BY NATALIE VON DER LEHR
PHOTO: LINDA TAMMISTO/UH

Research for the clinic and the bench

The results of a new study on the genetics behind the benign tumor leiomyoma combine the possibilities of clinical implications and a greater understanding of fundamental biological processes. The findings of Professor Lauri Aaltonen's research group at the University of Helsinki were recently published in *Science*.

Netta Mäkinen.

Leiomyomas are benign smooth muscle tumors in the uterus and affect up to 60 per cent of women by the age of 45. Regardless of their benign status these tumors often cause difficult symptoms such as heavy menstrual bleeding with subsequent anaemia and abdominal pain. Infertility might also be a consequence. Relatively little is known about how and why leiomyomas develop.

"The starting point for this project was an observation of our collaborators ten years ago. They found a familial segregation for leiomyomas and we wanted to know more, both about the hereditary and non-hereditary factors behind the disease," says Lauri Aaltonen.

THE HUNT FOR GENETIC FACTORS

To learn more about the genetics behind the disease Aaltonen and his team started to collect tumor material.

"We did not select tumors from patients with a family history of leiomyomas, we just took any patients," explains Lauri Aaltonen.

His doctoral students, Netta Mäkinen and Miika Mehine, then sequenced over 20,000 genes from eighteen tumors and compared the results to those from paired normal tissue samples. In order to do this they used a method called exome sequencing which is based on selective sequencing of the coding regions of the genome.

"When we started the study at the end of 2009 sequencing the whole genome was still too expensive. Exome sequencing was the best alternative at the time, we really tried to do things as early as possible and position ourselves at the forefront of research," says Aaltonen about the choice of method.

Netta Mäkinen and Lauri Aaltonen.

“This is a giant step in discovering the birth mechanism of leiomyomas and the very first step towards develop-ing specific medical drugs. Let us hope that that journey has now begun.”

FINDINGS OF VALUE FOR THE CLINIC

The results of the study pointed towards a mutation of MED12, which is part of the mediator complex involved in gene transcription.

“Were we surprised? Yes and no. The results of unbiased genetic approaches are very unpredictable, almost anything can come up,” explains Aaltonen.

After identification of a mutated MED12 as a possible culprit behind leiomyomas the research team went on to find out if they could validate the results in an additional data set of 207 uterine leiomyomas. The frequency of MED12 mutations, in particular those affecting codon 44 – normally a glycine – was striking.

“Finding this specific mutation area in most leiomyomas gives us an exceptionally good starting point to develop targeted medical treatments to curb the growth of these tumors,” Aaltonen explains.

The possibility of being able to treat leiomyomas, apart from sparing many women the painful symptoms, would also decrease the need for hysterectomies, which is a common method of removing the tumors.

FINDINGS OF VALUE FOR THE BENCH

Apart from providing a starting point for the development of tumor-specific drugs, the findings of the study are also valuable in answering questions in basic biological research. MED12 is a component of the mediator complex that is a giant apparatus aiding in the transcription of genes to produce functional proteins. MED12 has been mainly described as a transcriptional repressor but can also work as an enhancer under some circumstances.

“We are probably looking at a mechanism that is highly tissue specific and that is not found in many other tumor types,” says Aaltonen.

His discovery of the glycine 44 mutational hotspot has already attracted considerable attention from the research community working with the mediator complex in more detail.

“This is a good starting point for functional studies. In future model systems containing the mutation will be a good tool, both to understand the basic biology and to test potential drugs,” Aaltonen says, once again making a connection between basic biology and clinical implications.

THE FUTURE WILL TELL

But like most researchers Aaltonen cautions against undue expectations. The development of new medicines takes time and the journey from a basic biological discovery to a drug on the shelf is usually long. He also emphasizes that the mutation that has been discovered should not be mixed up with hereditary predisposition. There is also another puzzle to solve for the team of Lauri Aaltonen, namely the genetics of the around thirty percent of leiomyomas that do not contain a mutation of MED12.

But still Lauri Aaltonen cannot hide his enthusiasm over his discovery.

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Article:
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