The best way to treat cancer is to kill it. Indeed, most cancer therapies work by killing tumour cells, be it directly or indirectly. Nevertheless, combined issues of toxicity and resistance limit the effectiveness of anti-cancer therapies. To address these, our research centres on understanding how mitochondria regulate cell death and inflammation, with the ultimate goal of improving cancer treatment.

Mitochondria, cell death and cancer
Apoptosis requires caspase protease activity, leading to widespread substrate cleavage and rapid cell death. During apoptosis, mitochondrial outer membrane permeabilisation (MOMP) occurs, a crucial event that is required for caspase activation. Following MOMP, mitochondrial intermembrane space proteins, such as cytochrome c, are released into the cytoplasm where they cause caspase activation and apoptosis. Given its key role in controlling cell survival, mitochondrial outer membrane integrity is highly regulated, largely through interactions between pro- and anti-apoptotic Bcl-2 proteins. Cancer cells often inhibit apoptosis by preventing MOMP, often through upregulation of anti-apoptotic Bcl-2 proteins. Importantly, this can be exploited therapeutically – newly developed anti-cancer therapeutics called BH3-mimetics target these apoptotic blocks.

A non-cell autonomous mechanism of drug resistance
Non-genetic means of drug tolerance or persistence are a major barrier to effective killing of cancer cells. Using BCL-2 targeting BH3-mimetics as prototypic cancer killing drugs, we aimed to understand mechanism(s) of drug persistence. Selection of drug resistant cells following BH3-mimetic (venetoclax) treatment revealed – perhaps not too surprisingly – that resistant cells expressed higher levels of anti-apoptotic BCL-2 and MCL-1. Importantly, venetoclax was found to upregulate BCL-2 and MCL-1 independent of apoptotic resistance, with treatment also leading to BCL-2 and MCL-1 upregulation in death resistant BAX/BAK deleted cells. We initially assumed that resistance was cell intrinsic; however, quickly found that upon venetoclax (or other therapies), cells release a factor that promotes BCL-2 and MCL-1 expression in neighbouring cells enabling therapeutic resistance. Consistent with the mechanism being a transient state of drug persistence (as opposed to a genetic mechanism of resistance), removal of apoptotic stress reverted resistant cells to a sensitive state.

Apoptotic stress triggers cells to release pro-survival FGF-2
We next aimed to understand how apoptotic stress could promote cell survival. We found that FGF-2 (pro-survival growth factor) could be released by cells upon apoptotic stress. Following binding its cognate receptors, FGF-2 activates MAPK, causing transcriptional upregulation of MCL-1 and BCL-2. Accordingly, neutralisation of FGF signalling or inhibition of MAPK reduced the emergence of drug persistence. Suggesting a potential relevance in human cancer, we found a correlation between FGF-activation, anti-apoptotic BCL-2 expression and worse prognosis in thymoma. In summary, we propose a model whereby apoptotic stress promotes survival (negatively impacting therapeutic efficacy) through an FGF-2 mediated, non-cell autonomous mechanism (Figure 1). Ongoing work aims to understand the occurrence of this mechanism in vivo, its impact on chemotherapy efficacy and mechanistic basis – how does BCL-2 inhibition lead to release of FGF-2?

Wound-healing as a physiological setting of apoptosis induced survival
Cancer processes are invariably subverted forms of physiological functions. Thus, we aimed to understand the “day job” of FGF2 driven survival signaling. Specifically, we investigated wound-healing, in collaboration with Yaron Fuchs (Technion). Interestingly, MCL-1 was found to be highly upregulated upon wound-healing in an FGF and MAPK dependent manner (Figure 2). Moreover, inhibition of MCL-1 upregulation – either through MAPK or FGF inhibition, reduced the kinetics of wound-healing. Our data suggests that wound-healing may represent a physiological setting of apoptotic stress induced survival. Cancer is often referred to as a wound that doesn’t heal, while speculative, constant cycles of wounding and repair – in our opinion – provide an ideal setting to promote transformation or therapeutic resistance, by engaging apoptotic stress induced survival.

Finally, we say a sad goodbye to long-time lab stalwarts, Joel Riley and Florian Bock. Both start their own labs in Maastricht (Flo) and Innsbruck (Joel). Can’t wait to see the exciting data coming out their new groups in due course, knock em dead guys! Huge welcome to Rosalie Heilig, who joins us as an SNF supported postdoc following her PhD in Lausanne.

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