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Shining a light on comorbidities

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The gravity of comorbidities came under the spotlight when it transpired that pre-existing medical conditions can severely increase the risk of coronavirus disease 2019 (COVID-19) complications, and that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger comorbidities. Generally, comorbidities can result in more disease complications, drug side effects, or even adverse events, and can hinder rehabilitation and increase the risk for hospital admission, disability, and mortality. Currently there is no specific matching between comorbid conditions and corresponding medications. This special issue on comorbidities and co-occurring disorders explores recent advances in the molecular details and clinical approaches geared towards a better understanding of how diseases and co-occurring medical conditions influence each other, and how we can better prevent, diagnose, and treat them.

The term ‘comorbidity’ was introduced by Feinstein in 1970 to describe ‘any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has [an] index disease under study’. Since then, the definition of this term has been debated and re-evaluated multiple times. Notably, it might be counterproductive to label any one condition as an index disease as it might prevent us from viewing the complex interactions between the diseases as a whole. Oftentimes, the term comorbidity is also used interchangeably with ‘multimorbidity’, which describes concurrent conditions without implying dependency or hierarchy of one disease over another. While multimorbidity is thus sometimes the preferred terminology, we chose ‘comorbidity’ as a theme for this special issue, as the term is associated with connecting co-occurring diseases through proven pathogenetic mechanisms. In contrast, multimorbidity evaluates disease burden regardless of any mechanistic connection between diseases.

Generally, development of comorbidity can be caused by acute or chronic infections, genetic defects, systematic metabolic changes, or environmental insults. There are multiple ways in which those causes can interact within the host. Some comorbidities might arise due to anatomic proximity or connection of diseased organs. Another cause for comorbidities can be a singular pathogenetic mechanism that can cause several disorders as it infects multiple organs. A prime example is SARS-CoV-2 infection that can trigger pulmonary pathology, but also multi-organ complications. Comorbidities might also be triggered by one disease, and in good instances, if one disease can be effectively managed, it might even lead to remission of the other disease. Another way in which comorbidities might be linked is that complications of one disease result in the manifestation of another disease. Lastly, comorbidities might also be caused by genetic alterations that influence the development of two or more diseases. For all the abovementioned possibilities, additional biological, psychological, behavioral, socioeconomic, and environmental factors can also affect the development of comorbidities.

There are currently several accepted methods for measuring comorbidity, aimed at helping the clinician to calculate the severity of co-occurring diseases of their patients and to estimate the long-term prognosis and mortality risk. However, these measures cannot provide specific guidance for therapy. Given the many possibilities of how diseases can be interrelated, additional biological and environmental influences, as well as drug–drug interactions, the effect of comorbid pathologies on particular clinical implications and therapy is always patient-specific.
In this issue of *Trends in Molecular Medicine*, Newman and Kamada review the associations between the two chronic conditions periodontitis and inflammatory bowel disease. They discuss direct pathways that include translocation of proinflammatory microbes from the oral cavity to the gut and immune priming, as well as indirect connections that involve systemic immune activation with possible non-specific effects on the gut. Lastly, they also holistically evaluate treatment of periodontitis and inflammatory bowel disease, underscoring the importance of recognizing and treating both conditions. Their opinion article conceptually addresses the way in which some comorbidities might arise due to the anatomic proximity of or connection between diseased organs.

Chronic stress, while not officially recognized as a separate disease, is often regarded as a significant cause of morbidity and mortality; however, the mechanistic link between stress and other defined diseases has yet to be fully characterized. Ky and colleagues explore the concept of allostatic load, a measurement of the physiological burden of chronic stress, as well as its potential role in disease pathogenesis as it relates to cardiovascular disease, cancer, and health-related disparities. Building from this framework, they then posit the potential implications of allostatic load on patient care and research in cardio-oncology.

Recognizing that cancer often co-occurs with depression, Li and colleagues review inflammatory biomarkers and their associations with both depression and the currently available pharmacotherapies and psychotherapies in cancer. Notably, they highlight how modulation of inflammatory neuroimmune pathways can slow tumor progression and reduce metastases. Based on these insights, they propose that biomarkers associated with depression in cancer may help with diagnosis, treatment monitoring, and research on novel drug targets. Conceptually, their review underscores that if one comorbidity can be effectively managed, it might even lead to remission of another disease.

Using a different perspective to disentangle relationships between two diseases, Lorentz and colleagues use epidemiological studies as a starting point to show both positive and negative associations between allergies and cancer. They review molecular links between the two diseases by analyzing how allergic diseases may protect against tumorigenesis by promoting immune surveillance, but also how carcinogenesis may be promoted through inflammatory responses from allergies.

Staying with the topic of oncology, Irshad and colleagues review how humoral and diminished T cell responses in patients with cancer and those undergoing cancer therapy influence prevention strategies against COVID-19. This review is a prime example of how not only one disease (cancer) can affect severity of another disease (COVID-19), but also how treatment of one disease (chemotherapy) has to be considered as a factor that additionally impacts the course of a secondary disease. Furthermore, this review highlights the importance of considering effectiveness of prevention strategies for patients with comorbidities.

Notably, the prevalence of comorbidities increases with age, and is often associated with longer exposure to environmental insults, reduced potential for regeneration, and increased vulnerability due to a declining immune system. A gradual dysregulation of immune functions during aging also affects vaccine efficacy. Goldstein and colleagues review key factors contributing to the age-related decline in vaccine efficacy, and they discuss methods to bolster vaccine efficacy in older adults.

Moving from strategies of infection prevention to managing infection in comorbidity, McIntyre and Busse review how viral respiratory infections can trigger asthma exacerbations: episodes of increased severity of asthma with difficulty breathing and decline in pulmonary function that can result in respiratory failure and death when severe. They also review biologics for treatment of
severe asthma for the prevention of exacerbations, and identify specific pathways of inflammation that contribute to altered pathophysiology and novel therapeutic targets and informative biomarkers.

The multifaceted insights into the relationships between different co-occurring diseases are notoriously difficult to navigate, and need to be thoroughly evaluated in order to effectively translate into therapies. Given the breadth of molecular medicine and the nearly endless combination of comorbidities, this collection of articles merely reflects a sample of a few diseases and mechanisms. This special issue may provide some suggestions of what directions preclinical and clinical studies might take for the specific diseases discussed, but might also provide frameworks for how to evaluate other comorbidities.

I hope you will enjoy this special issue discussing key questions and offering provocative ideas. Many thanks to all authors and reviewers for their contributions. As always, we are happy to hear from our readers and welcome any comments at tmm@cell.com or @TrendsMolecMed.