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COMMENT

Harmful vimentin manifests itself as multiorgan failure

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Intermediate filaments (IFs) are composed of more than 70 different IF proteins, all of which are expressed in a tissue- and differentiation state-specific manner. They show a remarkable diversity when it comes to primary sequences, protein interactions, and expression in various tissues [1]. Their unique roles in different cell types and tissues are reflected by their involvement, as a cause of or predisposition, in more than 80 human tissue-specific diseases [2][1]. The article by Cogne et al. [3], reports on a novel missense variant in the gene of the IF vimentin (c.1160T>C; p.(Leu387Pro)), resulting in a harmful form of vimentin ($Vim^{p.(Leu387Pro)}$). This is the first report on a serious disease-causing variant of human vimentin.

Among the large family of IF proteins, vimentin is one that is familiar to many researchers, as it is the major IF protein of mesenchymal cells. It is frequently used as a developmental marker of cells and tissues, as it becomes upregulated upon epithelial-mesenchymal transition (EMT). Employing vimentin as an EMT marker also facilities the detection of diseases, as EMT is also involved in both fibrosis and metastasis of tumor cells. In this respect, article search engines will highlight more than 28,000 hits with the keyword vimentin. Vimentin also shows a remarkable sequence homology between species, from fish to humans [2], indicating that this IF protein has crucial and evolutionary conserved physiological roles. Despite all the attention and the signs of obvious importance, vimentin remained for a long time an enigma in terms of its functions.

Mutations in IF genes as a cause for human disease gained significant attention when lamin mutations were shown to be the primary cause of premature aging disease progeria [2]. The described harmful vimentin mutation has a multiorgan disease manifestation with progeroid features. The results show effects on craniofacial development, on the peripheral nervous system, as well as on adipose tissue and skin. The destructive effects of the variant could be confirmed in cell models, which demonstrated how gravely the change disturbs filament assembly and organization. Furthermore, the effects of the variant could also be recapitulated in zebrafish where it, similarly as in the human patient, impaired craniofacial development, peripheral axon branching, and fat distribution. The data suggest that the $Vim^{p.(Leu387Pro)}$ variant acts as a dominant-negative or gain-of-function mutation with extensive effects on the development and homeostasis on a broad range of tissues and organs.

It is informative to compare the effects obtained with this disease-causing vimentin variant to those that have been observed in mice lacking vimentin (Vim−/−). These mice show a remarkable repertoire of phenotypes, many of which reflect especially inhibited cell activation and cell dynamics as well as compromised ability to counteract stresses that involve disruption of tissue integrity. More detailed analyses of Vim−/− mice have then revealed that loss of vimentin leads to, for example, impaired wound healing due to defects in EMT and the capacity of fibroblasts to proliferate and migrate, decreased flow-induced dilation of resistance arteries [4] reflecting a role in the mechanotransduction of shear stress, disturbed homing of leukocytes to lymph nodes, lack of integrity in the vascular endothelium, disturbance of fat accumulation, and morphological changes in glial cells[2]. Recent studies have brought light into the mechanisms underlying these effects, as vimentin has been shown to participate in a number of

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[1] For further information, see also The Human Intermediate Filament Database http://www.interfil.org/.

[2] Ridge et al. The True Character of Vimentin is Revealed Under Pressure—Two Decades of Research on Vimentin Knockout Mice. Review article under assessment for publication.

critical cellular functions, often related to the organization of proteins that are involved in adhesion, migration, and cell signaling. These latter studies of vimentin as an integrator and organizer of signaling and adhesion molecules explain the observed effects in the Vim−/− mice [2].

The results of Cogne et al. partly overlap with those obtained from Vim−/− mice but there is a distinct difference. Many of the phenotypes in the Vim−/− mice are manifested only when the mice are challenged with some kind of stress, whereas normal development seems only mildly affected. In contrast, already in the heterozygous state, the described disease-causing vimentin variant significantly disturbs normal development even in the absence of any challenge or stress. However, there is also clear congruence, for example, the effects on adipose tissue can be seen both in the patient with the missense variant and in in the Vim−/− mice [5]. Furthermore, the effects on the vascular endothelium in the Vim−/− mice [6, 7] could be just a milder variant of the cardiovascular disturbance observed in the patient with the vimentin variant. In this respect, the harmful gain-of-function effects of the vimentin variant may reflect bona fide inhibition of more specific functional features of vimentin. In comparison, the effects observed in the absence of vimentin are likely to rather reflect lost regulatory functions that can be observed only when the system is challenged by a suitable stress.

Taken together, the study of Cogne et al. represents a clear breakthrough in the field of vimentin research. Obviously, the study will provide a benchmark for human geneticists to search for vimentin variants with similar phenotypes. Furthermore, the study highlights some physiological mechanistic features of vimentin that can be related as a continuum to the effects that are obtained when vimentin is lacking. The variant will, therefore, be a valuable tool to dissect vimentin functions both in cellular and animal models lacking vimentin and when the vimentin variant is co-expressed together with normal vimentin.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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