CANCER

Fat and the fate of pancreatic tumours

In obese people with pancreatic cancer, the many interactions between fat cells and the inflammatory microenvironment surrounding the tumour lead to below-average prognosis and chemotherapy outcome.

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The increasing prevalence of obesity will have an even greater effect on the health-care system than previously predicted, because obesity turns out to be a major risk factor for the development of cancer[1]. Obese individuals have a substantially elevated risk for a type of pancreatic cancer known as pancreatic ductal adenocarcinoma, which is the fourth most-common cause of cancer-associated death[1]. An inflammatory microenvironment is a hallmark of cancer, but little is known about how alterations in the surrounding connective tissue (stroma) contribute to tumour initiation and progression in obesity. Writing in *Cancer Discovery*, Incio *et al.*[2] report their investigation into how fat cells in the microenvironment surrounding cancer cells contribute to tumour initiation and progression in both mice and humans.

Tumour formation in the pancreas involves striking structural distortion of tissue, which is attributed to the disruption of digestive-enzyme-containing acinar cells, tissue infiltration by immune cells, a strong fibrotic response (also known as fibrosis, the formation of excess connective tissue or collagen protein around the tumour), and a higher than usual level of deposition of extracellular-matrix material. Cancer lesions in obese individuals are commonly associated with increased fat-cell (adipocyte) content compared with tumours from non-obese patients; however, the function of these fat cells in pancreatic cancer remained unclear until now.

Incio and colleagues show that, in mice, adipocytes, along with immune cells and pancreatic stellate cells, signal through the IL-1β protein and the AT1 angiotensin receptor to drive migration of immune cells called neutrophils to the tumour microenvironment. This increases the inflammatory and fibrotic response in the pancreatic-cancer microenvironment in a way that results in poor response to chemotherapy and poor prognosis.

In obese mice, the tumour microenvironment was shown to contain adipocytes that are increased in both size and number, partly as a result of tumours invading the neighbouring white adipose tissues. The researchers observed an abundant fibrotic response in tumour areas that were enriched in adipocytes or located adjacent to adipose tissue. These results suggest that fibrosis is a hallmark of adipose tissue in obese subjects with pancreatic cancer, and that the accumulation of the extracellular-matrix protein collagen, a component of the fibrotic response, in the vicinity of fat cells is a prominent characteristic of obesity. Incio and colleagues also found that adipocyte infiltration into the tumour microenvironment correlates with worse prognosis and treatment outcome in patients.

The authors hypothesized that, in people with pancreatic cancer, obesity-associated adipocyte accumulation increases fibrosis, promotes tumour progression and hinders the delivery and efficacy of chemotherapeutics. When they checked the percentage of perfused blood vessels in a given area of mouse tumour, they found that it was significantly reduced in obese animals. To determine whether impeded perfusion through blood vessels is responsible for inefficient delivery of chemotherapeutic agents, the authors measured the uptake of the chemotherapy drug 5-fluorouracil in mice. Obesity significantly decreased tumour uptake of the drug compared with uptake in non-obese control animals, thereby reducing the chemotherapy's efficacy (Fig. 1).

Chronic fibrosis is thought to have a crucial role in enhancing tumour growth and in attenuating drug delivery. However, in previous studies, inhibition of chronic fibrosis by either inhibitor compounds[3] or genetic mutations[3,4] resulted in increased immunosuppression, accelerated tumour growth and decreased survival, implying that tumour stroma may be restrictive to tumour growth.

By contrast, Incio *et al.* show that inhibition of the major pro-fibrotic pathway of AT1 signalling in mice inhibited tumour progression. The authors propose that migration into the tissue of tumour-associated neutrophils and IL-1β production are leading drivers in the regulation of tumour growth in this context, although changes in vascular perfusion due to reduced blood pressure also play a minor part. When the authors depleted neutrophils or blocked the activity of IL-1β using antibody treatment, the immunosuppressive microenvironment was reshaped and the progression of pancreatic cancer was reduced.

50 Years Ago

'We wuz robbed' — The World Cup which has recently been enacted in Britain may have been fun to watch, but there is no question that it was a thoroughly badly designed experiment … The mere fact that a Poisson distribution can describe so well the distribution of scores by individual teams goes a long way to suggest that the teams were much of a muchness in talent and their scores were independent of each other. From this point of view, the decision that the outcome of the whole competition should depend on the outcome of a single game between the two so-called finalists was as much of a farce as a great many West German supporters already know it to have been … If, for example, it were agreed that … no team should be declared the winner until its score exceeds that of its opponent by three standard deviations of Poisson distribution, it might be necessary to design the game of football so that it would be practicable for one side to score 100 goals or so … Such a change could easily be brought about, possibly by widening the goalposts or by abolishing goalkeepers.

From *Nature* 13 August 1966

100 Years Ago

The History of the Family. By Prof. W. Goodsell — In what sense is it right to speak of the history of the family? … Can it be said to have a history? … Some such questions as these arise in one's mind as one takes up Prof. Goodsell's book … even a casual reader will be struck by a want of precise references in certain of the chapters … Where is the "weight of evidence" which shows that polygamy is unpopular among savage women? The author gives several reasons why *we* condemn it, but there is surely room for doubt …

From *Nature* 10 August 1916