Microbiota components that improve endocrine control of metabolism in obesity and ageing

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The external environment influences chronic disease risk, including obesity, prediabetes and functional decline during ageing. The intestinal microbiota has emerged as a factor that can propagate external cues to alter host metabolism. However, the stimuli and biological sensors that underpin host metabolic dysfunction, or functional decline such as decreased skeletal muscle strength and slowing of movement during aging are ill-defined. Increased inflammation during obesity or ageing (*i.e.* inflammaging) has been proposed as a contributor to poor endocrine control and sarcopenia, but the participatory immune components are ill-defined.

We sought to define aspects of the microbiota that regulate both insulin and IGF-1 action, since these a common nodes of prediabetes and sarcopenia. We hypothesized that specific components derived from bacteria represent post-biotics that alter metabolism. We found that a specific component of the bacterial cell wall (*i.e.* muramyl dipeptide) reduced insulin resistance during both obesity and bacterial (*i.e.* endotoxin) stress. We identified the innate immune receptor (Nod2) and transcriptional regulator (Irf4) involved in insulin sensitizing properties of this post-biotic in mice. We initially hypothesized that germ-free mice (devoid of any bacteria) and mice lacking immune sensors for the bacterial cell wall would be partially protected from age-related inflammation and sarcopenia. We found that germ-free mice had worse indicators of sarcopenia compared to conventionally housed, (colonized) specific pathogen free mice. We found that Nod1-null mice had worse indicators of sarcopenia compared to WT mice.

Our results highlight that commensal bacterial factors can protect against insulin resistance and sarcopenia.