A malign microenvironment

Dr Ezio Laconi investigates how biochemical and metabolic changes in tissues, which occur as individuals grow older, heighten the risk of developing neoplastic diseases such as cancer.

Why did you develop an interest in neoplastic disease, particularly in the ageing population?

The conceptual basis of my research was largely framed by my interactions with the prominent scientist Dr Emmanuel Farber, who died last year at the age of 93. Farber was Head of the Department of Pathology at the University of Toronto, Canada, where I earned my PhD.

Some fundamental points were established back then. Firstly, overt cancer is often the outcome of a long-term biological process. It can take decades to unfold and is the end result of a series of mechanistically related events. Secondly, despite the fact that cancer cells are typically hyper-proliferative, most agents and exposures associated with increased risk are toxic and/or growth-suppressive to their target cells. Accordingly, many human cancers emerge from a background of chronic toxicity.

We know that chronic toxicity may foster the emergence of neoplastic disease. We, and other groups, are considering the possibility that ageing favours the emergence of neoplastic disease via alterations in the tissue microenvironment.

Which mechanisms cause the liver’s regenerative capacity to decline with age?

Neither the biological nor molecular mechanisms have been fully elucidated. However, we have data that support two complementary hypotheses: the inherent capacity of the hepatocyte to respond to growth stimuli appears to be relatively compromised by age, and there is also evidence suggesting that the stimulus for liver regeneration may partly wane over time.

What were the core findings from your study on hepatocyte growth in young and aged livers?

We used a cell transplantation model developed in our laboratory to ask a simple question: what would happen if we transplanted hepatocytes isolated from the same (young) donor into the livers of animals of different ages? At the time, the obvious answer seemed that the younger the recipient, the better it would be able to sustain the growth of transplanted cells: thus, clusters of donor-derived cells would be larger in younger hosts. Interestingly, however, the results were completely the opposite. The tissue environment of the aged liver is more stimulatory than that of a young liver, which could contribute to the imposition of a cancer-prone tissue landscape during ageing.

How does the liver’s decline in regenerative potential affect older people’s health?

Under normal conditions, residual regenerative capacity is sufficient to guarantee normal liver function and the ability to cope with mild insults. However, the situation changes if there is a sudden increase in functional demand and/or sudden loss of tissue mass. Reduced regenerative potential may translate into impairment of liver function, which may lead to acute liver failure.

Another scenario is chronic liver disease, which is often associated with increased hepatocyte senescence and decreased regenerative capacity; the latter may contribute to the potentiation of healing processes, leading to increased scarring, liver fibrosis and cirrhosis.

To what extent does the microenvironment play a key role in the pathogenesis of neoplastic disease?

It plays a major role. Based on our results, I proposed an important distinction between tissue and the tumour microenvironment. The tissue microenvironment can be exemplified by alterations associated with ageing: that is, decreased functional proficiency and chronic activation of ‘healing’ processes. On the other hand, the tumour microenvironment has more to do with the consequences of tumour expansion. As this occurs, tumour cells experience increasing difficulties with finding adequate oxygen and nutrient supplies, and this forces them to react. For example, they learn to generate new blood vessels and tend to migrate to other tissue sites, searching for food. Many cells do not succeed, but those few that do will take the lead and become more and more aggressive. Thus, the harsh conditions of the tumour microenvironment cause aggressively malignant cancer cells.

How has your research shown that hepatocyte transplantation delays the emergence of hepatocellular carcinoma?

We have induced persistent alterations in the liver to determine a neoplastic-prone tissue landscape following the administration of naturally occurring pyrrolizidine alkaloids. If no further treatment is given, a significant incidence of pre-neoplastic and neoplastic lesions develops within a year. However, if animals are transplanted with normal hepatocytes, these repopulate and ‘rejuvenate’ the liver, and fewer pre-neoplastic and neoplastic lesions emerge. These results cannot, however, be interpreted to suggest easy shortcuts to the cancer problem: health is a holistic concept and must not be treated in separate compartments.
Living well into old age

Studies at the University of Cagliari, Italy, are providing insights into the mechanisms of cancer and ageing. Findings indicate that cumulative damage to tissues from environmental exposure, diet and lifestyle contributes to the heightened incidence of chronic diseases in older people.

The increasing life expectancy of populations across the world brings with it a rising incidence of age-related disorders, from hearing loss and changes in vision to cancer and cardiovascular, neurodegenerative and metabolic diseases. Indeed, the burden of age-associated chronic disease, in terms of diminished quality of life for older people and capacity problems for health systems, is poised to become heavier in the coming decades.

According to Dr Ezio Laconi of the Department of Biomedical Sciences at the University of Cagliari, the main risk factor for developing neoplastic diseases is an individual’s environmental context, including unhealthy diet, smoking and hyper-competitive social drive. The cumulative effects of long-term exposure to these harmful conditions set the stage for chronic toxicity within the body.

Indeed, the loss of biological function that comes with ageing is underpinned by the body’s response to these toxic conditions. While the body’s regenerative mechanisms are designed to protect damaged tissue, they can in fact have the opposite effect. Cytokines, growth factors and proteases in aged tissues stimulate the heightened activation of healing processes, triggering inflammation, cell loss and scarring. This effectively creates a tissue environment in which neoplastic cells can grow and flourish.

Microenvironment effects
In 2007, Laconi made a clear distinction between the influences of the tumour and tissue microenvironments in the processes of neoplastic disease. In his analysis, the structural integrity of the architecture of normal tissue was found to support the fundamental signalling processes necessary for tissue health. Uncontrolled cell growth in cancer and other neoplastic conditions, however, relies on the transformation of tissue structure and architecture from its normal state to a disrupted, dysfunctional state. This in turn disturbs signalling, which allows neoplastic cells to emerge and eventually migrate from their original site to other parts of the body. Such transformations can arise from damage caused by injury and toxic conditions in addition to ageing.

There are curious similarities between the ways that ageing and cancer start, and how they progress. “These similarities are very important because they tell us two things: first, preventing cancer altogether might be just as difficult and unrealistic as preventing ageing; and second, delaying or slowing the ageing process is not only good for our overall health, but also has the added advantage of decreasing the risk of neoplasia,” emphasises Laconi.

Essentially, the similarities between ageing and cancer processes are tied to the loss of integrity of the tissue microenvironment; if external cues transform the normal tissue microenvironment to be tumour-prone, neoplastic cells can emerge. For instance, Laconi’s work on the liver has shown that the senescent tissue environment prompts the growth of pre-neoplastic parenchymal cells in the liver, which typically progress into the most common form of liver cancer, hepatocellular carcinoma.
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**LIVER INVESTIGATIONS**

The ability of the liver to regenerate following damage that occurs beyond birth is connected to its unique detoxification role. However, over the past few decades, it has become increasingly apparent that its capacity to regenerate significantly declines with ageing.

Laconi recently conducted a study in an attempt to establish why this is the case. Excitingly, he found evidence that hepatocytes in the senescent liver autonomously reduce their replication abilities in response to environmental cues. He also discovered that the removal of aged hepatocytes, even from a tumour microenvironment, delays the onset of hepatocellular carcinoma.

In the study, Laconi transplanted healthy hepatocytes into the livers of rats with induced vulnerability to hepatocellular carcinoma, thus mimicking liver tissue senescence. After a year, most of the senescent cells in the rats’ liver tissue had been supplanted by healthy cells, and, although 50 per cent of the control subjects had developed hepatocellular carcinoma, none of the transplanted group had. To Laconi, these factors confirmed that the re-establishment of the normal tissue microenvironment holds great promise as an approach to limit the development of neoplastic disease and reduce the risk of cancer.

**TOWARDS HEALTHY AGEING**

While it is uncertain whether cancer and ageing may ultimately become ‘reversible’ diseases through medical interventions such as cell transplantation, Laconi is doubtful that the rejuvenation of tissues constitutes a viable strategy for warding off the growing prevalence of neoplastic diseases. He sees these diseases more as a social than a medical problem, flagging up preservation of a normal, healthy tissue microenvironment throughout life as the key to healthy ageing: “Slowing or delaying ageing can be done to some extent, as long as we do not aim for immortality,” he admits. “Yet, it involves paying special attention to our lifestyle, both as individuals and a society.”

Healthy ageing is a long-term process that starts at least soon after birth, if not from the moment of conception. Policy makers and healthcare professionals across the world therefore need to do more when it comes to promoting healthy ageing. However, such initiatives require concerted planning and, above all, the framing and sending of consistent messages: “Encouraging healthy ageing while promoting hyper-competitive lifestyles from childhood would likely lead to more social isolation and over-eating,” Laconi asserts.

At present, he is carrying out further investigations into the role of cell senescence in the onset of neoplastic disease. He is also exploring how ageing and the calorific content of diet affect the different stages of carcinogenesis, especially in terms of changes in the tissue microenvironment. Through delivering a greater understanding of the biological and molecular mechanisms of neoplasia, this work should contribute to improving approaches to prevention, diagnosis and therapy of neoplastic disease. The hope is that it will also help to elucidate processes in chronic diseases other than cancer.