

## Journal Scan

### **Cancer cells enter dormancy after cannibalizing mesenchymal stem/stromal cells (MSCs)**

Patients with breast cancer often develop malignant regrowth of residual drug-resistant dormant tumor cells years after primary treatment, a process defined as cancer relapse. Deciphering the causal basis of tumor dormancy therefore has obvious therapeutic significance. Because cancer cell behavior is strongly influenced by stromal cells, particularly the mesenchymal stem/stromal cells (MSCs) that are actively recruited into tumor-associated stroma, the authors assessed the impact of MSCs on breast cancer cell (BCC) dormancy. Using 3D cocultures to mimic the cellular interactions of an emerging tumor niche, the authors observed that MSCs sequentially surrounded the BCCs, promoted formation of cancer spheroids, and then were internalized/degraded through a process resembling the well-documented yet ill-defined clinical phenomenon of cancer cell cannibalism. This suspected feeding behavior was less appreciable in the presence of a rho kinase inhibitor and in 2D monolayer cocultures. Notably, cannibalism of MSCs enhanced survival of BCCs deprived of nutrients but suppressed their tumorigenicity, together suggesting the cancer cells entered dormancy. Transcriptome profiles revealed that the resulting BCCs acquired a unique molecular signature enriched in prosurvival factors and tumor suppressors, as well as inflammatory mediators that demarcate the secretome of senescent cells, also referred to as the senescence-associated secretory phenotype. Overall, the results of this study provide intriguing evidence that cancer cells under duress enter dormancy after cannibalizing MSCs. This 3D coculture model could provide a valuable tool to understand the antitumor activity of MSCs and cell cannibalism further, and therefore open new therapeutic avenues for the prevention of cancer recurrence.

#### **Comment**

Breast cancer cells relapse after decades of mastectomy is seen particularly in the patients of ductal carcinoma of the breast. The residual breast cancer cells cross talk with mesenchymal stem cells to form cancer spheroids. The BCCs cannibalise MSCs by entosis (cell-in-cell invasion) attain dormancy (under duress) and induce cancer relapse. The authors developed a useful therapeutic tool with 3D coculture model of BCCs and MSCs to know the mechanism of action of breast cancer relapse. The study is useful to develop therapeutics against breast cancer relapse and maybe extrapolated to treat other cancer relapses.

*Bartosh TJ, Ullah M, Zeitouni S, Beaver J, Prockop DJ. Cancer cells enter dormancy after cannibalizing mesenchymal stem/stromal cells (MSCs). Proc Natl AcadSci U S A. 2016 Oct 18;113(42):E6447-E6456.*

### **IL-22 controls iron-dependent nutritional immunity against systemic bacterial infections**

Host immunity limits iron availability to pathogenic bacteria, but whether immunity limits pathogenic bacteria from accessing host heme, the major source of iron in the body, remains unclear. Using *Citrobacter rodentium* (a mouse enteric pathogen) and *Escherichia coli* (a major cause of sepsis in humans) as models, the authors found that interleukin-22 (IL-22), a cytokine best known for its ability to promote epithelial barrier function, also suppresses the systemic growth of bacteria by



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limiting iron availability to the pathogen. To understand the mechanistic basis of IL-22–dependent iron retention in the host, using an unbiased proteomic approach, the authors identified that IL-22 induces the production of the plasma hemoglobin scavenger haptoglobin and the heme scavenger hemopexin (HPX). Moreover, the antimicrobial effect of IL-22 depends on the induction of hemopexin expression, whereas haptoglobin was dispensable. Impaired pathogen clearance in infected *I122<sup>Δ</sup>/Δ* mice was restored by hemopexin administration, and hemopexin-deficient mice had increased pathogen loads after infection. These studies reveal a previously unrecognized host defense mechanism regulated by IL-22 that relies on the induction of hemopexin to limit heme availability to bacteria, leading to suppression of bacterial growth during systemic infections.

### Comment

Nutritional immunity, a defense strategy involves limiting the iron availability to the pathogenic bacteria via hepcidin-dependent or hepcidin-independent mechanisms. But, pathogens overcome host iron limitation strategies through production of siderophores, hemophores and heme/hemoprotein receptors. The authors proved that administration of IL-22 or HPX scavenges the plasma heme which limits the availability of heme iron to the pathogens. The study may be applied to control other bacterial infections.

*Sakamoto K, Kim YG, Hara H, Kamada N, Caballero-Flores G, Tolosano E, Soares MP, Puente JL, Inohara N, Núñez G. IL-22 controls iron-dependent nutritional immunity against systemic bacterial infections. SciImmunol. 2017 Feb;2(8). pii: eaai8371.*

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### Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients

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Coronary artery disease is an inflammatory disorder characterized by narrowing of coronary arteries due to atherosclerotic plaque formation. Accumulating epidemiological evidence supports an association between oral bacterial diseases and coronary artery disease, but have failed to prove a causal link between the two. The recent surge in microbial identification and analyses techniques has led to the identification of a number of bacteria in atherosclerotic plaque samples from coronary artery disease patients. In this study, the authors present a meta-analysis from published studies that have independently investigated the presence of bacteria within atherosclerotic plaque samples in coronary artery disease patients. Data were collated from 63 studies covering 1791 patients spread over a decade. Immunohistochemistry, immunofluorescence, real-time polymerase chain reaction (PCR), nested PCR, and 16S rRNA gene sequencing were also used to identify bacteria. Their analysis confirmed the presence of 23 oral commensal bacteria, either individually or in co-existence, within atherosclerotic plaques in patients undergoing carotid endarterectomy, catheter-based atherectomy, or similar procedures. Of these 23 bacteria, 5 (*Campylobacter rectus*, *Porphyromonas gingivalis*, *Porphyromonas endodontalis*, *Prevotella intermedia*, *Prevotella nigrescens*) were found to be unique to coronary plaques, while the other 18 were additionally present in non-cardiac organs, and associated with over 30 non-cardiac disorders. Authors analyzed these 36 secretory proteins in context of the host immune system and categorized them on the basis of their potential to influence oral cavity and immune system that could lead to inflammation through pro-inflammatory cytokines such as monocyte chemo-attractant protein 1, IL-6, and IL-8. In addition, authors also listed resident colonizers, both commensal and pathogenic bacteria have been shown to form biofilm structures and role of migratory bacteria can form biofilm structures within atherosclerotic plaques. The authors have also given key roles of 23 atherosclerotic plaque-associated oral commensal bacteria in disease pathology. This work provides a resource whose immediate implication is the necessity to

systematically catalog landscapes of atherosclerotic plaque-associated oral commensal bacteria in human patient populations.

### **Comment**

Human health maintenance is contributed by human microbiota. The oral cavity is a complex part of the human system and a number of factors work in synergy to maintain its homoeostasis. The oral system serves as a major route for the entry of bacteria to populate and establish a microenvironment within the human system. This meta-analysis shows the potential of the 23 atherosclerotic plaque-associated oral commensal bacteria in disease pathology. In the study, 19 genomes from 23 atherosclerotic plaque-associated oral commensal bacteria were selected, annotated and established molecular profiling factors that contribute to plaque formation. Hence, a genomic platform has been established to enable bacterial and molecular profiling of factors that contribute to plaque formation. This has paved way for studies which could study these microbe–plaque axes to unravel the full extent of linkage between host microbiome with atherosclerosis.

*Chhibber-Goel J, Singhal V, Bhowmik D, Vivek R, Parakh N, Bhargava B and Sharma A. Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients. npj Biofilms and Microbiomes 2016; 2:7; doi:10.1038/s41522-016-0009-7.*

### **Reviewers**

**V. Suresh, A. R. Bitla**

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