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Unifying Disease Mechanisms; Looking at Similarities and Differences

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In the past century the medical sciences have made great strides in diagnostics by using a reductionist approach. Complex disease phenotypes have been meticulously dissected molecularly often resulting in clear genetic definitions. However, the development of therapies is lagging behind our ability to screen and diagnose these diseases in the lab. One reason for the lag in therapy development may be that our enhanced diagnostic capacity has led to the definition of many orphan diseases; afflictions that affect only a small number of people. Therefore it may be time for a more holistic approach; an investigation of systems as a whole, which Systems biology tries to achieve. Science needs to look for commonalities between disease mechanisms wherever possible to enhance the chance of finding common footholds for therapies that target multiple diseases.

One example of a complex genetic disease that might benefit from a focus on commonalities is Limb Girdle Muscular Dystrophy (LGMD). LGMD is commonly regarded as a group of rare heterogeneous genetic disorders characterized by progressive muscle wasting and weakness [1]. Thus far more than 20 different genetic loci have been causally linked to the LGMD phenotype. Disruptions in the 20 different loci result in disease manifestations that are categorized on the basis of differences that are largely clear but can be very subtle. Current research objectives often overlook the huge similarities in the various disease forms, while targeting mainly the differences.

Most LGMD forms have been linked to protein coding genes, and in many cases a disease model exists. Based on commonalities in protein function LGMD has been divided into major disease mechanisms [2]: 1) a structural defect at the muscle membrane (Sarcoglycans [3]), 2) muscle membrane repair deficiency (Dysferlin [4]), 3) defects in sarcomere remodeling, cytoskeleton structure and cytoskeleton-membrane interactions (Calpain 3 [5]). With the identification of TMEM16E/ANO5 mutations in LGMD2L a possible fourth disease mechanism has been uncovered that regards ion channel dysfunction [6]. Closer inspection of these pathogenic mechanisms may give an idea of further commonalities between the LGMD types.

In all forms of LGMD, muscle tissue is correctly formed and functional. Concomitantly, in all three pathogenic mechanisms described above, deregulation of muscle maintenance seems to be central. In many forms of LGMD an increased level of regeneration has been reported. This suggests that when muscle maintenance processes fail, damaged muscle fibers need to be replaced. Muscle has a high capacity for regeneration, but it is limited. To maintain correct muscle function specific molecular signaling pathways exist that mechanically or chemically sense contraction and resulting damage, and that need to respond appropriately. The molecular interactions between the membrane repair protein Dysferlin (LGMD2B) and the caveolae component Caveolin 3 (LGMD1A, 7) and the muscle specific cysteine protease Calpain3 (LGMD2A,[8]) provide an indication for a connecting molecular network that underlie muscle maintenance and LGMD pathogenicity. A recent proteomic study on Dysferlin [9], uncovered a large protein network that includes several of the proteins linked to LGMD, and hints at a broader membrane maintenance role for these proteins.

Unraveling further molecular interactions and their localizations in muscle would provide access to potential protein networks that underlie the individual forms of LGMD. An overlap between these networks may provide further unification of the disease. The newly discovered interactions may provide a different basis for extending the molecular networks in muscle maintenance and LGMD pathogenicity. Moreover, they may provide new therapeutic perspectives by focusing on similarities instead of differences.

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