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Regulation of skeletal muscle recovery

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VALORIZATION

The aging of the world's population is one of the main forces driving the development and the increasing burden of chronic diseases such as chronic obstructive pulmonary disease (COPD), of which the prevalence is rising and which is already the third leading cause of death worldwide [1]. Interestingly, loss of lung function is one of the characteristics of 'normal' aging, and was already reported by Falzone *et al*., in 1956 [2]. Overall, aging is characterized by changes in physiological structure and function, of which, Rosenberg noted, the loss of muscle mass is perhaps the most striking [3-5]. To describe this phenomenon, Rosenberg proposed the term 'sarcopenia' in 1989 (From the Greek words 'sarx' (flesh) and 'penia' (loss)) [6].

While, to date, there is still no international consensus on the diagnostic criteria for sarcopenia, several working groups have developed objective definitions of sarcopenia, all including both a low muscle mass together with low muscle function (strength or performance) [7-11]. Depending on the definition used, the prevalence of sarcopenia in 60-70 year olds is 5-13%, and rises to 11-50% in >80 year olds [12]. However, sarcopenia is not only a disease of the elderly, but is also associated with chronic diseases such as COPD, and is an integral part of the disease-related wasting syndrome called 'cachexia' [11]. Interestingly, compared to the same age group, the prevalence of sarcopenia is significantly higher in COPD patients, reaching 14-40% in 60-70 year olds [13, 14]. Importantly, besides that sarcopenia is an adverse health outcome and is associated with chronic diseases, it is also an independent risk factor for other adverse outcomes such as cognitive decline, injurious falls, and loss of independence, and is a powerful predictor of mortality [14-17]. Together, this has led to the recent recognition of sarcopenia as an independent disease entity with an ICD-10-CM (M62.84) code [18].

Prominent researchers in the field of sarcopenia have predicted that the recognition of sarcopenia as an independent disease will lead to an accelerated development and availability of diagnostic tools, as well as a growing interest by physicians in integrating the diagnostic assessment of sarcopenia in routine clinical practice [18]. Furthermore, the recognition of sarcopenia as an independent disease is expected to increase the interest of pharmaceutical and nutritional companies in developing drugs and medical nutrition to treat sarcopenia [18]. This process is nicely illustrated in a 'from bench to bedside' translational research continuum (Figure 1), which also emphasizes the importance of adequate observation and recognition of the disease in the process.

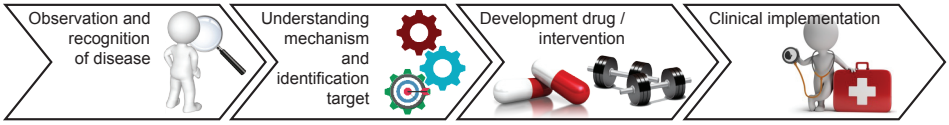

Figure 1. | Translational research continuum

Importantly, the etiology of sarcopenia is multi-factorial [7, 12]. Added to the well-established heterogeneity of the COPD population, it is evident that, next to generic interventions such as stimulating a physically active lifestyle, targeted primary and secondary prevention of sarcopenia in COPD patients is not easy. Adequate early intervention and the development of tailored treatment plans for sarcopenia in COPD patients requires the identification of more homogeneous risk populations, *e.g.* by sub-classification of endotypes, as a first step in the translational research continuum. Given the complexity of the disease, an integrated and unbiased approach is required to identify relevant endotypes. In chapter 5 of this thesis, we used an unbiased clustering-based approach to address the heterogeneity in the molecular rehabilitation responses that may be underlying to a progressive decline in muscle mass and function. Through this novel approach, we identified two major patient clusters which were characterized by an 'early' versus 'late' stage molecular response pattern to PR. This opens up avenues for personalization of the intensity and duration of PR, and for selective additional nutritional and pharmaceutical interventions based on the molecular response pattern. Another important observation was that no cluster of non-responders was identified, illustrating the importance of PR, when feasible, as primary approach to treat sarcopenia in advanced COPD before considering additional pharmaceutical or nutritional interventions. These findings are of relevance to medical and paramedical caregivers, medical decision and policy makers and health insurance companies.

The integrative analysis of molecular data, adopted in both chapters 4 and 5, can also be applied to different research fields and to answer various types of research questions. For example, such an approach can be used by fundamental researchers to gain more insight in potential molecular alterations in highly dynamic processes, such as cellular proliferation and differentiation. Furthermore, it can be used in a clinical (research) setting to identify distinct endotypes that respond differentially to treatment, to improve accurate diagnosis, develop specific drugs, nutraceuticals, and lifestyle interventions, and/or provide a targeted treatment to the appropriate patient group to improve cost-effectiveness.

To date, the most effective treatment for sarcopenia is resistance-type exercise training, which induces protein turnover signaling to facilitate skeletal muscle remodeling. To promote a gain in muscle mass, it is frequently noted that additional pharmacological anabolic triggers, can be used to combat the blunted anabolic response to exercise training in elderly and COPD patients. However, this thesis shows in chapter 3 that anabolic signaling is already increased at baseline in muscle wasted COPD patients. Based on this, we could speculate that pharmacological anabolic stimuli may have a limited effect in this population, reducing cost-effectiveness of such treatments. Nevertheless, several studies showed that anabolic stimuli such as recombinant growth hormone [19], anabolic steroids [20-23], and an Activin type II receptor blocker [24], did induce or promote a gain in muscle mass in COPD patients. Importantly, these studies collectively showed no improvements in muscle function, indicating that increasing muscle mass alone is not sufficient to promote exercise performance. This dissociation between improvements in muscle mass and muscle function may be due to their respective determination by the balance versus the rate of muscle protein turnover, as discussed in chapter 8. Indeed, these anabolic stimuli promote a positive protein turnover balance, but do not necessarily increase the rate of protein turnover. Importantly, these anabolic stimuli signal through the PI3K-AKT1 pathway, which may even result in a decrease in the protein turnover rate by suppression of protein degradation. As such, these anabolic stimuli may inhibit muscle repair and remodeling, which are required for the recovery and maintenance of muscle quality and function. In chapter 3, we showed that in addition to the increased baseline protein synthesis signaling, protein degradation signaling was also increased in muscle wasted COPD patients, suggesting ongoing skeletal muscle repair and remodeling. This information is of value for rehabilitation physicians, as it demands caution with general implementation of additional anabolic stimuli in exercise-based pulmonary rehabilitation. Nevertheless, a supportive environment for anabolism is important for improvement of both muscle mass and muscle function, emphasizing the requirement for integrating nutritional support as part of PR.

Furthermore, in this thesis we report several indications for alterations in postnatal myogenesis in COPD patients. However, studying the individual processes involved in postnatal myogenesis is not yet feasible *in vivo*, and even difficult *in vitro*. In chapter 6, we describe the development of a novel *in vitro* model to efficiently study postnatal myogenesis. This model can be used by basic researchers to further unravel the molecular mechanisms involved in postnatal myogenesis, which may lead to the discovery of *in vivo* applicable biomarkers or drug targets. Moreover, the model can be used as a screening tool for potential nutritional or pharmaceutical compounds that

promote muscle mass and quality, and thereby contribute to a more efficient drug or intervention development. In addition, *in vitro* (pre)screening of compounds will reduce the need for animal studies, reducing research costs, as well as contributing to the 3R's of animal research. Moreover, fundamental biological insights obtained using this *in vitro* system are likely relevant for the optimization of stem cell-based therapies. Optimization of such therapies will not only be important for the field of aging and chronic disease related muscle pathologies, but also for the treatment of muscle dystrophies.

In conclusion, this thesis provides both new scientific insights, as well as tools for further knowledge development. This will support crucial steps in the translational research continuum, hopefully contributing to a future with sarcopenia as a treatable, and maybe even preventable, disease.

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