrent skin abscesses (no. 24 in Table 1 and Figure 1) (111). MLK1 deficiency causes reduced phagocytosis and almost complete abrogation of neutrophils spreading properties (112). MLK1 participates in differentiation of megakaryocytes and mild thrombocytopenia has been noted in patients with MKL1 deficiency (113).

Finally, LoF variants of the gene coding for the transcription factor CCAAT enhancer binding protein epsilon (C/EBPε) cause a PID called AR neutrophil-specific granule deficiency-1 (SGD) (114), whereas heterozygous GoF variants have been recently related to an autoinflammatory disease called the C/EBPε-associated autoinflammation and immune impairment of neutrophils (CAIN; no. 25 in Table 1 and Figure 1). Patients with CAIN display recurrent fevers characterized by abdominal pain, lasting 4–5 days, and skin inflammatory manifestations, such as sterile abscesses, pyoderma gangrenosum and oral ulcerations. The mutant C/EBPε causes deregulated transcription of interleukins and interferon response genes in neutrophils (115).

**DISCUSSION**

The field of autoinflammation is moving from a gene-centric view of innate immune-mediated diseases towards a systems-based concept, which describes how various convergent molecular pathways, including actin cytoskeleton, contribute to the autoinflammatory process (116) and to a number of conditions characterized by the coexistence of inflammation, autoimmunity and defective immune response. Indeed, the complex regulation of the actin remodeling represents an example of autoinflammatory diseases merging with immunodeficiencies. Despite the wide range of symptoms associated with these disorders, some features may suggest the diagnosis, such as recurrent fevers or infections, atypical skin manifestations (from severe viral infections to eczema and sterile abscesses), cytopenias and defects of chemotaxis and lymphocytes proliferation. Cytopenias may be secondary to the abnormal release of immune cells from the bone marrow and/or impairments in the immune synopsis, while the abnormal diapedesis associated with an altered vessels wall and the increased cell apoptosis in the skin matrix, called cytothripsis, may favor cutaneous manifestations (86). Cytoskeleton-targeted therapies, such as colchicine, may play new roles in these disorders. The study of the molecular and modular diversity of these immune responses to the changing conditions has only recently become possible through the development of the new “omics”-based screening technologies (117). The adoption of “omics” and systems-based concepts will have implications for the discovery of novel diseases and for the possible development of targeted diagnostic tests and treatment options.

**AUTHOR CONTRIBUTIONS**

RP drafted the manuscript. FP, SV, and MG reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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