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Lamin A expression in circulating osteoprogenitors as a potential biomarker for frailty: The Nepean Osteoporosis and Frailty (NOF) Study

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ABSTRACT

Lamin A is a protein of the nuclear lamina. Low levels of lamin A expression are associated with osteosarcopenia in mice. In this study, we hypothesized that low lamin A expression is also associated with frailty in humans. We aimed to develop a non-invasive method to quantify lamin A expression in epithelial and circulating osteoprogenitor (COP) cells, and to determine the relationship between lamin A expression and frailty in older individuals. COP cells and buccal swabs were obtained from 66 subjects (median age 74; 60% female; 26 non-frail, 23 pre-frail, and 17 frail) participating at the Nepean Osteoporosis and Frailty (NOF) Study. We quantified physical performance and disability, and stratified frailty in this population. Lamin A expression in epithelial and COP cells was quantified by flow cytometry. Linear regression models estimated the relationship between lamin A expression in buccal and COP cells, and prevalent disability and frailty. Lamin A expression in buccal cells showed no association with either disability or frailty. Low lamin A expression values in COP cells were associated with frailty. Frail individuals showed 60% lower levels of lamin A compared to non-frail (95% CI −36 to −74%, $p < 0.001$) and 62% lower levels compared to pre-frail (95%CI −40 to −76%, $p < 0.001$). In summary, we have identified lamin A expression in COP cells as a strong indicator of frailty. Further work is needed to understand lamin A expression as a risk stratifier, biomarker, or therapeutic target in frail older persons.

1. Introduction

Frailty is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, disability, hospitalization, and mortality (Clegg et al., 2013; Xue, 2011). Biologically, frailty is the consequence of a combination of multiple components such as sarcopenia, inflammation, co-morbidities, and hormonal deficiency (Morley et al., 2006). Clinical identification of frailty is a cornerstone of geriatric medicine and aged care. The most frequently used definition for frailty focuses on the evaluation of five domains (nutritional status, energy, physical activity, mobility, and strength), which has established five clinical criteria for defining the frail phenotype (Fried et al., 2001). More recently, other definitions have been proposed, which define frailty as an accumulation of multiple biological and functional deficits (de Vries et al., 2010; Searle et al., 2008).

In general, the definitions of frailty are based more on clinical than

Abbreviations: COP, circulating osteoprogenitor; NOF, Nepean Osteoporosis and Frailty; HGPS, Hutchinson Gilford Progeria Syndrome; MMSE, mini mental state examination; GDS, geriatric depression scale; CCI, Charlson comorbidity index; BMI, body mass index; OARS, Older Americans Resource Scale; ADL, activities of daily living; IADL, instrumental activities of daily living; PASE, Physical Activity Scale for the Elderly; CES-D, f; CSHA, Canadian Study of Health and Aging; QUS, quantitative ultrasound; SOS, speed of sound; BUA, broadband ultrasound attenuation; SI, stiffness index; TSH, thyroid stimulating hormone; EDTA, ethylenediaminetetraacetic acid; PBMC, peripheral blood mononuclear cells; FMO, fluorescence minus one; PMT, photomultiplier tube; G-MFI, general median fluorescence intensity; IL-6, interleukin 6

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biological criteria, which limits the accuracy of the diagnosis, and has prevented a consensus on the recognition of frailty as a geriatric syndrome. In addition, attempts to find a biological marker for frailty has yielded highly variable results. Among the multiple proposed biomarkers for frailty, only two have been consistently correlated with the clinical diagnosis: interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) (Calvani et al., 2017; Soysal et al., 2016). However, the validity of these biomarkers has been confounded by the high prevalence of inflammatory findings in aging individuals (Fougère et al., 2016). Due to the limitations in accurately diagnosing frailty, a recent Delphi consensus by experts in the field (Rodríguez-Mañas et al., 2013) concluded that "Additional experimental work is needed to identify the specific combination of clinical and laboratory biomarkers that can be used for the diagnosis of frailty."

Investigating a robust biomarker for frailty, and based on the hypothesis that frailty is a mesenchymal disease (Joseph et al., 2005; Tong et al., 2011), Gunawardene et al. (2016) reported the association between low percentage of circulating osteoprogenitor (COP) cells with disability and frailty in older persons. In their study, lower percentages of COP cells (%COP) were associated with frailty, disability, and poor physical performance. In addition, older adults with COP cells in the lower quartile were more likely to be frail identified by either Fried's criteria (Fried et al., 2001) or Rockwood's frailty index (Searle et al., 2008). Interestingly, the association between %COP and frailty was stronger than IL-6.

However, although COP cells are considered as a surrogate of the stem cells population in the body (Pignolo and Kassem, 2011), there is no evidence that a reduction in %COP is also associated with a reduction in their capacity to differentiate into mesenchymal tissues. In addition, studies looking at age-related changes in %COP cells have shown divergent results (Egan et al., 2011; Gunawardene et al., 2016; Gunawardene et al., 2017). Therefore, we propose that a more accurate and stronger indicator of mesenchymal stem cells (MSC) function and differentiation potential would be a more robust and reliable biomarker for frailty.

Lamin A, a protein of the nuclear lamina, is required for bone and muscle formation (Akter et al., 2009; Bermeo et al., 2015; Li et al., 2011; Tong et al., 2011). Lamins form the lamina that maintains the shape and strength of the nucleus. They also play a role in several nuclear processes including DNA replication and transcription (Gruenbaum et al., 2005). A-type lamins are absent from all pre-implantation stage embryonic cells. Subsequently, A-type lamins appear asynchronously in various tissues, a process that seems to be affected by aging and disease (Hutchison and Worman, 2004).

In aged C57BL/6 mice (24-month-old), levels of lamin A expression are decreased in aging chondrocytes and osteoblasts (Duque and Rivas, 2006). Regarding the role of lamin A in human disease, abnormalities in lamin A processing have been linked to the Hutchinson Gilford Progeria Syndrome (HGPS) (Gonzalo et al., 2017), a type of progeria with major defects in the musculoskeletal system including severe osteoporosis and spontaneous fractures (de Paula Rodrigues et al., 2002; Korf, 2008). Therefore, our overall hypothesis was that decreasing levels of lamin A expression in MSC play a role in the pathogenesis of age-related diseases of the mesenchyme, such as frailty, thus identification of levels of lamin A expression could constitute a robust biomarker for frailty in older persons. We also aimed to develop and validate a new non-invasive method to quantify lamin A expression, which could be used as a biomarker for frailty in clinical settings in the future.

2. Methods

2.1. Participants

The Nepean Osteoporosis and Frailty (NOF) Study is a cross-sectional study of community-dwelling elderly participants, aged > 65 years, recruited between March and December 2013 in Western Sydney (Gunawardene et al., 2016). Exclusion criteria included: a Barthel scale < 40%, MMSE < 18/30, GDS > 10/15, history of fracture within the last three months, use of any type of osteoporosis treatment, and previous history of myelodysplastic or myeloproliferative disorder. A clinician investigator recorded participants' background variables and medical history and performed a detailed anamnesis and clinical examination. The clinical research assistant performed an extensive assessment of functional status including performance testing, questionnaires, and technical examinations. A blood sample was collected in the morning. The Nepean Blue Mountains Local Health District Human Research Ethics Committee approved the research protocols. Written informed consent was obtained from all participants or their legally appointed proxy decision-maker.

2.2. Clinical assessment

For comorbidities, Charlson comorbidity index (CCI) (Charlson et al., 1987) was calculated according to the comorbidities reported in the participants' hospital/physician files following ICD-10 codes. Depressive symptoms were assessed using the GDS. Height was measured with a digital stadiometer. Nutritional assessment was performed by body mass index (BMI) calculation and by completing the Mini-nutritional Assessment (MNA) tool. Cognition was assessed using the MMSE.

2.3. Disability assessment

The Barthel index (Mahoney and Barthel, 1965) and the Older Americans Resource Scale (OARS) (Fillenbaum and Smyer, 1981) were used to identifying disability in the participants, testing their performance in ADLs and instrumental ADLs (IADLs) respectively.

2.4. Physical performance assessment

Grip strength was measured following the Groningen Elderly Test using a Smedley Hand Dynamometer. The best of three attempts (with 30 s rest between them) was recorded. Gait was assessed using a GAIT Rite® (CIR Systems Inc., Havertown, PA) instrumented walkway (810 cm × 89 cm × 0.625 cm, sample rate = 80 Hz) positioned along a straight section of the walkway to record spatiotemporal gait data.

2.5. Determination of frailty status

Participants were categorized as non-frail, pre-frail, or frail according to validated and widely utilized frailty screening criteria (Fried et al., 2001). These criteria are based on the presence or absence of five measurable characteristics: slowed motor performance (by walking speed), weakness (by grip strength), low physical activity level (by Physical Activity Scale for the Elderly [PASE]), weight loss, and self-reported exhaustion on CES-D Scale. Individuals fitting three or more criteria were defined as frail, those fitting one or two criteria, as pre-frail, and those with none of the criteria were deemed as non-frail.

In addition, and considering frailty in relation to the accumulation of deficits, and that Frailty Indices comprising different variables and applied to different populations increase with age and correlate strongly with poor outcomes (Ritt et al., 2016), we used the Rockwood's frailty index as a second clinical measure of frailty in this population. To identify the 70 clinical deficits included in this index, we used a similar approach to the Canadian Study of Health and Aging (CSHA) clinical assessment (Searle et al., 2008). Items included the presence and severity of current diseases, ability in performing the ADLs, and physical and neurological signs from clinical examinations. Each deficit was dichotomized or trichotomized and mapped to the interval 0–1 to represent the severity or frequency of the problem with a higher index indicating frailty.